



## Clinical trial results:

### A Phase 3, Placebo-Controlled, Randomised, Observer-Blinded Study to Evaluate the Efficacy, Safety, And Tolerability of a Clostridium Difficile Vaccine in Adults 50 Years of Age and Older

#### Summary

|                          |                                        |
|--------------------------|----------------------------------------|
| EudraCT number           | 2016-003866-14                         |
| Trial protocol           | SK BG SE HU BE CZ GB DE FI PT ES PL FR |
| Global end of trial date | 21 December 2021                       |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 16 December 2022 |
| First version publication date | 16 December 2022 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | B5091007 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03090191 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                                             |
|------------------------------|-------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Pfizer Inc.                                                                                                 |
| Sponsor organisation address | 235 E 42nd Street, New York, United States, NY 10017                                                        |
| Public contact               | Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact           | Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.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                       | 11 February 2022 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 21 December 2021 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate that Pfizer's C difficile vaccine is effective in reducing the incidence of a first primary episode of CDI and to evaluate the safety profile of Pfizer's C difficile vaccine as measured by the percentage of subjects reporting local reactions and systemic events, Adverse Events (AEs), and Serious Adverse Events (SAEs).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trials subjects were followed.

Background therapy: -

Evidence for comparator: -

|                                                           |               |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment                          | 29 March 2017 |
| 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 | Argentina: 118          |
| Country: Number of subjects enrolled | Australia: 258          |
| Country: Number of subjects enrolled | Belgium: 19             |
| Country: Number of subjects enrolled | Bulgaria: 868           |
| Country: Number of subjects enrolled | Canada: 449             |
| Country: Number of subjects enrolled | Chile: 37               |
| Country: Number of subjects enrolled | Colombia: 456           |
| Country: Number of subjects enrolled | Czechia: 141            |
| Country: Number of subjects enrolled | Germany: 301            |
| Country: Number of subjects enrolled | Spain: 204              |
| Country: Number of subjects enrolled | Finland: 119            |
| Country: Number of subjects enrolled | France: 60              |
| Country: Number of subjects enrolled | United Kingdom: 224     |
| Country: Number of subjects enrolled | Hungary: 600            |
| Country: Number of subjects enrolled | Japan: 1062             |
| Country: Number of subjects enrolled | Korea, Republic of: 175 |
| Country: Number of subjects enrolled | Peru: 61                |
| Country: Number of subjects enrolled | Poland: 671             |
| Country: Number of subjects enrolled | Portugal: 75            |

|                                      |                      |
|--------------------------------------|----------------------|
| Country: Number of subjects enrolled | Slovakia: 369        |
| Country: Number of subjects enrolled | Sweden: 185          |
| Country: Number of subjects enrolled | Taiwan: 89           |
| Country: Number of subjects enrolled | United States: 10899 |
| Worldwide total number of subjects   | 17440                |
| EEA total number of subjects         | 3612                 |

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)                      | 5925  |
| From 65 to 84 years                       | 11184 |
| 85 years and over                         | 331   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 18095 subjects signed the informed consent form (ICF). Among that 560 subjects did not meet all eligibility criteria, were not randomised and vaccinated. Overall, 17535 subjects were randomised. Among those, 17440 subjects received at least 1 dose of the investigational product.

### 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                | Investigator, Subject          |

### Arms

|                              |                               |
|------------------------------|-------------------------------|
| Are arms mutually exclusive? | Yes                           |
| <b>Arm title</b>             | Clostridium difficile Vaccine |

Arm description:

Subjects received Clostridium difficile vaccine 200 microgram total toxoid per dose intramuscularly at Months 0, 1 and 6.

|                                        |                       |
|----------------------------------------|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | Clostridium difficile |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Injection             |
| Routes of administration               | Intramuscular use     |

Dosage and administration details:

Subjects received 200 microgram total toxoid per dose intramuscularly.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Subjects received placebo (normal saline solution of 0.9 percent [%] sodium chloride) intramuscularly at Months 0, 1 and 6.

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Placebo                |
| Investigational medicinal product name | Normal saline solution |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Injection              |
| Routes of administration               | Intramuscular use      |

Dosage and administration details:

Subjects received Normal saline solution of 0.9 percent [%] sodium chloride intramuscularly.

| <b>Number of subjects in period 1</b> | <b>Clostridium difficile Vaccine</b> | <b>Placebo</b> |
|---------------------------------------|--------------------------------------|----------------|
| Started                               | 8722                                 | 8718           |
| Vaccinated at Month 0 (Dose 1)        | 8722                                 | 8718           |
| Vaccinated at Month 1 (Dose 2)        | 8311                                 | 8331           |
| Vaccinated at Month 6 (Dose 3)        | 7894                                 | 7967           |
| Completed                             | 5532                                 | 5575           |
| Not completed                         | 3190                                 | 3143           |
| Adverse event, serious fatal          | 368                                  | 358            |
| Physician decision                    | 77                                   | 66             |
| Consent withdrawn by subject          | 2160                                 | 2133           |
| Adverse event, non-fatal              | 87                                   | 72             |
| Site terminated                       | 7                                    | 8              |
| Unspecified                           | 66                                   | 60             |
| Lost to follow-up                     | 382                                  | 394            |
| Protocol deviation                    | 43                                   | 52             |

## Baseline characteristics

### Reporting groups

|                                                                                                                             |                               |
|-----------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| Reporting group title                                                                                                       | Clostridium difficile Vaccine |
| Reporting group description:                                                                                                |                               |
| Subjects received Clostridium difficile vaccine 200 microgram total toxoid per dose intramuscularly at Months 0, 1 and 6.   |                               |
| Reporting group title                                                                                                       | Placebo                       |
| Reporting group description:                                                                                                |                               |
| Subjects received placebo (normal saline solution of 0.9 percent [%] sodium chloride) intramuscularly at Months 0, 1 and 6. |                               |

| Reporting group values                             | Clostridium difficile Vaccine | Placebo | Total |
|----------------------------------------------------|-------------------------------|---------|-------|
| Number of subjects                                 | 8722                          | 8718    | 17440 |
| Age categorical                                    |                               |         |       |
| Units: Subjects                                    |                               |         |       |
| In utero                                           | 0                             | 0       | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0                             | 0       | 0     |
| Newborns (0-27 days)                               | 0                             | 0       | 0     |
| Infants and toddlers (28 days-23 months)           | 0                             | 0       | 0     |
| Children (2-11 years)                              | 0                             | 0       | 0     |
| Adolescents (12-17 years)                          | 0                             | 0       | 0     |
| Adults (18-64 years)                               | 2962                          | 2963    | 5925  |
| From 65-84 years                                   | 5597                          | 5587    | 11184 |
| 85 years and over                                  | 163                           | 168     | 331   |
| Age Continuous                                     |                               |         |       |
| Units: Years                                       |                               |         |       |
| arithmetic mean                                    | 68.0                          | 68.1    |       |
| standard deviation                                 | ± 7.5                         | ± 7.5   | -     |
| Sex: Female, Male                                  |                               |         |       |
| Units: Subjects                                    |                               |         |       |
| Female                                             | 4472                          | 4501    | 8973  |
| Male                                               | 4250                          | 4217    | 8467  |
| Race (NIH/OMB)                                     |                               |         |       |
| Units: Subjects                                    |                               |         |       |
| American Indian or Alaska Native                   | 53                            | 54      | 107   |
| Asian                                              | 754                           | 725     | 1479  |
| Native Hawaiian or Other Pacific Islander          | 20                            | 14      | 34    |
| Black or African American                          | 663                           | 666     | 1329  |
| White                                              | 6891                          | 6922    | 13813 |
| More than one race                                 | 327                           | 322     | 649   |
| Unknown or Not Reported                            | 14                            | 15      | 29    |
| Ethnicity (NIH/OMB)                                |                               |         |       |
| Units: Subjects                                    |                               |         |       |
| Hispanic or Latino                                 | 1119                          | 1143    | 2262  |
| Not Hispanic or Latino                             | 7546                          | 7515    | 15061 |
| Unknown or Not Reported                            | 57                            | 60      | 117   |



## End points

### End points reporting groups

|                                                                                                                             |                               |
|-----------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| Reporting group title                                                                                                       | Clostridium difficile Vaccine |
| Reporting group description:                                                                                                |                               |
| Subjects received Clostridium difficile vaccine 200 microgram total toxoid per dose intramuscularly at Months 0, 1 and 6.   |                               |
| Reporting group title                                                                                                       | Placebo                       |
| Reporting group description:                                                                                                |                               |
| Subjects received placebo (normal saline solution of 0.9 percent [%] sodium chloride) intramuscularly at Months 0, 1 and 6. |                               |

### Primary: Number of First Primary Episodes of Clostridium Difficile Infection (CDI) (Definition 1) Follow-up After Dose 3

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                 |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Number of First Primary Episodes of Clostridium Difficile Infection (CDI) (Definition 1) Follow-up After Dose 3 |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                 |
| CDI definition 1 for a primary episode of CDI(no previous CDI onset in prior 8 weeks)defined as either a) presence of diarrhea(passage of 3 or more unformed stools[Bristol stool chart types 5-7]) in 24 or fewer consecutive hours,stool sample positive for toxin B gene(by polymerase chain reaction[PCR]) and positive for toxin A and/or toxin B,as measured in central laboratory;or b)Pseudomembranous colitis diagnosed at colonoscopy, at surgery, or histopathologically;and corresponding stool sample positive for toxin B gene(via PCR)as measured in central laboratory. End of surveillance period was defined as accumulation of at least 40 CDI cases. Per Protocol-3 analysis population included all randomised subjects who received dose 1, dose 2, and dose 3 of investigational product to which they were randomised and had no major protocol violations up to and including 14 days after dose 3. Here, "Number of Subjects Analysed" signifies subjects evaluable for this end point. |                                                                                                                 |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Primary                                                                                                         |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                 |
| From 14 days after Dose 3 to the end of the surveillance period (mean follow-up after dose 3 was 34.2 months)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                 |

| End point values            | Clostridium difficile Vaccine | Placebo         |  |  |
|-----------------------------|-------------------------------|-----------------|--|--|
| Subject group type          | Reporting group               | Reporting group |  |  |
| Number of subjects analysed | 7707                          | 7805            |  |  |
| Units: Episodes             | 17                            | 25              |  |  |

### Statistical analyses

|                                                                                                                                                                                                                               |                                              |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| Statistical analysis title                                                                                                                                                                                                    | Clostridium difficile vaccine versus Placebo |
| Statistical analysis description:                                                                                                                                                                                             |                                              |
| Vaccine efficacy(VE)=100*(1-infection rate ratio[IRR]),IRR=calculated ratio of first primary CDI incidence between Clostridium difficile vaccine group and placebo group. 96.4% CI was estimated using Clopper-Pearson-Method |                                              |
| Comparison groups                                                                                                                                                                                                             | Clostridium difficile Vaccine v Placebo      |

|                                         |                            |
|-----------------------------------------|----------------------------|
| Number of subjects included in analysis | 15512                      |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[1]</sup> |
| Parameter estimate                      | Vaccine efficacy           |
| Point estimate                          | 31                         |
| Confidence interval                     |                            |
| level                                   | Other: 96.4 %              |
| sides                                   | 2-sided                    |
| lower limit                             | -38.7                      |
| upper limit                             | 66.6                       |

Notes:

[1] - Lower bound of confidence interval greater than 20% demonstrate vaccine efficacy.

### **Primary: Number of First Primary Episodes of Clostridium Difficile Infection (CDI) (Definition 1) Follow-up After Dose 2**

|                 |                                                                                                                 |
|-----------------|-----------------------------------------------------------------------------------------------------------------|
| End point title | Number of First Primary Episodes of Clostridium Difficile Infection (CDI) (Definition 1) Follow-up After Dose 2 |
|-----------------|-----------------------------------------------------------------------------------------------------------------|

End point description:

CDI definition 1 for primary episode of CDI(no previous CDI onset in prior 8 weeks) defined as either a)presence of diarrhea(passage of 3 or more unformed stools[Bristol stool chart types 5-7]) in 24 or fewer consecutive hours, and stool sample positive for toxin B gene(by polymerase chain reaction [PCR]) and positive for toxin A and/or toxin B, as measured in central laboratory; or b)Pseudomembranous colitis diagnosed at colonoscopy, at surgery, or histopathologically; and corresponding stool sample positive for toxin B gene (via PCR) as measured in central laboratory. End of surveillance period was defined as accumulation of at least 40 CDI cases. Per Protocol-2 analysis population included all randomised subjects who received dose 1 and dose 2 of the investigational product to which they were randomized and had no major protocol violations up to and including 14 days after dose 2. Here,"Number of Subjects Analysed" signifies subjects evaluable for this end point.

