



## Clinical trial results:

### A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Effect of Efpeglenatide on Cardiovascular Outcomes in Type 2 Diabetes Patients at High Cardiovascular Risk

#### Summary

|                          |  |
|--------------------------|--|
| EudraCT number           | 2017-002954-35                         |
| Trial protocol           | SK HU LV SE NO LT EE DK ES FI BG IT RO |
| Global end of trial date | 10 December 2020                       |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 06 November 2021 |
| First version publication date | 06 November 2021 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | EFC14828 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |                 |
|------------------------------------|-----------------|
| ISRCTN number                      | -               |
| ClinicalTrials.gov id (NCT number) | NCT03496298     |
| WHO universal trial number (UTN)   | U1111-1186-2533 |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Sanofi-aventis Recherche & Développement   |
| Sponsor organisation address | 1 avenue Pierre Brossolette, Chilly Mazarin Cedex, France, 91380                         |
| Public contact               | Sanofi aventis recherche & développement, Trial Transparency Team, Contact-US@sanofi.com |
| Scientific contact           | Sanofi aventis recherche & développement, Trial Transparency Team, Contact-US@sanofi.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                       | 15 April 2021    |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 10 December 2020 |
| Was the trial ended prematurely?                     | Yes              |

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate that, efpeglenatide 4 and 6 miligrams (mg) was noninferior to placebo on 3-point major adverse cardiac event (MACE) in Type 2 diabetes mellitus (T2DM) subjects at high cardiovascular (CV) risk.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy:

Any antihyperglycemic treatment was allowed as background therapy with the exception of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors.

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 27 April 2018 |
| 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 | Norway: 25    |
| Country: Number of subjects enrolled | Poland: 164   |
| Country: Number of subjects enrolled | Slovakia: 132 |
| Country: Number of subjects enrolled | Spain: 56     |
| Country: Number of subjects enrolled | Sweden: 41    |
| Country: Number of subjects enrolled | Bulgaria: 184 |
| Country: Number of subjects enrolled | Denmark: 20   |
| Country: Number of subjects enrolled | Estonia: 30   |
| Country: Number of subjects enrolled | Finland: 34   |
| Country: Number of subjects enrolled | Germany: 107  |
| Country: Number of subjects enrolled | Hungary: 181  |
| Country: Number of subjects enrolled | Italy: 60     |
| Country: Number of subjects enrolled | Latvia: 35    |
| Country: Number of subjects enrolled | Lithuania: 44 |

|                                      |                         |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Argentina: 380          |
| Country: Number of subjects enrolled | Canada: 325             |
| Country: Number of subjects enrolled | Chile: 212              |
| Country: Number of subjects enrolled | India: 98               |
| Country: Number of subjects enrolled | Mexico: 251             |
| Country: Number of subjects enrolled | Peru: 81                |
| Country: Number of subjects enrolled | Romania: 96             |
| Country: Number of subjects enrolled | Russian Federation: 224 |
| Country: Number of subjects enrolled | Serbia: 76              |
| Country: Number of subjects enrolled | South Africa: 90        |
| Country: Number of subjects enrolled | Turkey: 118             |
| Country: Number of subjects enrolled | United States: 754      |
| Country: Number of subjects enrolled | Ukraine: 194            |
| Country: Number of subjects enrolled | Korea, Republic of: 64  |
| Worldwide total number of subjects   | 4076                    |
| EEA total number of subjects         | 1209                    |

Notes:

| <b>Subjects enrolled per age group</b>    |      |
|---|------|
| In utero                                  | 0    |
| Preterm newborn - gestational age < 37 wk | 0    |
| Newborns (0-27 days)                      | 0    |
| Infants and toddlers (28 days-23 months)  | 0    |
| Children (2-11 years)                     | 0    |
| Adolescents (12-17 years)                 | 0    |
| Adults (18-64 years)                      | 1954 |
| From 65 to 84 years                       | 2108 |
| 85 years and over                         | 14   |

## Subject disposition

### Recruitment

Recruitment details:

Study was conducted at 344 active sites in 28 countries. 5732 subjects were screened between 27 April 2018 and 25 April 2019; of whom 4076 subjects were randomised by interactive response technology (1:1:1 ratio) to receive placebo, efpeglenatide 4 mg or efpeglenatide 6 mg. Screen failures were mainly due to inclusion criteria not met.

### Pre-assignment

Screening details:

Randomisation was stratified by the current or potential future use of a sodium-glucose co-transporter-2 (SGLT2) inhibitor: current use; potential future use; neither current nor potential future use.

### Period 1

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

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Placebo |

Arm description:

Subjects received placebo (matched to Efpeglenatide) as subcutaneous (SC) injection once weekly up to end of treatment (median duration: 19.8 months).

|  |  |
|--|--|
| Arm type                               | Placebo                                      |
| Investigational medicinal product name | Placebo                                      |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

Dosage and administration details:

Placebo (matched to Efpeglenatide) as SC injection once weekly up to end of treatment.

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | Efpeglenatide 4mg |
|------------------|-------------------|

Arm description:

Subjects received Efpeglenatide as SC injection 2 milligrams (mg) per week for 4 weeks then 4 mg per week up to end of treatment (median duration: 19.9 months).

|  |  |
|--|--|
| Arm type                               | Experimental                                 |
| Investigational medicinal product name | Efpeglenatide 4mg                            |
| Investigational medicinal product code | SAR439977                                    |
| Other name                             |  |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

Dosage and administration details:

Efpeglenatide as SC injection 2 mg per week for 4 weeks then 4 mg per week up to end of treatment.

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | Efpeglenatide 6 mg |
|------------------|--------------------|

Arm description:

Subjects received Efpeglenatide as SC injection 2 mg per week for 4 weeks, then 4 mg per week for 4 weeks and then 6 mg per week up to end of treatment (median duration: 20 months).

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |  |
|--|--|
| Investigational medicinal product name | Efpeglenatide 6 mg                           |
| Investigational medicinal product code | SAR439977                                    |
| Other name                             |  |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

Dosage and administration details:

Efpeglenatide as SC injection 2 mg per week for 4 weeks, then 4 mg per week for 4 weeks and then 6 mg per week up to end of treatment.

| <b>Number of subjects in period 1</b>         | Placebo | Efpeglenatide 4mg | Efpeglenatide 6 mg |
|---|---------|-------------------|--------------------|
| Started                                       | 1359    | 1359              | 1358               |
| Randomised and treated                        | 1358    | 1358              | 1357               |
| Completed                                     | 42      | 36                | 23                 |
| Not completed                                 | 1317    | 1323              | 1335               |
| Randomised and not treated                    | 1       | 1                 | 1                  |
| Study terminated by Sponsor                   | 1050    | 1063              | 1071               |
| Adverse event                                 | 49      | 68                | 79                 |
| Unspecified                                   | 29      | 20                | 23                 |
| Physician decision (other than adverse event) | 12      | 17                | 10                 |
| Withdrawal by subject                         | 176     | 154               | 151                |

## Baseline characteristics

### Reporting groups

|   |                    |
|---|--------------------|
| Reporting group title   | Placebo            |
| Reporting group description:  |                    |
| Subjects received placebo (matched to Efpeglenatide) as subcutaneous (SC) injection once weekly up to end of treatment (median duration: 19.8 months).                                |                    |
| Reporting group title   | Efpeglenatide 4mg  |
| Reporting group description:  |                    |
| Subjects received Efpeglenatide as SC injection 2 milligrams (mg) per week for 4 weeks then 4 mg per week up to end of treatment (median duration: 19.9 months).                      |                    |
| Reporting group title   | Efpeglenatide 6 mg |
| Reporting group description:  |                    |
| Subjects received Efpeglenatide as SC injection 2 mg per week for 4 weeks, then 4 mg per week for 4 weeks and then 6 mg per week up to end of treatment (median duration: 20 months). |                    |

| Reporting group values | Placebo | Efpeglenatide 4mg | Efpeglenatide 6 mg |
|------------------------|---------|-------------------|--------------------|
| Number of subjects     | 1359    | 1359              | 1358               |
| Age categorical        |         |                   |                    |
| Units: Subjects        |         |                   |                    |

|  |        |        |        |
|--|--------|--------|--------|
| Age continuous   |        |        |        |
| Units: years   |        |        |        |
| arithmetic mean  | 64.4   | 64.6   | 64.7   |
| standard deviation   | ± 8.3  | ± 8.2  | ± 8.2  |
| Gender categorical   |        |        |        |
| Units: Subjects  |        |        |        |
| Female   | 419    | 442    | 483    |
| Male   | 940    | 917    | 875    |
| Race (NIH/OMB)   |        |        |        |
| Units: Subjects  |        |        |        |
| American Indian or Alaska Native   | 11     | 8      | 8      |
| Asian  | 98     | 87     | 82     |
| Native Hawaiian or Other Pacific Islander  | 0      | 1      | 2      |
| Black or African American  | 50     | 38     | 55     |
| White  | 1162   | 1192   | 1180   |
| More than one race   | 4      | 9      | 5      |
| Unknown or Not Reported  | 34     | 24     | 26     |
| Body Mass Index (BMI)  |        |        |        |
| In both Efpeglenatide 4 mg and Efpeglenatide 6 mg arm, only 1357 subjects were involved in the evaluation of the specified baseline measure. |        |        |        |
| Units: kilogram metre per square (kg/m <sup>2</sup> )  |        |        |        |
| arithmetic mean  | 32.40  | 32.81  | 32.90  |
| standard deviation   | ± 6.01 | ± 6.22 | ± 6.21 |

| Reporting group values | Total |  |  |
|------------------------|-------|--|--|
| Number of subjects     | 4076  |  |  |

|  |      |  |  |
|--|------|--|--|
| Age categorical<br>Units: Subjects   |      |  |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation  | -    |  |  |
| Gender categorical<br>Units: Subjects  |      |  |  |
| Female   | 1344 |  |  |
| Male   | 2732 |  |  |
| Race (NIH/OMB)<br>Units: Subjects  |      |  |  |
| American Indian or Alaska Native   | 27   |  |  |
| Asian  | 267  |  |  |
| Native Hawaiian or Other Pacific Islander  | 3    |  |  |
| Black or African American  | 143  |  |  |
| White  | 3534 |  |  |
| More than one race   | 18   |  |  |
| Unknown or Not Reported  | 84   |  |  |
| Body Mass Index (BMI)  |      |  |  |
| In both Efpeglenatide 4 mg and Efpeglenatide 6 mg arm, only 1357 subjects were involved in the evaluation of the specified baseline measure. |      |  |  |
| Units: kilogram metre per square (kg/m <sup>2</sup> )<br>arithmetic mean<br>standard deviation   | -    |  |  |

## End points

### End points reporting groups

|   |                         |
|---|-------------------------|
| Reporting group title   | Placebo                 |
| Reporting group description:<br>Subjects received placebo (matched to Efpeglenatide) as subcutaneous (SC) injection once weekly up to end of treatment (median duration: 19.8 months).                                |                         |
| Reporting group title   | Efpeglenatide 4mg       |
| Reporting group description:<br>Subjects received Efpeglenatide as SC injection 2 milligrams (mg) per week for 4 weeks then 4 mg per week up to end of treatment (median duration: 19.9 months).                      |                         |
| Reporting group title   | Efpeglenatide 6 mg      |
| Reporting group description:<br>Subjects received Efpeglenatide as SC injection 2 mg per week for 4 weeks, then 4 mg per week for 4 weeks and then 6 mg per week up to end of treatment (median duration: 20 months). |                         |
| Subject analysis set title  | Efpeglenatide 4 mg+6 mg |
| Subject analysis set type   | Intention-to-treat      |
| Subject analysis set description:<br>Included all subjects who received either Efpeglenatide 4 mg or 6 mg as SC injection once weekly up to end of treatment (median duration: 19.9 months).                          |                         |

### Primary: Time to First Occurrence of Major Adverse Cardiovascular Events (MACE): Event Rate Per 100 Subject-years for First Occurrence of Major Cardiovascular (CV) Event - Non-Inferiority Analysis

|  |  |
|--|--|
| End point title  | Time to First Occurrence of Major Adverse Cardiovascular Events (MACE): Event Rate Per 100 Subject-years for First Occurrence of Major Cardiovascular (CV) Event - Non-Inferiority Analysis <sup>[1]</sup> |
| End point description:<br>All MACE positively adjudicated by the clinical endpoint committee (CEC) were used in the analysis of the composite outcome of first occurrence to CV death, non-fatal myocardial infarction (MI), and non-fatal stroke. Kaplan-Meier curves of the cumulative event rate by treatment groups were used to depict the first occurrence of MACE over time. The event rate per 100 subject-years (calculated by 100*number of subjects with events/sum of time at risk (days) over all subjects/365.25) measured in terms of number of events per 100 subject-years was reported. Analysis was performed on intent-to-treat (ITT) population that included all randomised subjects irrespective of compliance with the study protocol and procedures and were analysed in the treatment group to which they were randomised. Data for this endpoint was planned to be collected and analysed for pooled population of subjects who received Efglenatide (at any dose: 4 mg and 6 mg) as pre-specified in the protocol. |  |
| End point type   | Primary  |
| End point timeframe:<br>From Day 1 until the date of first adjudicated and confirmed occurrence of major CV event (maximum duration: up to 31.5 months)  |  |
| Notes:<br>[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data was reported for applicable arms in the endpoint.  |  |

| End point values                    | Placebo          | Efpeglenatide 4 mg+6 mg |  |  |
|-------------------------------------|------------------|-------------------------|--|--|
| Subject group type                  | Reporting group  | Subject analysis set    |  |  |
| Number of subjects analysed         | 1359             | 2717                    |  |  |
| Units: events per 100 subject-years |                  |                         |  |  |
| number (confidence interval 95%)    | 5.3 (4.4 to 6.3) | 3.9 (3.4 to 4.5)        |  |  |



## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Efpeglenatide 4 mg+6 mg versus Placebo |
| Statistical analysis description:   |  |
| Hazard ratio and 95% Confidence Interval (CI) were obtained from a Cox proportional hazards model with region (North America, Latin America, Europe, other), randomisation stratum of SGLT2 inhibitor use (current use, potential future use, neither current nor potential future use) and treatment (efpeglenatide 4 mg, efpeglenatide 6 mg, placebo) as fixed effect factor. |  |
| Comparison groups   | Placebo v Efpeglenatide 4 mg+6 mg      |
| Number of subjects included in analysis   | 4076                                   |
| Analysis specification  | Pre-specified                          |
| Analysis type   | non-inferiority <sup>[2]</sup>         |
| P-value   | < 0.0001 <sup>[3]</sup>                |
| Method  | Logrank                                |
| Parameter estimate  | Hazard ratio (HR)                      |
| Point estimate  | 0.732                                  |
| Confidence interval   |  |
| level   | 95 %                                   |
| sides   | 2-sided                                |
| lower limit   | 0.583                                  |
| upper limit   | 0.918                                  |

Notes:

[2] - Non-inferiority of efpeglenatide 4 mg+6 mg versus placebo was to be claimed if the upper bound of the 2-sided 95% CI of the hazard ratio for the incidence was  $\leq 1.8$  and  $\leq 1.3$ .

[3] - One-sided p-value based on log rank test of hazard ratio for the incidence  $\leq 1.8$  and  $\leq 1.3$ .

## Secondary: Time to First Occurrence of Major Adverse Cardiovascular Events: Event Rate Per 100 Subject-years for First Occurrence of Major Cardiovascular Event - Superiority Analysis

|                 |  |
|-----------------|--|
| End point title | Time to First Occurrence of Major Adverse Cardiovascular Events: Event Rate Per 100 Subject-years for First Occurrence of Major Cardiovascular Event - Superiority Analysis <sup>[4]</sup> |
|-----------------|--|

End point description:

All MACE positively adjudicated by the CEC were used in the analysis of the composite outcome of first occurrence to CV death, non-fatal MI, and non-fatal stroke. Kaplan-Meier curves of the cumulative event rate by treatment groups were used to depict the first occurrence of MACE over time. The event rate per 100 subject-years (calculated by  $100 \times \text{number of subjects with events} / \text{sum of time at risk (days)} / \text{all subjects} / 365.25$ ) measured in terms of number of events per 100 subject-years was reported. Analysis was performed on ITT population. Data for this endpoint was planned to be collected and analysed for pooled population of subjects who received Efpeglenatide (at any dose: 4 mg and 6 mg) as pre-specified in the protocol.

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

End point timeframe:

From Day 1 until the date of first adjudicated and confirmed occurrence of major CV event (maximum duration: up to 31.5 months)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data was reported for applicable arms in the endpoint.

| End point values                    | Placebo          | Efpeglenatide 4 mg+6 mg |  |  |
|-------------------------------------|------------------|-------------------------|--|--|
| Subject group type                  | Reporting group  | Subject analysis set    |  |  |
| Number of subjects analysed         | 1359             | 2717                    |  |  |
| Units: events per 100 subject-years |                  |                         |  |  |
| number (confidence interval 95%)    | 5.3 (4.4 to 6.3) | 3.9 (3.4 to 4.5)        |  |  |

## Statistical analyses

| Statistical analysis title  | Efpeglenatide 4 mg+6 mg versus Placebo |
|---|--|
| Statistical analysis description:   |  |
| Hazard ratio and 95% CI were obtained from a Cox proportional hazards model with region (North America, Latin America, Europe, other), randomisation stratum of SGLT2 inhibitor use (current use, potential future use, neither current nor potential future use) and treatment (efpeglenatide 4 mg, efpeglenatide 6 mg, placebo) as fixed effect factor. |  |
| Comparison groups   | Placebo v Efpeglenatide 4 mg+6 mg      |
| Number of subjects included in analysis   | 4076                                   |
| Analysis specification  | Pre-specified                          |
| Analysis type   | superiority <sup>[5]</sup>             |
| P-value   | = 0.0069 <sup>[6]</sup>                |
| Method  | Logrank                                |
| Parameter estimate  | Hazard ratio (HR)                      |
| Point estimate  | 0.732                                  |
| Confidence interval   |  |
| level   | 95 %                                   |
| sides   | 2-sided                                |
| lower limit   | 0.583                                  |
| upper limit   | 0.918                                  |

Notes:

[5] - Superiority was claimed when the upper bound of the 2-sided 95% CI of hazard ratio was less than 1.

[6] - Two-sided p-values based on log rank test of hazard ratio.

## Secondary: Time to First Occurrence of the Expanded Major Adverse Cardiovascular Events Composite Events: Event Rate Per 100 Subject-years for First Occurrence of Expanded Major Cardiovascular Event

|                 |  |
|-----------------|--|
| End point title | Time to First Occurrence of the Expanded Major Adverse Cardiovascular Events Composite Events: Event Rate Per 100 Subject-years for First Occurrence of Expanded Major Cardiovascular Event <sup>[7]</sup> |
|-----------------|--|

End point description:

All MACE positively adjudicated by the CEC were used in the analysis of the expanded outcome of first occurrence to CV death (including fatal MI and fatal stroke), non-fatal MI, non-fatal stroke, coronary revascularisation or hospitalisation for unstable angina. Kaplan-Meier curves of the cumulative event rate by treatment groups were used to depict the first occurrence of MACE over time. The event rate per 100 subject-years (calculated by 100\*number of subjects with events/sum of time at risk (days) over all subjects/365.25) measured in terms of number of events per 100 subject-years was reported. Data analysis was also performed independently by external steering committee for the publication. Analysis was performed on ITT population. Data for this endpoint was planned to be collected and analysed for pooled population of subjects who received Efpeglenatide (at any dose: 4 mg and 6 mg) as pre-specified in the protocol.