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

End point timeframe:

From 14 days after Dose 2 to the end of the surveillance period (mean follow-up after dose 2 was 36 months)

| <b>End point values</b>     | Clostridium difficile Vaccine | Placebo         |  |  |
|-----------------------------|-------------------------------|-----------------|--|--|
| Subject group type          | Reporting group               | Reporting group |  |  |
| Number of subjects analysed | 8139                          | 8184            |  |  |
| Units: Episodes             | 24                            | 34              |  |  |

### **Statistical analyses**

|                                   |                                              |
|-----------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b> | Clostridium difficile vaccine versus Placebo |
|-----------------------------------|----------------------------------------------|

Statistical analysis description:

Vaccine efficacy(VE)=100\*(1-infection rate ratio[IRR]),IRR=calculated ratio of first primary CDI incidence between Clostridium difficile vaccine group and placebo group. 96.4% CI was estimated using Clopper-Pearson-Method.

|                   |                                         |
|-------------------|-----------------------------------------|
| Comparison groups | Clostridium difficile Vaccine v Placebo |
|-------------------|-----------------------------------------|

|                                         |                            |
|-----------------------------------------|----------------------------|
| Number of subjects included in analysis | 16323                      |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[2]</sup> |
| Parameter estimate                      | Vaccine efficacy           |
| Point estimate                          | 28.6                       |
| Confidence interval                     |                            |
| level                                   | Other: 96.4 %              |
| sides                                   | 2-sided                    |
| lower limit                             | -28.4                      |
| upper limit                             | 61                         |

Notes:

[2] - Lower bound of confidence interval greater than 20% demonstrate vaccine efficacy.

### Primary: Percentage of Subjects Reporting Local Reactions (LR) Within 7 Days After Dose 1

|                 |                                                                                                 |
|-----------------|-------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects Reporting Local Reactions (LR) Within 7 Days After Dose 1 <sup>[3]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------|

End point description:

Local reactions included redness, swelling and pain at injection site. These were recorded by subjects in an electronic diary (e-diary). Redness and swelling were measured and recorded in measuring device units. One measuring device unit= 0.5 centimeter (cm) and graded as mild: 2.5 to 5.0 cm, moderate: greater than (>) 5.0 to 10.0 cm, severe: >10.0 cm. Grade 4 indicated necrosis or exfoliative dermatitis for redness and necrosis for swelling. Pain at injection site was graded as mild: did not interfere with daily activity, moderate: interfered with daily activity, severe: prevented daily activity. Grade 4 indicated emergency room visit or hospitalisation. Safety analysis population included all subjects who received at least 1 dose of the investigational product. Here, "Number of Subjects Analysed" signifies subjects evaluable for this end point.

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

End point timeframe:

Within 7 days after Dose 1 at Month 0

Notes:

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

Justification: Only descriptive data was planned for this endpoint.

| End point values                 | Clostridium difficile Vaccine | Placebo          |  |  |
|----------------------------------|-------------------------------|------------------|--|--|
| Subject group type               | Reporting group               | Reporting group  |  |  |
| Number of subjects analysed      | 8558                          | 8510             |  |  |
| Units: Percentage of subjects    |                               |                  |  |  |
| number (confidence interval 95%) |                               |                  |  |  |
| Redness: Mild                    | 1.5 (1.3 to 1.8)              | 0.6 (0.4 to 0.7) |  |  |
| Redness: Moderate                | 0.5 (0.4 to 0.7)              | 0.3 (0.2 to 0.4) |  |  |
| Redness: Severe                  | 0.4 (0.3 to 0.6)              | 0.2 (0.1 to 0.3) |  |  |
| Redness: Grade 4                 | 0 (0.0 to 0.0)                | 0 (0.0 to 0.0)   |  |  |
| Swelling: Mild                   | 1.5 (1.3 to 1.8)              | 0.5 (0.3 to 0.7) |  |  |
| Swelling: Moderate               | 0.9 (0.8 to 1.2)              | 0.3 (0.2 to 0.5) |  |  |
| Swelling: Severe                 | 0.3 (0.2 to 0.5)              | 0.1 (0.0 to 0.2) |  |  |
| Swelling: Grade 4                | 0 (0.0 to 0.0)                | 0 (0.0 to 0.0)   |  |  |
| Pain at injection site: Mild     | 17.5 (16.7 to 18.3)           | 6.2 (5.7 to 6.8) |  |  |
| Pain at injection site: Moderate | 2.2 (1.9 to 2.5)              | 0.8 (0.6 to 1.0) |  |  |
| Pain at injection site: Severe   | 0.1 (0.0 to 0.2)              | 0.1 (0.1 to 0.2) |  |  |
| Pain at injection site: Grade 4  | 0 (0.0 to 0.0)                | 0.1 (0.0 to 0.1) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Subjects Reporting Local Reactions (LR) Within 7 Days After Dose 2

|                 |                                                                                                 |
|-----------------|-------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects Reporting Local Reactions (LR) Within 7 Days After Dose 2 <sup>[4]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------|

End point description:

Local reactions included redness, swelling and pain at injection site. These were recorded by subjects in an e-diary. Redness and swelling were measured and recorded in measuring device units. One measuring device unit= 0.5 cm and graded as mild: 2.5 to 5.0 cm, moderate: > 5.0 to 10.0 cm, severe: >10.0 cm. Grade 4 indicated necrosis or exfoliative dermatitis for redness and necrosis for swelling. Pain at injection site was graded as mild: did not interfere with daily activity, moderate: interfered with daily activity, severe: prevented daily activity. Grade 4 indicated emergency room visit or hospitalisation. Safety analysis population included all subjects who received at least 1 dose of the investigational product. Here, "Number of Subjects Analysed" signifies subjects evaluable for this end point.

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

End point timeframe:

Within 7 days after Dose 2 at Month 1

Notes:

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

Justification: Only descriptive data was planned for this endpoint.

| End point values                 | Clostridium difficile Vaccine | Placebo           |  |  |
|----------------------------------|-------------------------------|-------------------|--|--|
| Subject group type               | Reporting group               | Reporting group   |  |  |
| Number of subjects analysed      | 8041                          | 8039              |  |  |
| Units: Percentage of subjects    |                               |                   |  |  |
| number (confidence interval 95%) |                               |                   |  |  |
| Redness: Mild                    | 2.6 (2.2 to 2.9)              | 0.3 (0.2 to 0.5)  |  |  |
| Redness: Moderate                | 2.2 (1.9 to 2.6)              | 0.2 (0.1 to 0.3)  |  |  |
| Redness: Severe                  | 0.9 (0.7 to 1.2)              | 0.1 (0.0 to 0.1)  |  |  |
| Redness: Grade 4                 | 0 (0.0 to 0.0)                | 0 (0.0 to 0.0)    |  |  |
| Swelling: Mild                   | 3.2 (2.8 to 3.6)              | 0.3 (0.2 to 0.53) |  |  |
| Swelling: Moderate               | 3.0 (2.6 to 3.4)              | 0.2 (0.1 to 0.3)  |  |  |
| Swelling: Severe                 | 0.9 (0.7 to 1.1)              | 0.1 (0.0 to 0.2)  |  |  |
| Swelling: Grade 4                | 0 (0.0 to 0.0)                | 0 (0.0 to 0.0)    |  |  |
| Pain at injection site: Mild     | 23.0 (22.1 to 23.9)           | 4.3 (3.9 to 4.8)  |  |  |
| Pain at injection site: Moderate | 4.5 (4.0 to 4.9)              | 0.7 (0.5 to 0.9)  |  |  |
| Pain at injection site: Severe   | 0.2 (0.1 to 0.3)              | 0.1 (0.0 to 0.1)  |  |  |
| Pain at injection site: Grade 4  | 0 (0.0 to 0.0)                | 0 (0.0 to 0.0)    |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Subjects Reporting Local Reactions (LR) Within 7 Days After Dose 3

|                 |                                                                                                 |
|-----------------|-------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects Reporting Local Reactions (LR) Within 7 Days After Dose 3 <sup>[5]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------|

End point description:

Local reactions included redness, swelling and pain at injection site. These were recorded by subjects in an e-diary. Redness and swelling were measured and recorded in measuring device units. One measuring device unit= 0.5 cm and graded as mild: 2.5 to 5.0 cm, moderate: > 5.0 to 10.0 cm, severe: >10.0 cm. Grade 4 indicated necrosis or exfoliative dermatitis for redness and necrosis for swelling. Pain at injection site was graded as mild: did not interfere with daily activity, moderate: interfered with daily activity, severe: prevented daily activity. Grade 4 indicated emergency room visit or hospitalisation. Safety analysis population included all subjects who received at least 1 dose of the investigational product. Here, "Number of Subjects Analysed" signifies subjects evaluable for this end point.

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

End point timeframe:

Within 7 days after Dose 3 at Month 6

Notes:

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

Justification: Only descriptive data was planned for this endpoint.

| End point values                 | Clostridium difficile Vaccine | Placebo          |  |  |
|----------------------------------|-------------------------------|------------------|--|--|
| Subject group type               | Reporting group               | Reporting group  |  |  |
| Number of subjects analysed      | 7526                          | 7569             |  |  |
| Units: Percentage of subjects    |                               |                  |  |  |
| number (confidence interval 95%) |                               |                  |  |  |
| Redness: Mild                    | 2.6 (2.3 to 3.0)              | 0.4 (0.2 to 0.5) |  |  |
| Redness: Moderate                | 2.4 (2.1 to 2.8)              | 0.2 (0.1 to 0.4) |  |  |
| Redness: Severe                  | 0.7 (0.5 to 0.9)              | 0.1 (0.0 to 0.1) |  |  |
| Redness: Grade 4                 | 0 (0.0 to 0.0)                | 0 (0.0 to 0.0)   |  |  |
| Swelling: Mild                   | 3.5 (3.1 to 3.9)              | 0.3 (0.2 to 0.5) |  |  |
| Swelling: Moderate               | 3.3 (2.9 to 3.7)              | 0.2 (0.1 to 0.4) |  |  |
| Swelling: Severe                 | 0.8 (0.6 to 1.1)              | 0 (0.0 to 0.0)   |  |  |
| Swelling: Grade 4                | 0 (0.0 to 0.0)                | 0 (0.0 to 0.0)   |  |  |
| Pain at injection site: Mild     | 21.0 (20.1 to 21.9)           | 3.6 (3.2 to 4.1) |  |  |
| Pain at injection site: Moderate | 4.5 (4.0 to 5.0)              | 0.8 (0.6 to 1.0) |  |  |
| Pain at injection site: Severe   | 0.2 (0.1 to 0.4)              | 0.1 (0.0 to 0.1) |  |  |
| Pain at injection site: Grade 4  | 0 (0.0 to 0.0)                | 0 (0.0 to 0.0)   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Subjects Reporting Systemic Events (SE) Within 7 Days After Dose 1

|                 |                                                                                                 |
|-----------------|-------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects Reporting Systemic Events (SE) Within 7 Days After Dose 1 <sup>[6]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------|

# End point description:

Systemic events included fever, fatigue, headache, joint pain, muscle pain and vomiting. These were recorded by subjects in an e-diary. Fever was categorised as: mild: (38.0 to 38.4 degree Celsius [deg C]), moderate: (38.5 to 38.9 deg C), severe (39.0 to 40.0 deg C), potentially life threatening (> 40.0 deg C). Fatigue, headache, joint pain and muscle pain were graded as mild: did not interfere with activity, moderate: some interference with activity, severe: prevented daily activity, grade 4: emergency room visit or hospitalisation. Vomiting was graded as mild: 1 to 2 times in 24 hours, moderate: >2 times in 24 hours, severe: required intravenous hydration, grade 4: emergency room visit or hospitalisation for hypotensive shock. Safety analysis population included all subjects who received at least 1 dose of the investigational product. Here, "Number of Subjects Analysed" signifies subjects evaluable for this end point.