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

End point timeframe:

From Day 1 until the date of first adjudicated and confirmed occurrence of major CV event (maximum duration: up to 31.5 months)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: Data was reported for applicable arms in the endpoint.

| End point values                    | Placebo         | Efpeglenatide 4 mg+6 mg |  |  |
|-------------------------------------|-----------------|-------------------------|--|--|
| Subject group type                  | Reporting group | Subject analysis set    |  |  |
| Number of subjects analysed         | 1359            | 2717                    |  |  |
| Units: events per 100 subject-years |                 |                         |  |  |
| number (not applicable)             | 6.8             | 5.4                     |  |  |

## Statistical analyses

| Statistical analysis title  | Efpeglenatide 4 mg+6 mg versus Placebo |
|---|--|
| Statistical analysis description:   |  |
| Hazard ratio and 95% CI were obtained from a Cox proportional hazards model with region (North America, Latin America, Europe, other), randomisation stratum of SGLT2 inhibitor use (current use, potential future use, neither current nor potential future use) and treatment (efpeglenatide 4 mg, efpeglenatide 6 mg, placebo) as fixed effect factor. |  |
| Comparison groups   | Placebo v Efpeglenatide 4 mg+6 mg      |
| Number of subjects included in analysis   | 4076                                   |
| Analysis specification  | Pre-specified                          |
| Analysis type   | superiority <sup>[8]</sup>             |
| P-value   | = 0.02 <sup>[9]</sup>                  |
| Method  | Logrank                                |
| Parameter estimate  | Hazard ratio (HR)                      |
| Point estimate  | 0.79                                   |
| Confidence interval   |  |
| level   | 95 %                                   |
| sides   | 2-sided                                |
| lower limit   | 0.65                                   |
| upper limit   | 0.96                                   |

Notes:

[8] - Superiority was claimed when the upper bound of the 2-sided 95% CI of hazard ratio was less than 1.

[9] - Two-sided p-values based on log rank test of hazard ratio.

## Secondary: Time to First Occurrence of Composite Renal Endpoint: Event Rate Per 100 Subject-years for First Occurrence of Composite Renal Endpoint

|                 |   |
|-----------------|---|
| End point title | Time to First Occurrence of Composite Renal Endpoint: Event Rate Per 100 Subject-years for First Occurrence of Composite Renal Endpoint <sup>[10]</sup> |
|-----------------|---|

End point description:

Composite renal endpoint: incident macroalbuminuria (defined as urinary albumin-to-creatinine ratio of greater than (>) 300, measured in mg of albumin to grams of creatinine or >33.9, measured in mg of albumin to millimoles of creatinine), plus increase in urinary albumin-to-creatinine ratio of at least 30% from Baseline, sustained decrease in eGFR of at least 40% for 30 days or more, renal-replacement therapy for 90 days or more and sustained eGFR of less than 15 ml per minute per 1.73 m<sup>2</sup> for 30 days or more. Kaplan-Meier curves of cumulative event rate depicted 1st occurrence of renal endpoint over time. Event rate per 100 subject-years (calculated by 100\*number of subjects with events/sum of time at risk (days) over all subjects/365.25) measured in terms of number of events per 100 subject-years was reported. ITT population. Data was planned to be collected and analysed for pooled population of subjects who received Efpeglenatide (at any dose:4mg/6mg) as pre-specified in protocol.

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

End point timeframe:

From Day 1 until the confirmed occurrence of composite renal endpoint (maximum duration: up to 31.5 months)

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data was reported for applicable arms in the endpoint.

| End point values                    | Placebo             | Efpeglenatide 4 mg+6 mg |  |  |
|-------------------------------------|---------------------|-------------------------|--|--|
| Subject group type                  | Reporting group     | Subject analysis set    |  |  |
| Number of subjects analysed         | 1359                | 2717                    |  |  |
| Units: events per 100 subject-years |                     |                         |  |  |
| number (confidence interval 95%)    | 11.6 (10.2 to 13.1) | 7.7 (6.9 to 8.6)        |  |  |

## Statistical analyses

| Statistical analysis title | Efpeglenatide 4 mg+6 mg versus Placebo |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

Hazard ratio and 95% CI were obtained from a Cox proportional hazards model with region (North America, Latin America, Europe, other), randomisation stratum of SGLT2 inhibitor use (current use, potential future use, neither current nor potential future use) and treatment (efpeglenatide 4 mg, efpeglenatide 6 mg, placebo) as fixed effect factor.

|   |                                   |
|---|-----------------------------------|
| Comparison groups                       | Placebo v Efpeglenatide 4 mg+6 mg |
| Number of subjects included in analysis | 4076                              |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority <sup>[11]</sup>       |
| P-value                                 | < 0.0001 <sup>[12]</sup>          |
| Method                                  | Logrank                           |
| Parameter estimate                      | Hazard ratio (HR)                 |
| Point estimate                          | 0.675                             |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | 0.574                             |
| upper limit                             | 0.794                             |

Notes:

[11] - Superiority was claimed when the upper bound of the 2-sided 95% CI of hazard ratio was less than 1.

[12] - Two-sided p-values based on log rank test of hazard ratio.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) data were collected from time of first injection of investigational medicinal product (IMP) to the last injection of IMP + 30 days (i.e., up to maximum duration of 31.5 months).

Adverse event reporting additional description:

AEs and deaths were treatment-emergent AEs (TEAEs): AEs that developed/worsened/became serious during the TEAE period (time from 1st to last injection of IMP + 30 days). Safety population: all randomised subjects who received at least 1 dose of double-blind treatment, regardless of amount of treatment administered, analysed according to treatment.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 23.1 |
|--------------------|------|

### Reporting groups

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

Reporting group description:

Subjects received placebo (matched to Efteglenatide) as SC injection once weekly up to end of treatment (median duration: 19.8 months).

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Efteglenatide 4 mg |
|-----------------------|--------------------|

Reporting group description:

Subjects received Efteglenatide as SC injection 2 mg per week for 4 weeks then 4 mg per week up to end of treatment (median duration: 19.9 months).

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Efteglenatide 6 mg |
|-----------------------|--------------------|

Reporting group description:

Subjects received Efteglenatide as SC injection 2 mg per week for 4 weeks, then 4 mg per week for 4 weeks and then 6 mg per week up to end of treatment (median duration: 20 months).

| Serious adverse events  | Placebo                | Efteglenatide 4 mg     | Efteglenatide 6 mg     |
|---|------------------------|------------------------|------------------------|
| Total subjects affected by serious adverse events                   |                        |                        |                        |
| subjects affected / exposed   | 298 / 1355<br>(21.99%) | 312 / 1360<br>(22.94%) | 275 / 1358<br>(20.25%) |
| number of deaths (all causes)                                       | 49                     | 40                     | 25                     |
| number of deaths resulting from adverse events                      |                        |                        |                        |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                        |                        |                        |
| Adenocarcinoma Metastatic   |                        |                        |                        |
| subjects affected / exposed   | 1 / 1355 (0.07%)       | 0 / 1360 (0.00%)       | 0 / 1358 (0.00%)       |
| occurrences causally related to treatment / all                     | 0 / 1                  | 0 / 0                  | 0 / 0                  |
| deaths causally related to treatment / all                          | 0 / 1                  | 0 / 0                  | 0 / 0                  |
| Adenocarcinoma Of Colon   |                        |                        |                        |
| subjects affected / exposed   | 1 / 1355 (0.07%)       | 1 / 1360 (0.07%)       | 3 / 1358 (0.22%)       |
| occurrences causally related to treatment / all                     | 0 / 1                  | 0 / 1                  | 0 / 3                  |
| deaths causally related to treatment / all                          | 0 / 0                  | 0 / 0                  | 0 / 0                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| Adenocarcinoma Pancreas                         |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Basal Cell Carcinoma                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Benign Neoplasm Of Scrotum                      |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Benign Neoplasm Of Skin                         |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Bladder Cancer                                  |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Bladder Cancer Recurrent                        |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Bladder Neoplasm                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Bladder Transitional Cell Carcinoma             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 3 / 1360 (0.22%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Breast Cancer                                   |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Breast Cancer Metastatic                        |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 1            |
| Cholangiocarcinoma                              |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0            |
| Chronic Lymphocytic Leukaemia                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Colon Cancer                                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Colorectal Cancer Metastatic                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0            |
| Cutaneous T-Cell Lymphoma                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Diffuse Large B-Cell Lymphoma Stage Iv          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Endometrial Cancer                              |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hepatocellular Carcinoma                        |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Leiomyosarcoma                                  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Lung Adenocarcinoma                             |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Lung Neoplasm Malignant                         |                  |                  |                  |
| subjects affected / exposed                     | 4 / 1355 (0.30%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            | 0 / 0            |
| Lung Cancer Metastatic                          |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 1            |
| Metastases To Liver                             |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0            |
| Metastases To Lung                              |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0            |
| Neuroendocrine Tumour Of The Lung Metastatic    |                  |                  |                  |



|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Non-Small Cell Lung Cancer Stage Iv             |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Oesophageal Adenocarcinoma Stage Iv             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0            |
| Oesophageal Carcinoma                           |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pancreatic Carcinoma                            |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0            |
| Pancreatic Carcinoma Metastatic                 |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Papillary Thyroid Cancer                        |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Prostate Cancer                                 |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 2 / 1360 (0.15%) | 3 / 1358 (0.22%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Prostate Cancer Metastatic                      |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Prostate Cancer Recurrent                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Prostatic Adenoma                               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Rectal Adenocarcinoma                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Rectal Cancer                                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Rectosigmoid Cancer Metastatic                  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Renal Cancer                                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Renal Cell Carcinoma                            |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Renal Cell Carcinoma Stage Iv                   |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Renal Neoplasm                                  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Renal Oncocytoma                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Small Cell Lung Cancer Metastatic               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 1            |
| Spinal Cord Neoplasm                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Squamous Cell Carcinoma                         |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Squamous Cell Carcinoma Of The Oral Cavity      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Thyroid Cancer                                  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Transitional Cell Carcinoma                     |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Vascular disorders                              |                  |                  |                  |
| Arterial Haemorrhage                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Aortic Stenosis                                 |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Arterial Occlusive Disease                      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Deep Vein Thrombosis                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Arteriosclerosis                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Dry Gangrene                                    |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Diabetic Vascular Disorder                      |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Essential Hypertension                          |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Extremity Necrosis                              |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 2 / 1360 (0.15%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hypertension                                    |                  |                  |                  |
| subjects affected / exposed                     | 3 / 1355 (0.22%) | 1 / 1360 (0.07%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hypertensive Emergency                          |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hypertensive Crisis                             |                  |                  |                  |
| subjects affected / exposed                     | 4 / 1355 (0.30%) | 4 / 1360 (0.29%) | 3 / 1358 (0.22%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 4            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0            |
| Hypotension                                     |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 4 / 1360 (0.29%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Intermittent Claudication                       |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Orthostatic Hypotension                         |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Lymphoedema                                     |                  |                  |                  |

|   |                  |                  |                   |
|---|------------------|------------------|-------------------|
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Peripheral Arterial Occlusive Disease           |                  |                  |                   |
| subjects affected / exposed                     | 8 / 1355 (0.59%) | 7 / 1360 (0.51%) | 10 / 1358 (0.74%) |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 8            | 0 / 10            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Peripheral Artery Stenosis                      |                  |                  |                   |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Peripheral Artery Occlusion                     |                  |                  |                   |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 1 / 1358 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Peripheral Circulatory Failure                  |                  |                  |                   |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Peripheral Artery Thrombosis                    |                  |                  |                   |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 2 / 1360 (0.15%) | 0 / 1358 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0             |
| Peripheral Embolism                             |                  |                  |                   |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Peripheral Ischaemia                            |                  |                  |                   |
| subjects affected / exposed                     | 3 / 1355 (0.22%) | 1 / 1360 (0.07%) | 2 / 1358 (0.15%)  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            | 0 / 3             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Peripheral Vascular Disorder                    |                  |                  |                   |

|  |                  |                  |                  |
|--|------------------|------------------|------------------|
| subjects affected / exposed                          | 5 / 1355 (0.37%) | 2 / 1360 (0.15%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 5            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            | 0 / 0            |
| Thrombosis   |                  |                  |                  |
| subjects affected / exposed                          | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            | 0 / 0            |
| Venous Thrombosis Limb                               |                  |                  |                  |
| subjects affected / exposed                          | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            | 0 / 0            |
| General disorders and administration site conditions |                  |                  |                  |
| Accidental Death                                     |                  |                  |                  |
| subjects affected / exposed                          | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            | 0 / 1            |
| Asthenia   |                  |                  |                  |
| subjects affected / exposed                          | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 3 / 1358 (0.22%) |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 1            | 0 / 3            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            | 0 / 0            |
| Cardiac Death  |                  |                  |                  |
| subjects affected / exposed                          | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all           | 0 / 1            | 0 / 1            | 0 / 0            |
| Chest Pain   |                  |                  |                  |
| subjects affected / exposed                          | 1 / 1355 (0.07%) | 2 / 1360 (0.15%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            | 0 / 0            |
| Death  |                  |                  |                  |
| subjects affected / exposed                          | 4 / 1355 (0.30%) | 5 / 1360 (0.37%) | 4 / 1358 (0.29%) |
| occurrences causally related to treatment / all      | 0 / 4            | 1 / 5            | 0 / 4            |
| deaths causally related to treatment / all           | 0 / 4            | 1 / 5            | 0 / 4            |
| Fatigue  |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Impaired Healing                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Non-Cardiac Chest Pain                          |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 6 / 1360 (0.44%) | 5 / 1358 (0.37%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 6            | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Peripheral Swelling                             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pyrexia   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Sudden Cardiac Death                            |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 5 / 1360 (0.37%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 2            | 1 / 5            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 2            | 1 / 5            | 0 / 2            |
| Vascular Stent Stenosis                         |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Sudden Death                                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 2 / 1360 (0.15%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 2            | 0 / 1            |
| Vascular Stent Thrombosis                       |                  |                  |                  |