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

# End point timeframe:

Within 7 days after Dose 1 at Month 0

# Notes:

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

Justification: Only descriptive data was planned for this endpoint.

| End point values                       | Clostridium difficile Vaccine | Placebo            |  |  |
|----------------------------------------|-------------------------------|--------------------|--|--|
| Subject group type                     | Reporting group               | Reporting group    |  |  |
| Number of subjects analysed            | 8558                          | 8510               |  |  |
| Units: Percentage of subjects          |                               |                    |  |  |
| number (confidence interval 95%)       |                               |                    |  |  |
| Headache: Mild                         | 11.6 (10.9 to 12.3)           | 10.1 (9.4 to 10.7) |  |  |
| Headache: Moderate                     | 5.8 (5.3 to 6.3)              | 5.4 (4.9 to 5.9)   |  |  |
| Headache: Severe                       | 0.5 (0.4 to 0.7)              | 0.6 (0.5 to 0.8)   |  |  |
| Headache: Grade 4                      | 0 (0.0 to 0.0)                | 0 (0.0 to 0.0)     |  |  |
| Vomiting: Mild                         | 1.1 (0.8 to 1.3)              | 0.7 (0.5 to 0.9)   |  |  |
| Vomiting: Moderate                     | 0.3 (0.2 to 0.4)              | 0.2 (0.1 to 0.3)   |  |  |
| Vomiting: Severe                       | 0.1 (0.0 to 0.1)              | 0.1 (0.0 to 0.1)   |  |  |
| Vomiting: Grade 4                      | 0 (0.0 to 0.0)                | 0 (0.0 to 0.0)     |  |  |
| New or worsening muscle pain: Mild     | 5.2 (4.7 to 5.7)              | 3.9 (3.5 to 4.3)   |  |  |
| New or worsening muscle pain: Moderate | 5.7 (5.2 to 6.2)              | 5.6 (5.1 to 6.1)   |  |  |
| New or worsening muscle pain: Severe   | 0.6 (0.4 to 0.8)              | 0.6 (0.5 to 0.8)   |  |  |
| New or worsening muscle pain: Grade 4  | 0.1 (0.0 to 0.1)              | 0 (0.0 to 0.0)     |  |  |
| New or worsening joint pain: Mild      | 4.0 (3.6 to 4.5)              | 3.3 (2.9 to 3.7)   |  |  |
| New or worsening joint pain: Moderate  | 5.2 (4.7 to 5.7)              | 5.0 (4.5 to 5.5)   |  |  |
| New or worsening joint pain: Severe    | 0.5 (0.4 to 0.7)              | 0.5 (0.3 to 0.6)   |  |  |
| New or worsening joint pain: Grade 4   | 0 (0.0 to 0.0)                | 0 (0.0 to 0.0)     |  |  |
| Fever: 38.0-38.4 deg C                 | 0.5 (0.3 to 0.6)              | 0.4 (0.3 to 0.5)   |  |  |
| Fever: 38.5-38.9 deg C                 | 0.2 (0.1 to 0.3)              | 0.2 (0.1 to 0.3)   |  |  |
| Fever: 39.0-40.0 deg C                 | 0.2 (0.1 to 0.3)              | 0.1 (0.1 to 0.2)   |  |  |
| Fever: >40.0 deg C                     | 0.1 (0.0 to 0.2)              | 0.1 (0.0 to 0.2)   |  |  |
| Fatigue: Mild                          | 11.6 (10.9 to 12.3)           | 10.2 (9.6 to 10.9) |  |  |
| Fatigue: Moderate                      | 10.6 (10.0 to 11.3)           | 10.4 (9.7 to 11.0) |  |  |
| Fatigue: Severe                        | 1.1 (0.9 to 1.3)              | 1.2 (1.0 to 1.5)   |  |  |
| Fatigue: Grade 4                       | 0.1 (0.0 to 0.1)              | 0 (0.0 to 0.0)     |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Subjects Reporting Systemic Events (SE) Within 7 Days After Dose 2

|                 |                                                                                                 |
|-----------------|-------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects Reporting Systemic Events (SE) Within 7 Days After Dose 2 <sup>[7]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------|

End point description:

Systemic events included fever, fatigue, headache, joint pain, muscle pain and vomiting. These were recorded by subjects in an e-diary. Fever was categorised as: mild: (38.0 to 38.4 deg C), moderate: (38.5 to 38.9 deg C), severe (39.0 to 40.0 deg C), potentially life threatening (> 40.0 deg C). Fatigue, headache, joint pain and muscle pain were graded as mild: did not interfere with activity, moderate: some interference with activity, severe: prevented daily activity, grade 4: emergency room visit or hospitalisation. Vomiting was graded as mild: 1 to 2 times in 24 hours, moderate: >2 times in 24 hours, severe: required intravenous hydration, grade 4: emergency room visit or hospitalisation for hypotensive shock. Safety analysis population included all subjects who received at least 1 dose of the investigational product. Here, "Number of Subjects Analysed" signifies subjects evaluable for this end point and "number analysed" signifies subjects evaluable for specific rows.

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

End point timeframe:

Within 7 days after Dose 2 at Month 1

Notes:

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

Justification: Only descriptive data was planned for this endpoint.

| End point values                                   | Clostridium difficile Vaccine | Placebo          |  |  |
|----------------------------------------------------|-------------------------------|------------------|--|--|
| Subject group type                                 | Reporting group               | Reporting group  |  |  |
| Number of subjects analysed                        | 8041                          | 8039             |  |  |
| Units: Percentage of subjects                      |                               |                  |  |  |
| number (confidence interval 95%)                   |                               |                  |  |  |
| Fatigue: Mild(n=8041, 8039)                        | 10.2 (9.6 to 10.9)            | 7.8 (7.2 to 8.4) |  |  |
| Fatigue: Moderate(n=8041, 8039)                    | 9.4 (8.7 to 10.0)             | 9.0 (8.4 to 9.6) |  |  |
| Fatigue: Severe(n=8041, 8039)                      | 1.0 (0.8 to 1.2)              | 1.0 (0.8 to 1.2) |  |  |
| Fatigue: Grade 4(n=8041, 8039)                     | 0 (0.0 to 0.0)                | 0 (0.0 to 0.0)   |  |  |
| Headache: Mild(n=8041, 8039)                       | 10.1 (9.4 to 10.8)            | 8.3 (7.7 to 9.0) |  |  |
| Headache: Moderate(n=8041, 8039)                   | 5.1 (4.6 to 5.6)              | 5.5 (5.0 to 6.1) |  |  |
| Headache: Severe(n=8041, 8039)                     | 0.5 (0.4 to 0.7)              | 0.4 (0.3 to 0.6) |  |  |
| Headache: Grade 4(n=8041, 8039)                    | 0 (0.0 to 0.0)                | 0 (0.0 to 0.0)   |  |  |
| Vomiting: Mild(n=8041, 8039)                       | 0.8 (0.6 to 1.0)              | 0.7 (0.5 to 0.9) |  |  |
| Vomiting: Moderate(n=8041, 8039)                   | 0.2 (0.1 to 0.4)              | 0.2 (0.1 to 0.3) |  |  |
| Vomiting: Severe(n=8041, 8039)                     | 0 (0.0 to 0.0)                | 0 (0.0 to 0.0)   |  |  |
| Vomiting: Grade 4(n=8041, 8039)                    | 0 (0.0 to 0.0)                | 0 (0.0 to 0.0)   |  |  |
| New or worsening muscle pain:Mild(n=8041,8039)     | 4.8 (4.3 to 5.3)              | 3.2 (2.9 to 3.6) |  |  |
| New or worsening muscle pain:Moderate(n=8041,8039) | 5.1 (4.6 to 5.6)              | 4.2 (3.8 to 4.7) |  |  |
| New or worsening muscle pain:Severe(n=8041,8039)   | 0.5 (0.4 to 0.7)              | 0.6 (0.4 to 0.8) |  |  |
| New or worsening muscle pain:Grade 4(n=8041,8039)  | 0 (0.0 to 0.0)                | 0 (0.0 to 0.0)   |  |  |
| New or worsening joint pain: Mild(n=8041, 8039)    | 3.8 (3.4 to 4.2)              | 2.9 (2.6 to 3.3) |  |  |

|                                                     |                  |                  |  |  |
|-----------------------------------------------------|------------------|------------------|--|--|
| New or worsening joint pain: Moderate (n=8041,8039) | 4.6 (4.1 to 5.0) | 3.9 (3.5 to 4.4) |  |  |
| New or worsening joint pain: Severe (n=8041,8039)   | 0.4 (0.3 to 0.6) | 0.5 (0.3 to 0.6) |  |  |
| New or worsening joint pain: Grade 4 (n=8041,8039)  | 0 (0.0 to 0.0)   | 0 (0.0 to 0.0)   |  |  |
| Fever: 38.0-38.4 deg C (n=8041,8038)                | 0.4 (0.3 to 0.6) | 0.4 (0.3 to 0.6) |  |  |
| Fever: 38.5-38.9 deg C (n=8041,8038)                | 0.2 (0.1 to 0.3) | 0.1 (0.0 to 0.2) |  |  |
| Fever: 39.0-40.0 deg C (n=8041,8038)                | 0.1 (0.0 to 0.2) | 0.2 (0.1 to 0.3) |  |  |
| Fever: >40.0 deg C (n=8041, 8038)                   | 0.1 (0.0 to 0.1) | 0.1 (0.0 to 0.1) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Percentage of Subjects Reporting Systemic Events (SE) Within 7 Days After Dose 3

|                 |                                                                                                 |
|-----------------|-------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects Reporting Systemic Events (SE) Within 7 Days After Dose 3 <sup>[8]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------|

End point description:

Systemic events included fever, fatigue, headache, joint pain, muscle pain and vomiting. These were recorded by subjects in an e-diary. Fever was categorised as: mild: (38.0 to 38.4 deg C), moderate: (38.5 to 38.9 deg C), severe (39.0 to 40.0 deg C), potentially life threatening (> 40.0 deg C). Fatigue, headache, joint pain and muscle pain were graded as mild: did not interfere with activity, moderate: some interference with activity, severe: prevented daily activity, grade 4: emergency room visit or hospitalisation. Vomiting was graded as mild: 1 to 2 times in 24 hours, moderate: >2 times in 24 hours, severe: required intravenous hydration, grade 4: emergency room visit or hospitalisation for hypotensive shock. Safety analysis population included all subjects who received at least 1 dose of the investigational product. Here, "Number of Subjects Analysed" signifies subjects evaluable for this end point and "number analysed" signifies subjects evaluable for specific rows.

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

End point timeframe:

Within 7 days after Dose 3 at Month 6

Notes:

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

Justification: Only descriptive data was planned for this endpoint.

| End point values                 | Clostridium difficile Vaccine | Placebo          |  |  |
|----------------------------------|-------------------------------|------------------|--|--|
| Subject group type               | Reporting group               | Reporting group  |  |  |
| Number of subjects analysed      | 7526                          | 7569             |  |  |
| Units: Percentage of subjects    |                               |                  |  |  |
| number (confidence interval 95%) |                               |                  |  |  |
| Fatigue: Mild (n=7526,7569)      | 9.2 (8.6 to 9.9)              | 7.0 (6.4 to 7.6) |  |  |
| Fatigue: Moderate (n=7526,7569)  | 9.4 (8.7 to 10.0)             | 8.0 (7.4 to 8.6) |  |  |
| Fatigue: Severe (n=7526,7569)    | 0.8 (0.6 to 1.0)              | 0.8 (0.6 to 1.0) |  |  |
| Fatigue: Grade 4 (n=7526,7569)   | 0 (0.0 to 0.0)                | 0 (0.0 to 0.0)   |  |  |
| Headache: Mild (n=7526,7569)     | 8.4 (7.8 to 9.0)              | 7.9 (7.3 to 8.5) |  |  |
| Headache: Moderate (n=7526,7569) | 5.7 (5.1 to 6.2)              | 4.7 (4.2 to 5.2) |  |  |
| Headache: Severe (n=7526,7569)   | 0.3 (0.2 to 0.5)              | 0.5 (0.3 to 0.6) |  |  |
| Headache: Grade 4 (n=7526,7569)  | 0 (0.0 to 0.0)                | 0 (0.0 to 0.0)   |  |  |
| Vomiting: Mild (n=7526,7569)     | 0.6 (0.5 to 0.8)              | 0.5 (0.4 to 0.7) |  |  |

|                                                    |                  |                  |  |  |
|----------------------------------------------------|------------------|------------------|--|--|
| Vomiting: Moderate(n=7526,7569)                    | 0.1 (0.0 to 0.2) | 0.2 (0.1 to 0.3) |  |  |
| Vomiting: Severe(n=7526,7569)                      | 0 (0.0 to 0.0)   | 0 (0.0 to 0.0)   |  |  |
| Vomiting: Grade 4(n=7526,7569)                     | 0 (0.0 to 0.0)   | 0 (0.0 to 0.0)   |  |  |
| New or worsening muscle pain:Mild(n=7526,7569)     | 4.0 (3.5 to 4.4) | 2.5 (2.2 to 2.9) |  |  |
| New or worsening muscle pain:Moderate(n=7526,7569) | 4.8 (4.3 to 5.3) | 4.1 (3.6 to 4.6) |  |  |
| New or worsening muscle pain:Severe(n=7526,7569)   | 0.5 (0.3 to 0.7) | 0.5 (0.3 to 0.7) |  |  |
| New or worsening muscle pain:Grade 4(n=7526,7569)  | 0 (0.0 to 0.0)   | 0 (0.0 to 0.0)   |  |  |
| New or worsening joint pain:Mild(n=7526,7569)      | 3.0 (2.6 to 3.4) | 2.5 (2.2 to 2.9) |  |  |
| New or worsening joint pain:Moderate(n=7526,7569)  | 4.4 (3.9 to 4.8) | 3.6 (3.2 to 4.0) |  |  |
| New or worsening joint pain:Severe(n=7526,7569)    | 0.4 (0.3 to 0.6) | 0.4 (0.3 to 0.5) |  |  |
| New or worsening joint pain:Grade 4(n=7526,7569)   | 0.1 (0.0 to 0.1) | 0 (0.0 to 0.0)   |  |  |
| Fever: 38.0-38.4 deg C(n=7525,7569)                | 0.4 (0.3 to 0.6) | 0.2 (0.1 to 0.4) |  |  |
| Fever: 38.5-38.9 deg C(n=7525,7569)                | 0.1 (0.1 to 0.2) | 0.1 (0.0 to 0.2) |  |  |
| Fever: 39.0-40.0 deg C(n=7525,7569)                | 0.1 (0.1 to 0.2) | 0.1 (0.0 to 0.2) |  |  |
| Fever: >40.0 deg C(n=7525,7569)                    | 0.1 (0.0 to 0.1) | 0.1 (0.1 to 0.2) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Subjects Reporting Adverse Events (AEs)

|                 |                                                                  |
|-----------------|------------------------------------------------------------------|
| End point title | Number of Subjects Reporting Adverse Events (AEs) <sup>[9]</sup> |
|-----------------|------------------------------------------------------------------|

End point description:

An AE was defined as any untoward medical occurrence in a subjects who received investigational product without regard to possibility of causal relationship. AEs included both serious and all non-serious adverse events. An SAE was defined as any untoward medical occurrence at any dose that resulted in any of the following outcomes: death; life-threatening (immediate risk of death); required inpatient hospitalisation or prolongation of existing hospitalisation; persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions); congenital anomaly/birth defect; or that was considered as an important medical event. AEs included both SAEs and all Non-SAEs (except local and systemic events). Safety analysis population included all subjects who received at least 1 dose of the investigational product.

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

End point timeframe:

From Day 1 of Dose 1 to 1 Month after Dose 3 (7 Months)

Notes:

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

Justification: Only descriptive data was planned for this endpoint.

| End point values            | Clostridium difficile Vaccine | Placebo         |  |  |
|-----------------------------|-------------------------------|-----------------|--|--|
| Subject group type          | Reporting group               | Reporting group |  |  |
| Number of subjects analysed | 8722                          | 8718            |  |  |
| Units: Subjects             |                               |                 |  |  |
| Any AEs                     | 4161                          | 4050            |  |  |
| Non-Serious AEs             | 3913                          | 3791            |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects Reporting Serious Adverse Events (SAEs)

|                 |                                                     |
|-----------------|-----------------------------------------------------|
| End point title | Number of Subjects Reporting Serious Adverse Events |
|-----------------|-----------------------------------------------------|

End point description:

An SAE was defined as any untoward medical occurrence at any dose that resulted in any of the following outcomes: death; life-threatening (immediate risk of death); required inpatient hospitalisation or prolongation of existing hospitalisation; persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions); congenital anomaly/birth defect; or that was considered as an important medical event. Safety analysis population included all participants who received at least 1 dose of the investigational product.

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

End point timeframe:

From Day 1 of Dose 1 up to 6 months after Dose 3 (up to Month 12)

Notes:

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

Justification: Only descriptive data was planned for this endpoint.

| End point values            | Clostridium difficile Vaccine | Placebo         |  |  |
|-----------------------------|-------------------------------|-----------------|--|--|
| Subject group type          | Reporting group               | Reporting group |  |  |
| Number of subjects analysed | 8722                          | 8718            |  |  |
| Units: Subjects             | 719                           | 722             |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of all Episodes of CDI (Definition 1 and 2) After Dose 3

|                 |                                                                 |
|-----------------|-----------------------------------------------------------------|
| End point title | Number of all Episodes of CDI (Definition 1 and 2) After Dose 3 |
|-----------------|-----------------------------------------------------------------|

End point description:

CDI definition 1 for primary episode of CDI(no previous CDI onset in prior 8 weeks),CDI definition 2 for recurrent episode(episode occurred 8 weeks or less after onset of previous episode[provided symptoms of previous episode resolved])were both defined as either a)presence of diarrhea,(passage of 3 or more unformed stools[Bristol stool chart types 5-7])in 24 or fewer consecutive hours,stool sample positive for toxin B gene(by PCR),positive for toxin A and/or B,measured in central laboratory;or b)Pseudomembranous colitis diagnosed at colonoscopy, surgery, histopathologically; corresponding stool sample positive for toxin B gene(via PCR)measured in central laboratory.Per Protocol-3 analysis population included all randomised subjects who received dose 1, dose 2, and dose 3 of investigational product to which they were randomized had no major protocol violations up to and including 14 days after dose 3. Here,"Number of Subjects Analysed" signifies subjects evaluable for this end point.

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

End point timeframe:

From 14 days after Dose 3 to the end of the surveillance period (mean follow-up after dose 3 was 34.2

| <b>End point values</b>     | Clostridium difficile Vaccine | Placebo         |  |  |
|-----------------------------|-------------------------------|-----------------|--|--|
| Subject group type          | Reporting group               | Reporting group |  |  |
| Number of subjects analysed | 7707                          | 7805            |  |  |
| Units: Episodes             | 28                            | 32              |  |  |

## Statistical analyses

| <b>Statistical analysis title</b>                                                                                        | Clostridium difficile vaccine versus Placebo |
|--------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| Statistical analysis description:<br>VE = 100*(1 - Hazard Ratio). 98.2% CI was estimated using Proportional Means Model. |                                              |
| Comparison groups                                                                                                        | Clostridium difficile Vaccine v Placebo      |
| Number of subjects included in analysis                                                                                  | 15512                                        |
| Analysis specification                                                                                                   | Pre-specified                                |
| Analysis type                                                                                                            | superiority                                  |
| Parameter estimate                                                                                                       | Vaccine efficacy                             |
| Point estimate                                                                                                           | 11.1                                         |
| Confidence interval                                                                                                      |                                              |
| level                                                                                                                    | Other: 98.2 %                                |
| sides                                                                                                                    | 2-sided                                      |
| lower limit                                                                                                              | -110.7                                       |
| upper limit                                                                                                              | 62.5                                         |

## Secondary: Time to Resolution for Subjects With First Primary Episodes of CDI (Definition 1) After Dose 3

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Time to Resolution for Subjects With First Primary Episodes of CDI (Definition 1) After Dose 3 |
| End point description:<br>Resolution of event was last day on which event was recorded in e-diary or date the event ends if it was unresolved during subject diary-recording period(end date collected on case report form[CRF]).CDI definition 1 for primary episode of CDI(no previous CDI onset in prior 8 weeks) defined as either a)presence of diarrhea(passage of 3 or more unformed stools[Bristol stool chart types 5-7]) in 24 or fewer consecutive hours, and stool sample positive for toxin B gene(by polymerase chain reaction [PCR]) and positive for toxin A and/or toxin B, as measured in central laboratory; or b)Pseudomembranous colitis diagnosed at colonoscopy, at surgery, or histopathologically; and corresponding stool sample positive for toxin B gene (via PCR) as measured in central laboratory. End of surveillance period was defined as accumulation of at least 40 CDI cases. Per Protocol-3 analysis population was analysed. Here,"Number of Subjects Analysed" signifies subjects evaluable for this end |                                                                                                |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Secondary                                                                                      |
| End point timeframe:<br>From 14 days after Dose 3 to the end of the surveillance period (mean follow-up after dose 3 was 34.2 months)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                |

| End point values              | Clostridium difficile Vaccine | Placebo         |  |  |
|-------------------------------|-------------------------------|-----------------|--|--|
| Subject group type            | Reporting group               | Reporting group |  |  |
| Number of subjects analysed   | 17                            | 24              |  |  |
| Units: Days                   |                               |                 |  |  |
| median (full range (min-max)) | 1.0 (1 to 18)                 | 4.0 (1 to 183)  |  |  |

## Statistical analyses

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b>       | Clostridium difficile vaccine versus Placebo |
| Comparison groups                       | Clostridium difficile Vaccine v Placebo      |
| Number of subjects included in analysis | 41                                           |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | superiority                                  |
| P-value                                 | = 0.0172                                     |
| Method                                  | Wilcoxon Rank Sum Test (2-sided)             |

## Secondary: Proportion of Subjects who Required Medical Attention During First Primary Episode of CDI (Definition 1) After Dose 3

|                 |                                                                                                                       |
|-----------------|-----------------------------------------------------------------------------------------------------------------------|
| End point title | Proportion of Subjects who Required Medical Attention During First Primary Episode of CDI (Definition 1) After Dose 3 |
|-----------------|-----------------------------------------------------------------------------------------------------------------------|

End point description:

CDI definition 1 for a primary episode of CDI (no previous CDI onset in prior 8 weeks) defined as either a) presence of diarrhea, defined as passage of 3 or more unformed stools (Bristol stool chart types 5-7) in 24 or fewer consecutive hours, and stool sample that was positive for toxin B gene (by PCR) and positive for toxin A and/or toxin B, as measured in central laboratory; or b) Pseudomembranous colitis diagnosed at colonoscopy, at surgery, or histopathologically; and corresponding stool sample that was positive for toxin B gene (via PCR) as measured in central laboratory. End of surveillance period was defined as accumulation of at least 40 CDI cases. Per Protocol-3 analysis population included all randomised subjects who received dose 1, dose 2, and dose 3 of the investigational product to which they were randomised and had no major protocol violations up to and including 14 days after dose 3. Here, "Overall Number of Subjects Analyzed" signifies subjects evaluable for this end point.

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

End point timeframe:

From 14 days after Dose 3 to the end of the surveillance period (mean follow-up after dose 3 was 34.2 months)

| End point values              | Clostridium difficile Vaccine | Placebo         |  |  |
|-------------------------------|-------------------------------|-----------------|--|--|
| Subject group type            | Reporting group               | Reporting group |  |  |
| Number of subjects analysed   | 17                            | 25              |  |  |
| Units: Proportion of subjects |                               |                 |  |  |
| number (not applicable)       | 0                             | 0.440           |  |  |

## Statistical analyses

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b>       | Clostridium difficile vaccine versus Placebo |
| Comparison groups                       | Clostridium difficile Vaccine v Placebo      |
| Number of subjects included in analysis | 42                                           |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | superiority                                  |
| Parameter estimate                      | Ratio of proportions                         |
| Point estimate                          | 0                                            |
| Confidence interval                     |                                              |
| level                                   | Other: 98.2 %                                |
| sides                                   | 2-sided                                      |
| lower limit                             | 0                                            |
| upper limit                             | 0.81                                         |

### Secondary: Number of Subjects With Recurrent Episodes of CDI (Definition 2) After Dose 3

|                 |                                                                               |
|-----------------|-------------------------------------------------------------------------------|
| End point title | Number of Subjects With Recurrent Episodes of CDI (Definition 2) After Dose 3 |
|-----------------|-------------------------------------------------------------------------------|

End point description:

CDI definition 2 for recurrent episode(an episode of CDI that occurred 8 weeks or less after onset of a previous CDI episode[provided symptoms of previous episode had resolved]),defined as either a)presence of diarrhea(passage of 3 or more unformed stools[Bristol stool chart types 5-7])in 24 or fewer consecutive hours; stool sample that was positive for toxin B gene (by PCR) and positive for toxin A and/or toxin B, as measured in central laboratory; or b) Pseudomembranous colitis diagnosed at colonoscopy, at surgery, or histopathologically; and corresponding stool sample that was positive for toxin B gene (by PCR) as measured in central laboratory. Per Protocol-3 analysis population included all randomised subjects who received dose 1, dose 2, and dose 3 of the investigational product to which they were randomised and had no major protocol violations up to and including 14 days after dose 3. Here, "Overall Number of Subjects Analyzed" signifies subjects evaluable for this end point.