|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Immune system disorders                         |                  |                  |                  |
| Drug Hypersensitivity                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hypersensitivity                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Reproductive system and breast disorders        |                  |                  |                  |
| Cervical Polyp                                  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Benign Prostatic Hyperplasia                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 2 / 1360 (0.15%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Endometriosis                                   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Postmenopausal Haemorrhage                      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Prostatic Atrophy                               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| Prostatitis                                     |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Respiratory, thoracic and mediastinal disorders |                  |                  |                  |
| Acute Pulmonary Oedema                          |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 1            |
| Acute Respiratory Distress Syndrome             |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0            |
| Acute Respiratory Failure                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 2 / 1360 (0.15%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0            |
| Asthma  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Bronchitis Chronic                              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Chronic Obstructive Pulmonary Disease           |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 4 / 1360 (0.29%) | 4 / 1358 (0.29%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            | 0 / 7            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Dyspnoea  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 2 / 1360 (0.15%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| Epistaxis                                       |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Lung Disorder                                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pleural Effusion                                |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0            |
| Pleurocutaneous Fistula                         |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pneumonia Aspiration                            |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pneumonitis                                     |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pneumothorax                                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pulmonary Embolism                              |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 2 / 1360 (0.15%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            | 0 / 0            |
| Pulmonary Oedema                                |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 3 / 1360 (0.22%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Respiratory Failure                             |                  |                  |                  |
| subjects affected / exposed                     | 3 / 1355 (0.22%) | 1 / 1360 (0.07%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 1            |
| Sleep Apnoea Syndrome                           |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Psychiatric disorders                           |                  |                  |                  |
| Delirium  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Depression                                      |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Major Depression                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Panic Attack                                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Suicidal Ideation                               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Product issues                                  |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| Device Fastener Issue                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Device Lead Issue                               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Device Loosening                                |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Investigations                                  |                  |                  |                  |
| Alanine Aminotransferase Increased              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Anticoagulation Drug Level Above Therapeutic    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Aspartate Aminotransferase Increased            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Blood Glucose Increased                         |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Blood Pressure Decreased                        |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| Blood Pressure Increased                        |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Heart Rate Abnormal                             |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hepatic Enzyme Increased                        |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Lipase Increased                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Liver Function Test Abnormal                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Plasminogen Activator Inhibitor Increased       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Troponin Increased                              |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Weight Decreased                                |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0            |
| Injury, poisoning and procedural complications  |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| Accidental Overdose                             |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 2 / 1360 (0.15%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Ankle Fracture                                  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Anastomotic Complication                        |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Arterial Bypass Occlusion                       |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Arterial Bypass Stenosis                        |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Brachial Plexus Injury                          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Craniocerebral Injury                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Fall  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 2 / 1360 (0.15%) | 4 / 1358 (0.29%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Femoral Neck Fracture                           |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Femur Fracture                                  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 3 / 1360 (0.22%) | 3 / 1358 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Fibula Fracture                                 |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Foot Fracture                                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Heat Exhaustion                                 |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hip Fracture                                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Humerus Fracture                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Joint Dislocation                               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Joint Injury                                    |                  |                  |                  |



|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Limb Injury                                     |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Limb Traumatic Amputation                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Lower Limb Fracture                             |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Lumbar Vertebral Fracture                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Meniscus Injury                                 |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 2 / 1360 (0.15%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Neck Injury                                     |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0            |
| Patella Fracture                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Peripheral Artery Restenosis                    |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Periprosthetic Fracture                         |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Postoperative Respiratory Failure               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Procedural Site Reaction                        |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Radius Fracture                                 |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Rib Fracture                                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Road Traffic Accident                           |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 2 / 1360 (0.15%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0            |
| Scapula Fracture                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Skin Laceration                                 |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Spinal Compression Fracture                     |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Spinal Fracture                                 |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Stomal Hernia                                   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Subdural Haematoma                              |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0            |
| Tibia Fracture                                  |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Upper Limb Fracture                             |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Vascular Graft Thrombosis                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Vascular Pseudoaneurysm                         |                  |                  |                  |

|   |                   |                   |                   |
|---|-------------------|-------------------|-------------------|
| subjects affected / exposed                     | 0 / 1355 (0.00%)  | 1 / 1360 (0.07%)  | 0 / 1358 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Wrist Fracture                                  |                   |                   |                   |
| subjects affected / exposed                     | 0 / 1355 (0.00%)  | 0 / 1360 (0.00%)  | 1 / 1358 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Congenital, familial and genetic disorders      |                   |                   |                   |
| Hypertrophic Cardiomyopathy                     |                   |                   |                   |
| subjects affected / exposed                     | 0 / 1355 (0.00%)  | 1 / 1360 (0.07%)  | 0 / 1358 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Cardiac disorders                               |                   |                   |                   |
| Acute Coronary Syndrome                         |                   |                   |                   |
| subjects affected / exposed                     | 0 / 1355 (0.00%)  | 1 / 1360 (0.07%)  | 0 / 1358 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Acute Left Ventricular Failure                  |                   |                   |                   |
| subjects affected / exposed                     | 0 / 1355 (0.00%)  | 1 / 1360 (0.07%)  | 2 / 1358 (0.15%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Acute Myocardial Infarction                     |                   |                   |                   |
| subjects affected / exposed                     | 2 / 1355 (0.15%)  | 1 / 1360 (0.07%)  | 2 / 1358 (0.15%)  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 0             | 0 / 1             |
| Angina Pectoris                                 |                   |                   |                   |
| subjects affected / exposed                     | 10 / 1355 (0.74%) | 8 / 1360 (0.59%)  | 17 / 1358 (1.25%) |
| occurrences causally related to treatment / all | 0 / 13            | 0 / 8             | 1 / 17            |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             | 0 / 0             |
| Angina Unstable                                 |                   |                   |                   |
| subjects affected / exposed                     | 23 / 1355 (1.70%) | 20 / 1360 (1.47%) | 10 / 1358 (0.74%) |
| occurrences causally related to treatment / all | 0 / 29            | 0 / 23            | 0 / 11            |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 1             | 0 / 0             |

|   |                   |                   |                   |
|---|-------------------|-------------------|-------------------|
| Aortic Valve Stenosis                           |                   |                   |                   |
| subjects affected / exposed                     | 0 / 1355 (0.00%)  | 2 / 1360 (0.15%)  | 1 / 1358 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Arrhythmia Supraventricular                     |                   |                   |                   |
| subjects affected / exposed                     | 1 / 1355 (0.07%)  | 0 / 1360 (0.00%)  | 0 / 1358 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Arteriosclerosis Coronary Artery                |                   |                   |                   |
| subjects affected / exposed                     | 0 / 1355 (0.00%)  | 0 / 1360 (0.00%)  | 2 / 1358 (0.15%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Atrial Fibrillation                             |                   |                   |                   |
| subjects affected / exposed                     | 12 / 1355 (0.89%) | 15 / 1360 (1.10%) | 12 / 1358 (0.88%) |
| occurrences causally related to treatment / all | 0 / 16            | 0 / 17            | 0 / 13            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             | 0 / 0             |
| Atrial Flutter                                  |                   |                   |                   |
| subjects affected / exposed                     | 2 / 1355 (0.15%)  | 2 / 1360 (0.15%)  | 5 / 1358 (0.37%)  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 2             | 0 / 6             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Atrial Tachycardia                              |                   |                   |                   |
| subjects affected / exposed                     | 1 / 1355 (0.07%)  | 1 / 1360 (0.07%)  | 0 / 1358 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Atrioventricular Block                          |                   |                   |                   |
| subjects affected / exposed                     | 0 / 1355 (0.00%)  | 1 / 1360 (0.07%)  | 1 / 1358 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Atrioventricular Block Complete                 |                   |                   |                   |
| subjects affected / exposed                     | 4 / 1355 (0.30%)  | 1 / 1360 (0.07%)  | 1 / 1358 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 1             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0             |
| Bradyarrhythmia                                 |                   |                   |                   |