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

End point timeframe:

From 14 days after Dose 3 to the end of the surveillance period (mean follow-up after dose 3 was 34.2 months)

| <b>End point values</b>     | Clostridium difficile Vaccine | Placebo         |  |  |
|-----------------------------|-------------------------------|-----------------|--|--|
| Subject group type          | Reporting group               | Reporting group |  |  |
| Number of subjects analysed | 7707                          | 7805            |  |  |
| Units: Subjects             | 5                             | 3               |  |  |

### Statistical analyses

|                                   |                                              |
|-----------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b> | Clostridium difficile vaccine versus Placebo |
|-----------------------------------|----------------------------------------------|

Statistical analysis description:

Vaccine efficacy(VE)=100\*(1-infection rate ratio[IRR]),IRR=calculated ratio of recurrent CDI incidence between Clostridium difficile vaccine group and placebo group. 98.2% CI was estimated using Clopper-Pearson-Method.

|                   |                                         |
|-------------------|-----------------------------------------|
| Comparison groups | Clostridium difficile Vaccine v Placebo |
|-------------------|-----------------------------------------|

|                                         |                  |
|-----------------------------------------|------------------|
| Number of subjects included in analysis | 15512            |
| Analysis specification                  | Pre-specified    |
| Analysis type                           | superiority      |
| Parameter estimate                      | Vaccine efficacy |
| Point estimate                          | -69.3            |
| Confidence interval                     |                  |
| level                                   | Other: 98.2 %    |
| sides                                   | 2-sided          |
| lower limit                             | -1533.1          |
| upper limit                             | 75.6             |

## Secondary: Number of all Episodes of CDI (Definition 1 and 2) After Dose 2

|                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title        | Number of all Episodes of CDI (Definition 1 and 2) After Dose 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| End point description: | <p>CDI definition 1 for primary episode of CDI(no previous CDI onset in prior 8 weeks),CDI definition 2 for recurrent episode(episode occurred 8 weeks or less after onset of previous episode[provided symptoms of previous episode resolved])were both defined as either a)presence of diarrhea,(passage of 3 or more unformed stools[Bristol stool chart types 5-7])in 24 or fewer consecutive hours,stool sample positive for toxin B gene(by PCR),positive for toxin A and/or B,measured in central laboratory;or</p> <p>b)Pseudomembranous colitis diagnosed at colonoscopy, surgery, histopathologically; corresponding stool sample positive for toxin B gene(via PCR)measured in central laboratory. Per Protocol-2 analysis population included all randomised subjects who received dose 1 and dose 2 of the investigational product to which they were randomized and had no major protocol violations up to and including 14 days after dose 2. Here,"Number of Subjects Analysed" signifies subjects evaluable for this end point.</p> |
| End point type         | Secondary                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| End point timeframe:   | <p>From 14 days after Dose 2 to the end of the surveillance period (mean follow-up after dose 2 was 36 months)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

| End point values            | Clostridium difficile Vaccine | Placebo         |  |  |
|-----------------------------|-------------------------------|-----------------|--|--|
| Subject group type          | Reporting group               | Reporting group |  |  |
| Number of subjects analysed | 8139                          | 8184            |  |  |
| Units: Episodes             | 37                            | 44              |  |  |

## Statistical analyses

|                                   |                                                                                           |
|-----------------------------------|-------------------------------------------------------------------------------------------|
| Statistical analysis title        | Clostridium difficile vaccine versus Placebo                                              |
| Statistical analysis description: | <p>VE = 100*(1 - Hazard Ratio). 98.2% CI was estimated using Proportional Means Model</p> |
| Comparison groups                 | Clostridium difficile Vaccine v Placebo                                                   |

|                                         |                  |
|-----------------------------------------|------------------|
| Number of subjects included in analysis | 16323            |
| Analysis specification                  | Pre-specified    |
| Analysis type                           | superiority      |
| Parameter estimate                      | Vaccine efficacy |
| Point estimate                          | 14.9             |
| Confidence interval                     |                  |
| level                                   | Other: 98.2 %    |
| sides                                   | 2-sided          |
| lower limit                             | -74.6            |
| upper limit                             | 58.5             |

## Secondary: Number of Subjects With Recurrent Episodes of CDI (Definition 2) After Dose 2

|                 |                                                                               |
|-----------------|-------------------------------------------------------------------------------|
| End point title | Number of Subjects With Recurrent Episodes of CDI (Definition 2) After Dose 2 |
|-----------------|-------------------------------------------------------------------------------|

End point description:

CDI definition 2 for recurrent episode(an episode of CDI that occurred 8 weeks or less after onset of a previous CDI episode[provided symptoms of previous episode had resolved]),defined as either a)presence of diarrhea(passage of 3 or more unformed stools[Bristol stool chart types 5-7])in 24 or fewer consecutive hours; stool sample that was positive for toxin B gene (by PCR) and positive for toxin A and/or toxin B, as measured in central laboratory; or b) Pseudomembranous colitis diagnosed at colonoscopy, at surgery, or histopathologically; and corresponding stool sample that was positive for toxin B gene (by PCR) as measured in central laboratory. Per Protocol-2 analysis population included all randomised subjects who received dose 1 and dose 2 of the investigational product to which they were randomized and had no major protocol violations up to and including 14 days after dose 2. Here,"Number of Subjects Analysed" signifies subjects evaluable for this end point.

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

End point timeframe:

From 14 days after Dose 2 to the end of the surveillance period (mean follow-up after dose 2 was 36 months)

| End point values            | Clostridium difficile Vaccine | Placebo         |  |  |
|-----------------------------|-------------------------------|-----------------|--|--|
| Subject group type          | Reporting group               | Reporting group |  |  |
| Number of subjects analysed | 8139                          | 8184            |  |  |
| Units: Subjects             | 6                             | 3               |  |  |

## Statistical analyses

|                            |                                              |
|----------------------------|----------------------------------------------|
| Statistical analysis title | Clostridium difficile vaccine versus Placebo |
|----------------------------|----------------------------------------------|

Statistical analysis description:

VE = 100\*(1 - IRR), where IRR= the calculated ratio of recurrent CDI incidence between the Clostridium difficile vaccine group and the placebo group. 98.2% CI was estimated using Clopper-Pearson-Method.

|                   |                                         |
|-------------------|-----------------------------------------|
| Comparison groups | Clostridium difficile Vaccine v Placebo |
|-------------------|-----------------------------------------|

|                                         |                  |
|-----------------------------------------|------------------|
| Number of subjects included in analysis | 16323            |
| Analysis specification                  | Pre-specified    |
| Analysis type                           | superiority      |
| Parameter estimate                      | Vaccine efficacy |
| Point estimate                          | -102.4           |
| Confidence interval                     |                  |
| level                                   | Other: 98.2 %    |
| sides                                   | 2-sided          |
| lower limit                             | -1770.1          |
| upper limit                             | 67.2             |

## Secondary: Number of First Primary Episode of CDI (Definition 1) After Dose 2 and Before Dose 3

|                 |                                                                                      |
|-----------------|--------------------------------------------------------------------------------------|
| End point title | Number of First Primary Episode of CDI (Definition 1) After Dose 2 and Before Dose 3 |
|-----------------|--------------------------------------------------------------------------------------|

### End point description:

CDI definition 1 for a primary episode of CDI (no previous CDI onset in the prior 8 weeks) was defined as either a) presence of diarrhea, defined as passage of 3 or more unformed stools (Bristol stool chart types 5-7) in 24 or fewer consecutive hours, and stool sample that was positive for the toxin B gene (by PCR) and positive for toxin A and/or toxin B, as measured in the central laboratory; or b) Pseudomembranous colitis diagnosed at colonoscopy, at surgery, or histopathologically; and corresponding stool sample that was positive for the toxin B gene (via PCR) as measured in the central laboratory. Per Protocol-2 analysis population included all randomised subjects who received dose 1 and dose 2 of the investigational product to which they were randomized and had no major protocol violations up to and including 14 days after dose 2. Here, "Number of Subjects Analysed" signifies subjects evaluable for this end point.

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

### End point timeframe:

From 14 days after Dose 2 to Dose 3 or the day the third vaccination was expected (168 days after Dose 2) for subjects who received only 2 doses

| End point values            | Clostridium difficile Vaccine | Placebo         |  |  |
|-----------------------------|-------------------------------|-----------------|--|--|
| Subject group type          | Reporting group               | Reporting group |  |  |
| Number of subjects analysed | 8139                          | 8184            |  |  |
| Units: Episodes             | 7                             | 8               |  |  |

## Statistical analyses

|                            |                                              |
|----------------------------|----------------------------------------------|
| Statistical analysis title | Clostridium difficile vaccine versus Placebo |
|----------------------------|----------------------------------------------|

### Statistical analysis description:

Vaccine efficacy(VE)=100\*(1-infection rate ratio[IRR]),IRR=calculated ratio of first primary CDI incidence between Clostridium difficile vaccine group and placebo group. 98.2% CI was estimated using Clopper-Pearson-Method.

|                   |                                         |
|-------------------|-----------------------------------------|
| Comparison groups | Clostridium difficile Vaccine v Placebo |
|-------------------|-----------------------------------------|

|                                         |                  |
|-----------------------------------------|------------------|
| Number of subjects included in analysis | 16323            |
| Analysis specification                  | Pre-specified    |
| Analysis type                           | superiority      |
| Parameter estimate                      | Vaccine efficacy |
| Point estimate                          | 12               |
| Confidence interval                     |                  |
| level                                   | Other: 98.2 %    |
| sides                                   | 2-sided          |
| lower limit                             | -246.7           |
| upper limit                             | 78.5             |

## Secondary: Number of Subjects With Recurrent Episode of CDI (Definition 2) After Dose 2 and Before Dose 3

|                 |                                                                                                |
|-----------------|------------------------------------------------------------------------------------------------|
| End point title | Number of Subjects With Recurrent Episode of CDI (Definition 2) After Dose 2 and Before Dose 3 |
|-----------------|------------------------------------------------------------------------------------------------|

End point description:

CDI definition 2 for recurrent episode(an episode of CDI that occurred 8 weeks or less after onset of a previous CDI episode[provided symptoms of previous episode had resolved]),defined as either a)presence of diarrhea(passage of 3 or more unformed stools[Bristol stool chart types 5-7])in 24 or fewer consecutive hours; stool sample that was positive for toxin B gene (by PCR) and positive for toxin A and/or toxin B, as measured in central laboratory; or b) Pseudomembranous colitis diagnosed at colonoscopy, at surgery, or histopathologically; and corresponding stool sample that was positive for toxin B gene (by PCR) as measured in central laboratory. Per Protocol-2 analysis population included all randomised subjects who received dose 1 and dose 2 of the investigational product to which they were randomized and had no major protocol violations up to and including 14 days after dose 2. Here,"Number of Subjects Analysed" signifies subjects evaluable for this end point.

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

End point timeframe:

From 14 days after Dose 2 to Dose 3 or the day the third vaccination was expected (168 days after Dose 2) for subjects who received only 2 doses

| End point values            | Clostridium difficile Vaccine | Placebo         |  |  |
|-----------------------------|-------------------------------|-----------------|--|--|
| Subject group type          | Reporting group               | Reporting group |  |  |
| Number of subjects analysed | 8139                          | 8184            |  |  |
| Units: Subjects             | 1                             | 0               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

LR and SE(added in other AEs):within 7days after each dose(systematic assessment);SAEs:Day1upto 6months after last dose(up to12months);other AEs:Day1upto1month after last dose(upto7months);All-Cause mortality:Day1 upto 6months after last dose(upto12months)

Adverse event reporting additional description:

Same event may appear as both an AE and SAE. However,what is presented are distinct events.An event may be categorised as serious in one subject and non-serious in another,or a subject may have experienced both a serious and non-serious event.Safety analysis population included all subjects who received at least 1 dose of investigational product.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 24.1   |

### Reporting groups

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Clostridium difficile Vaccine |
|-----------------------|-------------------------------|

Reporting group description:

Participants were randomized to receive a single dose of Clostridium difficile vaccine 200 microgram total toxoid per dose intramuscularly at Months 0, 1 and 6.