|   |                   |                  |                  |
|---|-------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 1355 (0.00%)  | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| Bradycardia                                     |                   |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%)  | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| Bundle Branch Block Left                        |                   |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%)  | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| Cardiac Arrest                                  |                   |                  |                  |
| subjects affected / exposed                     | 5 / 1355 (0.37%)  | 2 / 1360 (0.15%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 4             | 0 / 1            | 0 / 0            |
| Cardiac Discomfort                              |                   |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%)  | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            | 0 / 0            |
| Cardiac Failure                                 |                   |                  |                  |
| subjects affected / exposed                     | 12 / 1355 (0.89%) | 4 / 1360 (0.29%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 12            | 0 / 4            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 3            | 0 / 0            |
| Cardiac Failure Acute                           |                   |                  |                  |
| subjects affected / exposed                     | 3 / 1355 (0.22%)  | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0            | 0 / 0            |
| Cardiac Failure Chronic                         |                   |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%)  | 4 / 1360 (0.29%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 4            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1            | 0 / 0            |
| Cardiac Failure Congestive                      |                   |                  |                  |

|   |                   |                   |                  |
|---|-------------------|-------------------|------------------|
| subjects affected / exposed                     | 3 / 1355 (0.22%)  | 2 / 1360 (0.15%)  | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 2             | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 2             | 0 / 0            |
| Cardiac Valve Disease                           |                   |                   |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%)  | 0 / 1360 (0.00%)  | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0            |
| Cardio-Respiratory Arrest                       |                   |                   |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%)  | 0 / 1360 (0.00%)  | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             | 0 / 0            |
| Cardiogenic Shock                               |                   |                   |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%)  | 1 / 1360 (0.07%)  | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 1             | 0 / 1            |
| Cardiomyopathy                                  |                   |                   |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%)  | 0 / 1360 (0.00%)  | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0            |
| Cardiomyopathy Acute                            |                   |                   |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%)  | 0 / 1360 (0.00%)  | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0             | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0            |
| Cardiovascular Insufficiency                    |                   |                   |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%)  | 1 / 1360 (0.07%)  | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             | 0 / 0            |
| Coronary Artery Disease                         |                   |                   |                  |
| subjects affected / exposed                     | 10 / 1355 (0.74%) | 14 / 1360 (1.03%) | 5 / 1358 (0.37%) |
| occurrences causally related to treatment / all | 0 / 11            | 0 / 14            | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             | 0 / 0            |
| Coronary Artery Occlusion                       |                   |                   |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 2 / 1360 (0.15%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Coronary Artery Stenosis                        |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 3 / 1360 (0.22%) | 3 / 1358 (0.22%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Left Ventricular Dysfunction                    |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Left Ventricular Failure                        |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0            |
| Mitral Valve Incompetence                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Myocardial Infarction                           |                  |                  |                  |
| subjects affected / exposed                     | 9 / 1355 (0.66%) | 4 / 1360 (0.29%) | 6 / 1358 (0.44%) |
| occurrences causally related to treatment / all | 0 / 10           | 0 / 4            | 0 / 6            |
| deaths causally related to treatment / all      | 0 / 5            | 0 / 2            | 0 / 3            |
| Myocardial Ischaemia                            |                  |                  |                  |
| subjects affected / exposed                     | 4 / 1355 (0.30%) | 0 / 1360 (0.00%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pericarditis                                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Sinus Node Dysfunction                          |                  |                  |                  |



|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 3 / 1358 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Sinus Tachycardia                               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Supraventricular Tachycardia                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 3 / 1358 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Tachycardia                                     |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 2 / 1360 (0.15%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Tricuspid Valve Incompetence                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Ventricular Arrhythmia                          |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Ventricular Tachycardia                         |                  |                  |                  |
| subjects affected / exposed                     | 3 / 1355 (0.22%) | 3 / 1360 (0.22%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 4            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Nervous system disorders                        |                  |                  |                  |
| Brain Injury                                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Carotid Artery Disease                          |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Carotid Artery Stenosis                         |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 3 / 1360 (0.22%) | 4 / 1358 (0.29%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            | 0 / 6            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Carotid Sinus Syndrome                          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Carpal Tunnel Syndrome                          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 3 / 1360 (0.22%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cerebrovascular Accident                        |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 2 / 1360 (0.15%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            | 0 / 0            |
| Cerebrovascular Disorder                        |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0            |
| Cerebrovascular Insufficiency                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cervical Radiculopathy                          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cervicobrachial Syndrome                        |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Diabetic Hyperosmolar Coma                      |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Dizziness                                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Encephalopathy                                  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Facial Paralysis                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Haemorrhagic Stroke                             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 1            |
| Headache  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hepatic Encephalopathy                          |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hydrocephalus                                   |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hypoglycaemic Encephalopathy                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hypoglycaemic Seizure                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 2 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hypoglycaemic Unconsciousness                   |                  |                  |                  |
| subjects affected / exposed                     | 4 / 1355 (0.30%) | 2 / 1360 (0.15%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 1 / 4            | 0 / 2            | 2 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Ischaemic Stroke                                |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Lacunar Stroke                                  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Lumbosacral Radiculopathy                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Metabolic Encephalopathy                        |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Myasthenia Gravis                               |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Myelopathy                                      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Neuropathy Peripheral                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Paraesthesia                                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Presyncope                                      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Radiculopathy                                   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Sciatica  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Seizure   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 3 / 1358 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Senile Dementia                                 |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Syncope   |                  |                  |                  |
| subjects affected / exposed                     | 4 / 1355 (0.30%) | 4 / 1360 (0.29%) | 7 / 1358 (0.52%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 5            | 0 / 7            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Toxic Encephalopathy                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Transient Ischaemic Attack                      |                  |                  |                  |
| subjects affected / exposed                     | 3 / 1355 (0.22%) | 4 / 1360 (0.29%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 4            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Vith Nerve Paralysis                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Vocal Cord Paresis                              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Blood and lymphatic system disorders            |                  |                  |                  |
| Acquired Haemophilia                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Anaemia   |                  |                  |                  |
| subjects affected / exposed                     | 3 / 1355 (0.22%) | 2 / 1360 (0.15%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Anaemia Vitamin B12 Deficiency                  |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Autoimmune Haemolytic Anaemia                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Blood Loss Anaemia                              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hypochromic Anaemia                             |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Iron Deficiency Anaemia                         |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Ear and labyrinth disorders                     |                  |                  |                  |
| Deafness Neurosensory                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Deafness Unilateral                             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Meniere's Disease                               |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Vertigo   |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Vertigo Positional                              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Vestibular Disorder                             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Eye disorders                                   |                  |                  |                  |
| Cataract  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Eyelid Ptosis                                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Open Angle Glaucoma                             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Retinal Artery Embolism                         |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Retinal Detachment                              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Vitreous Haemorrhage                            |                  |                  |                  |



|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| <b>Gastrointestinal disorders</b>               |                  |                  |                  |
| Abdominal Incarcerated Hernia                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Abdominal Pain                                  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Abdominal Pain Upper                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Abdominal Strangulated Hernia                   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Ascites   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Chronic Gastritis                               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 2 / 1360 (0.15%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Colitis   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 5 / 1358 (0.37%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 6            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Colitis Ischaemic                               |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Diabetic Gastroparesis                          |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Diarrhoea                                       |                  |                  |                  |
| subjects affected / exposed                     | 3 / 1355 (0.22%) | 2 / 1360 (0.15%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Diverticulum                                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Diverticulum Intestinal Haemorrhagic            |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Duodenal Ulcer                                  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Duodenitis                                      |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Dyspepsia                                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Faecaloma                                       |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 2 / 1360 (0.15%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gastric Ulcer                                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gastric Ulcer Haemorrhage                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gastritis                                       |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gastritis Erosive                               |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gastrointestinal Haemorrhage                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gastrointestinal Perforation                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gastrooesophageal Reflux Disease                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gastrooesophageal Sphincter Insufficiency       |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Ileus   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0            |
| Inguinal Hernia                                 |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 2 / 1360 (0.15%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Intestinal Ischaemia                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 1            |
| Intestinal Obstruction                          |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Intra-Abdominal Haemorrhage                     |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Large Intestine Polyp                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Mallory-Weiss Syndrome                          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Mechanical Ileus                                |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Mesenteric Artery Stenosis                      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 2 / 1360 (0.15%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Nausea  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Obstructive Pancreatitis                        |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Oesophageal Disorder                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Oesophagitis                                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Palatal Disorder                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pancreatitis Acute                              |                  |                  |                  |
| subjects affected / exposed                     | 4 / 1355 (0.30%) | 3 / 1360 (0.22%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 3 / 4            | 3 / 3            | 1 / 2            |
| deaths causally related to treatment / all      | 1 / 2            | 0 / 0            | 0 / 1            |
| Pancreatitis Chronic                            |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Peptic Ulcer                                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Retroperitoneal Haemorrhage                     |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Small Intestinal Obstruction                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Subileus  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Umbilical Hernia                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Varices Oesophageal                             |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Vomiting  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 3 / 1360 (0.22%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1            | 1 / 3            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hepatobiliary disorders                         |                  |                  |                  |
| Autoimmune Hepatitis                            |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0            |
| Bile Duct Stone                                 |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cholecystitis                                   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 4 / 1360 (0.29%) | 3 / 1358 (0.22%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cholecystitis Acute                             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 4 / 1360 (0.29%) | 3 / 1358 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0            | 2 / 4            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cholecystitis Chronic                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cholelithiasis                                  |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 1 / 1360 (0.07%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cholestasis                                     |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Chronic Hepatitis                               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hepatic Cirrhosis                               |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hepatic Cyst                                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hyperbilirubinaemia                             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hyperplastic Cholecystopathy                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Jaundice  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Skin and subcutaneous tissue disorders          |                  |                  |                  |
| Angioedema                                      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 2 / 1360 (0.15%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Dermal Cyst                                     |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Diabetic Foot                                   |                  |                  |                  |
| subjects affected / exposed                     | 8 / 1355 (0.59%) | 8 / 1360 (0.59%) | 4 / 1358 (0.29%) |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 8            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Haemorrhage Subcutaneous                        |                  |                  |                  |



|   |                  |                   |                   |
|---|------------------|-------------------|-------------------|
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%)  | 0 / 1358 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Ischaemic Skin Ulcer                            |                  |                   |                   |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%)  | 0 / 1358 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Skin Ulcer                                      |                  |                   |                   |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 5 / 1360 (0.37%)  | 1 / 1358 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 5             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Renal and urinary disorders                     |                  |                   |                   |
| Acute Kidney Injury                             |                  |                   |                   |
| subjects affected / exposed                     | 9 / 1355 (0.66%) | 10 / 1360 (0.74%) | 10 / 1358 (0.74%) |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 10            | 0 / 11            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1             | 0 / 2             |
| Chronic Kidney Disease                          |                  |                   |                   |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 2 / 1360 (0.15%)  | 1 / 1358 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Diabetic Nephropathy                            |                  |                   |                   |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%)  | 1 / 1358 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Haematuria                                      |                  |                   |                   |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%)  | 1 / 1358 (0.07%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Hydronephrosis                                  |                  |                   |                   |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 1 / 1360 (0.07%)  | 0 / 1358 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0             |
| Nephrolithiasis                                 |                  |                   |                   |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 2 / 1360 (0.15%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Nephropathy Toxic                               |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Renal Colic                                     |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Renal Failure                                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Renal Impairment                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 2 / 1360 (0.15%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Tubulointerstitial Nephritis                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Ureterolithiasis                                |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Urinary Bladder Polyp                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Urinary Retention                               |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Endocrine disorders                             |                  |                  |                  |
| Goitre  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Thyroid Mass                                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Thyroiditis Chronic                             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Musculoskeletal and connective tissue disorders |                  |                  |                  |
| Arthralgia                                      |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Arthropathy                                     |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Back Pain                                       |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 2 / 1360 (0.15%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Bursitis  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| Cervical Spinal Stenosis                        |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Exostosis                                       |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Groin Pain                                      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Intervertebral Disc Degeneration                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Intervertebral Disc Protrusion                  |                  |                  |                  |
| subjects affected / exposed                     | 3 / 1355 (0.22%) | 1 / 1360 (0.07%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Lumbar Spinal Stenosis                          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 2 / 1360 (0.15%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Meniscal Degeneration                           |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Muscular Weakness                               |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Osteoarthritis                                  |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 4 / 1355 (0.30%) | 2 / 1360 (0.15%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 4            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Osteochondritis                                 |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Osteochondrosis                                 |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pain In Extremity                               |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pathological Fracture                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Polymyalgia Rheumatica                          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Rotator Cuff Syndrome                           |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 3