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Participants were randomized to receive a single dose of placebo (normal saline solution of 0.9 percent [%] sodium chloride) intramuscularly at Months 0, 1 and 6.

| Serious adverse events                                              | Clostridium difficile Vaccine | Placebo            |  |
|---------------------------------------------------------------------|-------------------------------|--------------------|--|
| Total subjects affected by serious adverse events                   |                               |                    |  |
| subjects affected / exposed                                         | 719 / 8722 (8.24%)            | 722 / 8718 (8.28%) |  |
| number of deaths (all causes)                                       | 369                           | 362                |  |
| number of deaths resulting from adverse events                      | 0                             | 0                  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                               |                    |  |
| Adenocarcinoma gastric                                              |                               |                    |  |
| subjects affected / exposed                                         | 2 / 8722 (0.02%)              | 0 / 8718 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 2                         | 0 / 0              |  |
| deaths causally related to treatment / all                          | 0 / 1                         | 0 / 0              |  |
| Adenocarcinoma of colon                                             |                               |                    |  |
| subjects affected / exposed                                         | 2 / 8722 (0.02%)              | 0 / 8718 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 2                         | 0 / 0              |  |
| deaths causally related to treatment / all                          | 0 / 1                         | 0 / 0              |  |
| B-cell lymphoma                                                     |                               |                    |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| B-cell small lymphocytic lymphoma stage III     |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Basal cell carcinoma                            |                  |                  |  |
| subjects affected / exposed                     | 3 / 8722 (0.03%) | 3 / 8718 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Benign breast neoplasm                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Benign neoplasm of bladder                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bladder cancer recurrent                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bladder cancer                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 4 / 8718 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Breast cancer                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 3 / 8718 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholangiocarcinoma                              |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colon cancer metastatic                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colon cancer                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Endometrial cancer recurrent                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatic cancer                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatocellular carcinoma                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Intestinal metastasis                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Intraductal proliferative breast lesion         |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Invasive ductal breast carcinoma                |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Laryngeal cancer                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lung adenocarcinoma                             |                  |                  |  |
| subjects affected / exposed                     | 4 / 8722 (0.05%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Lung carcinoma cell type unspecified stage IV   |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| Lung neoplasm malignant                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lung neoplasm                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Malignant melanoma                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastases to abdominal cavity                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastases to liver                             |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Metastases to lung                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Metastases to lymph nodes                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Metastases to peritoneum                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Myxofibrosarcoma                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neuroendocrine carcinoma                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Non-Hodgkin's lymphoma                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Non-small cell lung cancer metastatic           |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Non-small cell lung cancer                      |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal cancer metastatic                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Oesophageal squamous cell carcinoma             |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ovarian cancer metastatic                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ovarian cancer                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatic carcinoma metastatic                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatic carcinoma                            |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Papillary thyroid cancer                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peritoneal neoplasm                             |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (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                     | 0 / 8722 (0.00%) | 4 / 8718 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Prostate cancer metastatic                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Prostate cancer stage I                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Prostate cancer                                 |                  |                  |  |
| subjects affected / exposed                     | 7 / 8722 (0.08%) | 7 / 8718 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Rectal cancer                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (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                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal cell carcinoma                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin cancer                                     |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 0 / 8718 (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 lung                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Squamous cell carcinoma of skin                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Squamous cell carcinoma                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 4 / 8718 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Transitional cell carcinoma                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ureteric cancer                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Uterine leiomyoma                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vascular disorders                              |                  |                  |  |
| Accelerated hypertension                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Aortic aneurysm                                 |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 3 / 8722 (0.03%) | 3 / 8718 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Aortic stenosis                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Arterial occlusive disease                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Deep vein thrombosis                            |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 7 / 8718 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Diabetic vascular disorder                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Extremity necrosis                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haematoma                                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemodynamic instability                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemorrhage                                     |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypertension                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Hypertensive crisis                             |                  |                  |  |
| subjects affected / exposed                     | 3 / 8722 (0.03%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypertensive emergency                          |                  |                  |  |
| subjects affected / exposed                     | 5 / 8722 (0.06%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypertensive urgency                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (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 / 8722 (0.06%) | 8 / 8718 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Iliac artery occlusion                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intermittent claudication                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Orthostatic hypotension                         |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 4 / 8718 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral arterial occlusive disease           |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral artery occlusion                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral ischaemia                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral vascular disorder                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subclavian steal syndrome                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subclavian vein thrombosis                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vein disorder                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Venous thrombosis                               |                  |                  |  |

|                                                      |                   |                   |  |
|------------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                          | 0 / 8722 (0.00%)  | 1 / 8718 (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 |                   |                   |  |
| Adverse drug reaction                                |                   |                   |  |
| subjects affected / exposed                          | 0 / 8722 (0.00%)  | 2 / 8718 (0.02%)  |  |
| occurrences causally related to treatment / all      | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0             |  |
| Asthenia                                             |                   |                   |  |
| subjects affected / exposed                          | 6 / 8722 (0.07%)  | 3 / 8718 (0.03%)  |  |
| occurrences causally related to treatment / all      | 0 / 6             | 0 / 3             |  |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0             |  |
| Chest discomfort                                     |                   |                   |  |
| subjects affected / exposed                          | 1 / 8722 (0.01%)  | 2 / 8718 (0.02%)  |  |
| occurrences causally related to treatment / all      | 0 / 1             | 0 / 2             |  |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0             |  |
| Chest pain                                           |                   |                   |  |
| subjects affected / exposed                          | 25 / 8722 (0.29%) | 32 / 8718 (0.37%) |  |
| occurrences causally related to treatment / all      | 0 / 27            | 0 / 32            |  |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0             |  |
| Complication of device insertion                     |                   |                   |  |
| subjects affected / exposed                          | 0 / 8722 (0.00%)  | 1 / 8718 (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                          | 1 / 8722 (0.01%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0             |  |
| Drug interaction                                     |                   |                   |  |
| subjects affected / exposed                          | 1 / 8722 (0.01%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0             |  |
| Drug withdrawal syndrome                             |                   |                   |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypothermia                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Impaired healing                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 3 / 8718 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Injection site haematoma                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Injection site pain                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Injection site swelling                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Non-cardiac chest pain                          |                  |                  |  |
| subjects affected / exposed                     | 4 / 8722 (0.05%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oedema peripheral                               |                  |                  |  |
| subjects affected / exposed                     | 3 / 8722 (0.03%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pacemaker generated arrhythmia                  |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pelvic mass                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pyrexia                                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sudden cardiac death                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Surgical failure                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Systemic inflammatory response syndrome         |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Immune system disorders                         |                  |                  |  |
| Anaphylactic reaction                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anaphylactic shock                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypersensitivity                                |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sarcoidosis                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Social circumstances                            |                  |                  |  |
| Physical assault                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Reproductive system and breast disorders        |                  |                  |  |
| Balanoposthitis                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Benign prostatic hyperplasia                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cervical dysplasia                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endometrial hyperplasia                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Female genital tract fistula                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| Heavy menstrual bleeding                        |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Postmenopausal haemorrhage                      |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Prostatitis                                     |                   |                   |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Prostatomegaly                                  |                   |                   |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Uterine polyp                                   |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 0 / 8718 (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 respiratory distress syndrome             |                   |                   |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Acute respiratory failure                       |                   |                   |  |
| subjects affected / exposed                     | 11 / 8722 (0.13%) | 12 / 8718 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 11            | 0 / 14            |  |
| deaths causally related to treatment / all      | 0 / 4             | 0 / 6             |  |
| Aspiration                                      |                   |                   |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| Asthma                                          |                   |                   |  |
| subjects affected / exposed                     | 7 / 8722 (0.08%)  | 6 / 8718 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 10            | 0 / 7             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Asthmatic crisis                                |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Atelectasis                                     |                   |                   |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bronchiectasis                                  |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 2 / 8718 (0.02%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Bronchospasm                                    |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 2 / 8718 (0.02%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Chronic obstructive pulmonary disease           |                   |                   |  |
| subjects affected / exposed                     | 33 / 8722 (0.38%) | 43 / 8718 (0.49%) |  |
| occurrences causally related to treatment / all | 0 / 37            | 0 / 44            |  |
| deaths causally related to treatment / all      | 0 / 9             | 0 / 12            |  |
| Cough                                           |                   |                   |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Dyspnoea                                        |                   |                   |  |
| subjects affected / exposed                     | 6 / 8722 (0.07%)  | 5 / 8718 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 6             | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Epistaxis                                       |                   |                   |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 3 / 8722 (0.03%) | 1 / 8718 (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                     | 3 / 8722 (0.03%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemothorax                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypercapnia                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Hypersensitivity pneumonitis                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypoxia                                         |                  |                  |  |
| subjects affected / exposed                     | 6 / 8722 (0.07%) | 4 / 8718 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Idiopathic pulmonary fibrosis                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Interstitial lung disease                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Nasal septum deviation                          |                  |                  |  |

|                                                 |                   |                  |  |
|-------------------------------------------------|-------------------|------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Pleural effusion                                |                   |                  |  |
| subjects affected / exposed                     | 5 / 8722 (0.06%)  | 3 / 8718 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 6             | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Pleurisy                                        |                   |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Pleuritic pain                                  |                   |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%)  | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Pneumothorax                                    |                   |                  |  |
| subjects affected / exposed                     | 3 / 8722 (0.03%)  | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Pulmonary embolism                              |                   |                  |  |
| subjects affected / exposed                     | 10 / 8722 (0.11%) | 4 / 8718 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 10            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 0            |  |
| Pulmonary fibrosis                              |                   |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0            |  |
| Pulmonary hypertension                          |                   |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%)  | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Pulmonary mass                                  |                   |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pulmonary oedema                                |                  |                  |  |
| subjects affected / exposed                     | 3 / 8722 (0.03%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Respiratory acidosis                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Respiratory arrest                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Respiratory distress                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Respiratory failure                             |                  |                  |  |
| subjects affected / exposed                     | 9 / 8722 (0.10%) | 4 / 8718 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 3            |  |
| Sleep apnoea syndrome                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Psychiatric disorders                           |                  |                  |  |
| Alcohol withdrawal syndrome                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 3 / 8718 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anxiety                                         |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Attention deficit hyperactivity disorder        |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Confusional state                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Delirium                                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Depression suicidal                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Depression                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 4 / 8718 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Major depression                                |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mental status changes                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Paranoia                                        |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Schizoaffective disorder                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Suicidal ideation                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Suicide attempt                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Product issues                                  |                  |                  |  |
| Device dislocation                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 3 / 8718 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Device loosening                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Device occlusion                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lead dislodgement                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatobiliary disorders                         |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| Bile duct stone                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Biliary colic                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Biliary obstruction                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Cholangitis acute                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholangitis sclerosing                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (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                     | 3 / 8722 (0.03%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Cholecystitis acute                             |                  |                  |  |
| subjects affected / exposed                     | 3 / 8722 (0.03%) | 5 / 8718 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholecystitis chronic                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholecystitis                                   |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholelithiasis                                  |                  |                  |  |
| subjects affected / exposed                     | 3 / 8722 (0.03%) | 5 / 8718 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gallbladder rupture                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatic cirrhosis                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatic function abnormal                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatic lesion                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatitis acute                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Investigations                                  |                  |                  |  |
| Anticoagulation drug level above therapeutic    |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood potassium decreased                       |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood pressure increased                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ejection fraction decreased                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Electrocardiogram ST segment elevation          |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Heart rate increased                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal function test abnormal                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Transaminases increased                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (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  |                  |                  |  |
| Accidental overdose                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 3 / 8718 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Acetabulum fracture                             |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Alcohol poisoning                               |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anaemia postoperative                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (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                     | 4 / 8722 (0.05%) | 4 / 8718 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arthropod sting                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bone contusion                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cartilage injury                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cervical vertebral fracture                     |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Clavicle fracture                               |                  |                  |  |

|                                                 |                  |                   |  |
|-------------------------------------------------|------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Combined tibia-fibula fracture                  |                  |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Concussion                                      |                  |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Contusion                                       |                  |                   |  |
| subjects affected / exposed                     | 4 / 8722 (0.05%) | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Craniocerebral injury                           |                  |                   |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1             |  |
| Facial bones fracture                           |                  |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Fall                                            |                  |                   |  |
| subjects affected / exposed                     | 6 / 8722 (0.07%) | 10 / 8718 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 10            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Femoral neck fracture                           |                  |                   |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 7 / 8718 (0.08%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 7             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Femur fracture                                  |                  |                   |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 4 / 8718 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Foot fracture                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Forearm fracture                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fractured coccyx                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (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                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hand fracture                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Head injury                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Heat exhaustion                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Heat stroke                                     |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hip fracture                                    |                  |                  |  |
| subjects affected / exposed                     | 3 / 8722 (0.03%) | 5 / 8718 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Humerus fracture                                |                  |                  |  |
| subjects affected / exposed                     | 4 / 8722 (0.05%) | 5 / 8718 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Incision site swelling                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Incisional hernia                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Injury                                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Intentional product misuse                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Joint dislocation                               |                  |                  |  |
| subjects affected / exposed                     | 6 / 8722 (0.07%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Joint injury                                    |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ligament rupture                                |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Limb injury                                     |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lumbar vertebral fracture                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Meniscus injury                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (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                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Muscle strain                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Musculoskeletal foreign body                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neck injury                                     |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 2 / 8718 (0.02%) |  |
| 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                     | 2 / 8722 (0.02%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pelvic fracture                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural complication                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural discharge                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural haematuria                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural haemorrhage                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Postoperative respiratory distress              |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Postoperative wound complication                |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Postpolypectomy syndrome                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (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 / 8722 (0.00%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Radius fracture                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rib fracture                                    |                  |                  |  |
| subjects affected / exposed                     | 5 / 8722 (0.06%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Road traffic accident                           |                  |                  |  |
| subjects affected / exposed                     | 5 / 8722 (0.06%) | 4 / 8718 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 2            |  |
| Sciatic nerve injury                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin laceration                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal compression fracture                     |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (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 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Stress fracture                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subcutaneous haematoma                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subdural haematoma                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Tendon rupture                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Toxicity to various agents                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Traumatic haemothorax                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary retention postoperative                 |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vascular graft thrombosis                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vascular procedure complication                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vascular pseudoaneurysm                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Wound decomposition                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (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                     | 0 / 8722 (0.00%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Wound evisceration                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (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                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Wrist fracture                                  |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Congenital, familial and genetic disorders      |                  |                  |  |
| Arnold-Chiari malformation                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Atrial septal defect                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Corneal dystrophy                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hereditary motor and sensory neuropathy         |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mobile caecum syndrome                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiac disorders                               |                  |                  |  |
| Acute coronary syndrome                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Acute left ventricular failure                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| Acute myocardial infarction                     |                   |                   |  |
| subjects affected / exposed                     | 20 / 8722 (0.23%) | 8 / 8718 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 20            | 0 / 8             |  |
| deaths causally related to treatment / all      | 0 / 6             | 0 / 2             |  |
| Angina pectoris                                 |                   |                   |  |
| subjects affected / exposed                     | 9 / 8722 (0.10%)  | 13 / 8718 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 10            | 0 / 16            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Angina unstable                                 |                   |                   |  |
| subjects affected / exposed                     | 4 / 8722 (0.05%)  | 9 / 8718 (0.10%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 10            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Aortic valve incompetence                       |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Arrhythmia                                      |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Arteriosclerosis coronary artery                |                   |                   |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Atrial fibrillation                             |                   |                   |  |
| subjects affected / exposed                     | 12 / 8722 (0.14%) | 15 / 8718 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 12            | 0 / 17            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 1             |  |
| Atrial flutter                                  |                   |                   |  |
| subjects affected / exposed                     | 4 / 8722 (0.05%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Atrioventricular block complete                 |                   |                   |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 1 / 8718 (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                     | 0 / 8722 (0.00%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Atrioventricular block                          |                   |                   |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%)  | 2 / 8718 (0.02%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bradycardia                                     |                   |                   |  |
| subjects affected / exposed                     | 3 / 8722 (0.03%)  | 3 / 8718 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cardiac arrest                                  |                   |                   |  |
| subjects affected / exposed                     | 3 / 8722 (0.03%)  | 6 / 8718 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 6             |  |
| deaths causally related to treatment / all      | 0 / 11            | 0 / 20            |  |
| Cardiac failure acute                           |                   |                   |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 3             |  |
| Cardiac failure chronic                         |                   |                   |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 1             |  |
| Cardiac failure congestive                      |                   |                   |  |
| subjects affected / exposed                     | 14 / 8722 (0.16%) | 17 / 8718 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 16            | 0 / 17            |  |
| deaths causally related to treatment / all      | 0 / 10            | 0 / 6             |  |
| Cardiac failure                                 |                   |                   |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 13 / 8722 (0.15%) | 10 / 8718 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 15            | 0 / 11            |  |
| deaths causally related to treatment / all      | 0 / 9             | 0 / 8             |  |
| Cardio-respiratory arrest                       |                   |                   |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 5             |  |
| Cardiogenic shock                               |                   |                   |  |
| subjects affected / exposed                     | 3 / 8722 (0.03%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 1             |  |
| Cardiopulmonary failure                         |                   |                   |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%)  | 2 / 8718 (0.02%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 4             |  |
| Cardiovascular disorder                         |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Coronary artery disease                         |                   |                   |  |
| subjects affected / exposed                     | 13 / 8722 (0.15%) | 8 / 8718 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 13            | 0 / 8             |  |
| deaths causally related to treatment / all      | 0 / 4             | 0 / 2             |  |
| Coronary artery insufficiency                   |                   |                   |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Coronary artery occlusion                       |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Coronary artery stenosis                        |                   |                   |  |

|                                                 |                   |                  |  |
|-------------------------------------------------|-------------------|------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 5 / 8718 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Ischaemic cardiomyopathy                        |                   |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0            |  |
| Left ventricular failure                        |                   |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%)  | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Myocardial infarction                           |                   |                  |  |
| subjects affected / exposed                     | 12 / 8722 (0.14%) | 4 / 8718 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 12            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 14            | 0 / 8            |  |
| Myocardial injury                               |                   |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%)  | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Myocardial ischaemia                            |                   |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%)  | 4 / 8718 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0            |  |
| Pericardial effusion                            |                   |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Pericarditis                                    |                   |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Pulseless electrical activity                   |                   |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Right ventricular failure                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sinus arrest                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (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                     | 3 / 8722 (0.03%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Supraventricular tachycardia                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 3 / 8718 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tachycardia                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ventricular arrhythmia                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (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                     | 2 / 8722 (0.02%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ventricular tachycardia                         |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 3 / 8718 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nervous system disorders                        |                  |                  |  |
| Aphasia                                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Balance disorder                                |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Brain injury                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Carotid artery disease                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (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 / 8722 (0.00%) | 1 / 8718 (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                     | 2 / 8722 (0.02%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebellar haemorrhage                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebellar infarction                           |                  |                  |  |

|                                                 |                   |                  |  |
|-------------------------------------------------|-------------------|------------------|--|
| subjects affected / exposed                     | 0 / 8722 (0.00%)  | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1            |  |
| Cerebral artery stenosis                        |                   |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 0 / 8718 (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                     | 1 / 8722 (0.01%)  | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Cerebral infarction                             |                   |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%)  | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1            |  |
| Cerebrovascular accident                        |                   |                  |  |
| subjects affected / exposed                     | 11 / 8722 (0.13%) | 7 / 8718 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 11            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 11            | 0 / 1            |  |
| Cerebrovascular disorder                        |                   |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Cerebrovascular insufficiency                   |                   |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%)  | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1            |  |
| Cervical radiculopathy                          |                   |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%)  | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Dementia Alzheimer's type                       |                   |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic hyperosmolar coma                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dizziness                                       |                  |                  |  |
| subjects affected / exposed                     | 3 / 8722 (0.03%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Encephalopathy                                  |                  |                  |  |
| subjects affected / exposed                     | 4 / 8722 (0.05%) | 3 / 8718 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Epilepsy                                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemorrhagic stroke                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Headache                                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hemiparesis                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatic encephalopathy                          |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypertensive encephalopathy                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypoaesthesia                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypoxic-ischaemic encephalopathy                |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ischaemic stroke                                |                  |                  |  |
| subjects affected / exposed                     | 6 / 8722 (0.07%) | 5 / 8718 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Lacunar infarction                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Loss of consciousness                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lumbar radiculopathy                            |                  |                  |  |
| subjects affected / exposed                     | 3 / 8722 (0.03%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metabolic encephalopathy                        |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Migraine                                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Myasthenia gravis                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Myelopathy                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neurological symptom                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (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                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Occipital neuralgia                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Paraesthesia                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Parkinson's disease                             |                  |                  |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Presyncope                                      |                   |                   |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%)  | 2 / 8718 (0.02%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Sciatica                                        |                   |                   |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Seizure                                         |                   |                   |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%)  | 2 / 8718 (0.02%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Spinal stroke                                   |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Spondylitic myelopathy                          |                   |                   |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Syncope                                         |                   |                   |  |
| subjects affected / exposed                     | 11 / 8722 (0.13%) | 13 / 8718 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 11            | 0 / 13            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Thrombotic cerebral infarction                  |                   |                   |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Transient global amnesia                        |                   |                   |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Transient ischaemic attack                      |                  |                  |  |
| subjects affected / exposed                     | 8 / 8722 (0.09%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Wernicke-Korsakoff syndrome                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (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 macrocytic                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anaemia                                         |                  |                  |  |
| subjects affected / exposed                     | 6 / 8722 (0.07%) | 8 / 8718 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 10           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood loss anaemia                              |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 0 / 8718 (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                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Immune thrombocytopenia                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (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                     | 3 / 8722 (0.03%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lymphadenitis                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ear and labyrinth disorders                     |                  |                  |  |
| Vertigo positional                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (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                     | 1 / 8722 (0.01%) | 3 / 8718 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Eye disorders                                   |                  |                  |  |
| Cataract                                        |                  |                  |  |
| subjects affected / exposed                     | 3 / 8722 (0.03%) | 4 / 8718 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Epiretinal membrane                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Retinal detachment                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Retinal vein occlusion                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vision blurred                                  |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Visual impairment                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (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 incarcerated hernia                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal pain upper                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal pain                                  |                  |                  |  |
| subjects affected / exposed                     | 5 / 8722 (0.06%) | 6 / 8718 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal wall haematoma                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anastomotic ulcer perforation                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ascites                                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Change of bowel habit                           |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chronic gastritis                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colitis ischaemic                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colitis                                         |                  |                  |  |
| subjects affected / exposed                     | 3 / 8722 (0.03%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Constipation                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diarrhoea                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diverticular perforation                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diverticulum intestinal                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diverticulum                                    |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Duodenal ulcer haemorrhage                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Duodenitis                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Enteritis                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Enterocolitis                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (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                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric ulcer haemorrhage                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric ulcer                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastritis erosive                               |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastritis                                       |                  |                  |  |
| subjects affected / exposed                     | 4 / 8722 (0.05%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal disorder                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal haemorrhage                    |                  |                  |  |
| subjects affected / exposed                     | 3 / 8722 (0.03%) | 3 / 8718 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Gastrointestinal motility disorder              |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal ulcer haemorrhage              |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrooesophageal reflux disease                |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haematemesis                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Haematochezia                                   |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Haemorrhoids                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hiatus hernia                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ileus                                           |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Impaired gastric emptying                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Incarcerated inguinal hernia                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Inguinal hernia                                 |                  |                  |  |
| subjects affected / exposed                     | 3 / 8722 (0.03%) | 3 / 8718 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intestinal obstruction                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intestinal perforation                          |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Irritable bowel syndrome                        |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Large intestine polyp                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 3 / 8718 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lower gastrointestinal haemorrhage              |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (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 / 8722 (0.01%) | 0 / 8718 (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                     | 2 / 8722 (0.02%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Obstructive pancreatitis                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal spasm                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal varices haemorrhage                 |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Oesophagitis haemorrhagic                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophagitis                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatitis acute                              |                  |                  |  |
| subjects affected / exposed                     | 8 / 8722 (0.09%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Pancreatitis chronic                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (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                     | 2 / 8722 (0.02%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Papilla of Vater stenosis                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Parotid gland enlargement                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peptic ulcer haemorrhage                        |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectal haemorrhage                              |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 4 / 8718 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectal prolapse                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (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                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Small intestinal obstruction                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Umbilical hernia                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Upper gastrointestinal haemorrhage              |                  |                  |  |
| subjects affected / exposed                     | 3 / 8722 (0.03%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Varices oesophageal                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vomiting                                        |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 4 / 8722 (0.05%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin and subcutaneous tissue disorders          |                  |                  |  |
| Blister                                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cellulite                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Decubitus ulcer                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic foot                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 3 / 8718 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Diabetic ulcer                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lichen planus                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pemphigoid                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rash maculo-papular                             |                  |                  |  |

|                                                 |                  |                   |  |
|-------------------------------------------------|------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Rash                                            |                  |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Skin disorder                                   |                  |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Skin ulcer haemorrhage                          |                  |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Skin ulcer                                      |                  |                   |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Renal and urinary disorders                     |                  |                   |  |
| Acute kidney injury                             |                  |                   |  |
| subjects affected / exposed                     | 9 / 8722 (0.10%) | 18 / 8718 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 10           | 0 / 19            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 3             |  |
| Calculus urinary                                |                  |                   |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Chronic kidney disease                          |                  |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Contracted bladder                              |                  |                   |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dysuria                                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haematuria                                      |                  |                  |  |
| subjects affected / exposed                     | 4 / 8722 (0.05%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hydronephrosis                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Incontinence                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lower urinary tract symptoms                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (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                     | 5 / 8722 (0.06%) | 3 / 8718 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nephrotic syndrome                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pelvi-ureteric obstruction                      |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal disorder                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (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                     | 1 / 8722 (0.01%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Renal tubular necrosis                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subcapsular renal haematoma                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ureterolithiasis                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urethral obstruction                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urethral stenosis                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary incontinence                            |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary retention                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 3 / 8718 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vesicoureteric reflux                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endocrine disorders                             |                  |                  |  |
| Basedow's disease                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (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 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypothyroidism                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Musculoskeletal and connective tissue disorders |                  |                  |  |
| Arthralgia                                      |                  |                  |  |
| subjects affected / exposed                     | 4 / 8722 (0.05%) | 9 / 8718 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 9            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arthritis                                       |                  |                  |  |
| subjects affected / exposed                     | 4 / 8722 (0.05%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| Arthropathy                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (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                     | 4 / 8722 (0.05%) | 9 / 8718 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 9            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bursitis                                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cervical spinal stenosis                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 3 / 8718 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chondropathy                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dupuytren's contracture                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Flank pain                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Foot deformity                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fracture malunion                               |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemarthrosis                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intervertebral disc degeneration                |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intervertebral disc disorder                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intervertebral disc protrusion                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Joint stiffness                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Joint swelling                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (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                     | 2 / 8722 (0.02%) | 3 / 8718 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Muscle spasms                                   |                  |                  |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 0 / 8718 (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                     | 0 / 8722 (0.00%)  | 3 / 8718 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Musculoskeletal chest pain                      |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Myalgia                                         |                   |                   |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%)  | 2 / 8718 (0.02%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Neck pain                                       |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Osteoarthritis                                  |                   |                   |  |
| subjects affected / exposed                     | 18 / 8722 (0.21%) | 15 / 8718 (0.17%) |  |
| occurrences causally related to treatment / all | 0 / 18            | 0 / 16            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pain in extremity                               |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pain in jaw                                     |                   |                   |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pseudarthrosis                                  |                   |                   |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rheumatoid arthritis                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rotator cuff syndrome                           |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sacral pain                                     |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal instability                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal osteoarthritis                           |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal pain                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal stenosis                                 |                  |                  |  |
| subjects affected / exposed                     | 4 / 8722 (0.05%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spondyloarthropathy                             |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spondylolisthesis                               |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Synovial disorder                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tendinous contracture                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tendonitis                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infections and infestations                     |                  |                  |  |
| Abdominal abscess                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abscess limb                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 3 / 8718 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abscess neck                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abscess                                         |                  |                  |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 8722 (0.00%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Appendicitis                                    |                   |                   |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%)  | 5 / 8718 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Arthritis bacterial                             |                   |                   |  |
| subjects affected / exposed                     | 3 / 8722 (0.03%)  | 2 / 8718 (0.02%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Arthritis infective                             |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bacteraemia                                     |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Bacterial infection                             |                   |                   |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bronchitis viral                                |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bronchitis                                      |                   |                   |  |
| subjects affected / exposed                     | 12 / 8722 (0.14%) | 11 / 8718 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 12            | 0 / 12            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bursitis infective                              |                   |                   |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 8722 (0.00%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cellulitis                                      |                   |                   |  |
| subjects affected / exposed                     | 23 / 8722 (0.26%) | 18 / 8718 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 24            | 0 / 19            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Chronic sinusitis                               |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 0 / 8718 (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                     | 1 / 8722 (0.01%)  | 3 / 8718 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Clostridium difficile infection                 |                   |                   |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%)  | 3 / 8718 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cystitis escherichia                            |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cystitis                                        |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 2 / 8718 (0.02%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Device related infection                        |                   |                   |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%)  | 3 / 8718 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Device related sepsis                           |                   |                   |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic foot infection                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diverticulitis                                  |                  |                  |  |
| subjects affected / exposed                     | 8 / 8722 (0.09%) | 7 / 8718 (0.08%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Empyema                                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Epididymitis                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Erysipelas                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 3 / 8718 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Escherichia bacteraemia                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (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                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Extradural abscess                              |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Folliculitis                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fournier's gangrene                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fracture infection                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fungal infection                                |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gangrene                                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gas gangrene                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastroenteritis rotavirus                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (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 / 8722 (0.02%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Gastroenteritis                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 3 / 8718 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal viral infection                |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haematoma infection                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemorrhagic fever with renal syndrome          |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemorrhagic fever                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (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                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatitis viral                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Herpes zoster                                   |                  |                  |  |

|                                                               |                  |                  |  |
|---------------------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                                   | 1 / 8722 (0.01%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all               | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all                    | 0 / 0            | 0 / 0            |  |
| Infected skin ulcer                                           |                  |                  |  |
| subjects affected / exposed                                   | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all                    | 0 / 0            | 0 / 0            |  |
| Infection                                                     |                  |                  |  |
| subjects affected / exposed                                   | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all               | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all                    | 0 / 0            | 0 / 0            |  |
| Infective exacerbation of chronic obstructive airways disease |                  |                  |  |
| subjects affected / exposed                                   | 3 / 8722 (0.03%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all               | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all                    | 0 / 0            | 0 / 0            |  |
| Influenza                                                     |                  |                  |  |
| subjects affected / exposed                                   | 6 / 8722 (0.07%) | 4 / 8718 (0.05%) |  |
| occurrences causally related to treatment / all               | 0 / 6            | 0 / 4            |  |
| deaths causally related to treatment / all                    | 0 / 0            | 0 / 0            |  |
| Intervertebral discitis                                       |                  |                  |  |
| subjects affected / exposed                                   | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all               | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all                    | 0 / 0            | 0 / 0            |  |
| Kidney infection                                              |                  |                  |  |
| subjects affected / exposed                                   | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all                    | 0 / 0            | 0 / 0            |  |
| Listeria sepsis                                               |                  |                  |  |
| subjects affected / exposed                                   | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all                    | 0 / 0            | 0 / 0            |  |
| Liver abscess                                                 |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Localised infection                             |                  |                  |  |
| subjects affected / exposed                     | 5 / 8722 (0.06%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lower respiratory tract infection               |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lung abscess                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lyme disease                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Medical device site joint infection             |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Meningitis bacterial                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (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 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ophthalmic herpes zoster                        |                  |                  |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 8722 (0.00%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Orchitis                                        |                   |                   |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Oropharyngeal candidiasis                       |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Osteomyelitis acute                             |                   |                   |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Osteomyelitis fungal                            |                   |                   |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Osteomyelitis                                   |                   |                   |  |
| subjects affected / exposed                     | 12 / 8722 (0.14%) | 11 / 8718 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 12            | 0 / 11            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Parotitis                                       |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pelvic abscess                                  |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Peritonitis                                     |                   |                   |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 8722 (0.00%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Peritonsillar abscess                           |                   |                   |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia aspiration                            |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 3 / 8718 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Pneumonia bacterial                             |                   |                   |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%)  | 2 / 8718 (0.02%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Pneumonia influenzal                            |                   |                   |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia pneumococcal                          |                   |                   |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%)  | 1 / 8718 (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                     | 0 / 8722 (0.00%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia                                       |                   |                   |  |
| subjects affected / exposed                     | 38 / 8722 (0.44%) | 39 / 8718 (0.45%) |  |
| occurrences causally related to treatment / all | 0 / 40            | 0 / 40            |  |
| deaths causally related to treatment / all      | 0 / 5             | 0 / 6             |  |
| Post procedural infection                       |                   |                   |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 3 / 8722 (0.03%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Postoperative wound infection                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Prostate infection                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pyelonephritis acute                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 3 / 8718 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pyelonephritis                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pyuria                                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (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                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Scrotal abscess                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sepsis                                          |                  |                  |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 16 / 8722 (0.18%) | 16 / 8718 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 16            | 0 / 16            |  |
| deaths causally related to treatment / all      | 0 / 6             | 0 / 3             |  |
| Septic arthritis staphylococcal                 |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Septic shock                                    |                   |                   |  |
| subjects affected / exposed                     | 3 / 8722 (0.03%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Staphylococcal bacteraemia                      |                   |                   |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%)  | 2 / 8718 (0.02%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Staphylococcal infection                        |                   |                   |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Staphylococcal sepsis                           |                   |                   |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Streptococcal bacteraemia                       |                   |                   |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%)  | 1 / 8718 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Subcutaneous abscess                            |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Tracheobronchitis                               |                   |                   |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Upper respiratory tract infection               |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 2 / 8718 (0.02%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Urinary tract infection bacterial               |                   |                   |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Urinary tract infection enterococcal            |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Urinary tract infection                         |                   |                   |  |
| subjects affected / exposed                     | 13 / 8722 (0.15%) | 10 / 8718 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 13            | 0 / 10            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 3             |  |
| Urosepsis                                       |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Viraemia                                        |                   |                   |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Viral infection                                 |                   |                   |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%)  | 0 / 8718 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Viral upper respiratory tract infection         |                   |                   |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vulval abscess                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Wound abscess                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Wound infection staphylococcal                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (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                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metabolism and nutrition disorders              |                  |                  |  |
| Alcoholic ketoacidosis                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dehydration                                     |                  |                  |  |
| subjects affected / exposed                     | 8 / 8722 (0.09%) | 5 / 8718 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 9            |  |
| Diabetes mellitus inadequate control            |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetes mellitus                               |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 4 / 8718 (0.05%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic ketoacidosis                           |                  |                  |  |
| subjects affected / exposed                     | 4 / 8722 (0.05%) | 5 / 8718 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic metabolic decompensation               |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gout                                            |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypercalcaemia                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyperglycaemia                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyperglycaemic hyperosmolar nonketotic syndrome |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyperkalaemia                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 8722 (0.02%) | 3 / 8718 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Hypertriglyceridaemia                           |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypervolaemia                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 3 / 8718 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Hypoglycaemia                                   |                  |                  |  |
| subjects affected / exposed                     | 4 / 8722 (0.05%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypokalaemia                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypomagnesaemia                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyponatraemia                                   |                  |                  |  |
| subjects affected / exposed                     | 3 / 8722 (0.03%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypoosmolar state                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypovolaemia                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 8722 (0.00%) | 2 / 8718 (0.02%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lactic acidosis                                 |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lactose intolerance                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (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                     | 0 / 8722 (0.00%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metabolic acidosis                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 0 / 8718 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Type 2 diabetes mellitus                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 8722 (0.01%) | 1 / 8718 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

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

| <b>Non-serious adverse events</b>                     | Clostridium difficile Vaccine | Placebo              |  |
|-------------------------------------------------------|-------------------------------|----------------------|--|
| Total subjects affected by non-serious adverse events |                               |                      |  |
| subjects affected / exposed                           | 5702 / 8722 (65.37%)          | 4314 / 8718 (49.48%) |  |
| Nervous system disorders                              |                               |                      |  |
| Headache (HEADACHE)                                   |                               |                      |  |
| alternative assessment type: Systematic               |                               |                      |  |
| subjects affected / exposed                           | 2615 / 8722 (29.98%)          | 2323 / 8718 (26.65%) |  |
| occurrences (all)                                     | 2615                          | 2323                 |  |
| General disorders and administration site conditions  |                               |                      |  |
| Fatigue (FATIGUE)                                     |                               |                      |  |
| alternative assessment type: Systematic               |                               |                      |  |

|                                                                                                                           |                         |                         |  |
|---------------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------------|--|
| subjects affected / exposed                                                                                               | 3240 / 8722<br>(37.15%) | 2820 / 8718<br>(32.35%) |  |
| occurrences (all)                                                                                                         | 3240                    | 2820                    |  |
| Injection site pain (PAIN)<br>alternative assessment type:<br>Systematic                                                  |                         |                         |  |
| subjects affected / exposed                                                                                               | 3596 / 8722<br>(41.23%) | 1056 / 8718<br>(12.11%) |  |
| occurrences (all)                                                                                                         | 3596                    | 1056                    |  |
| Injection site swelling (SWELLING)<br>alternative assessment type:<br>Systematic                                          |                         |                         |  |
| subjects affected / exposed                                                                                               | 1846 / 8722<br>(21.16%) | 414 / 8718 (4.75%)      |  |
| occurrences (all)                                                                                                         | 1846                    | 414                     |  |
| Skin and subcutaneous tissue disorders<br>Injection site erythema (REDNESS)<br>alternative assessment type:<br>Systematic |                         |                         |  |
| subjects affected / exposed                                                                                               | 1879 / 8722<br>(21.54%) | 653 / 8718 (7.49%)      |  |
| occurrences (all)                                                                                                         | 1879                    | 653                     |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia (JOINT PAIN)<br>alternative assessment type:<br>Systematic  |                         |                         |  |
| subjects affected / exposed                                                                                               | 1583 / 8722<br>(18.15%) | 1354 / 8718<br>(15.53%) |  |
| occurrences (all)                                                                                                         | 1583                    | 1354                    |  |
| Myalgia (MUSCLE PAIN)<br>alternative assessment type:<br>Systematic                                                       |                         |                         |  |
| subjects affected / exposed                                                                                               | 1856 / 8722<br>(21.28%) | 1487 / 8718<br>(17.06%) |  |
| occurrences (all)                                                                                                         | 1856                    | 1487                    |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                          |
|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 28 September 2020 | Clarified that if an SAE was reported after subject Visit 6, all the requirements will apply, including the respect of the reporting timelines as if the SAE occurred within the reporting period. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported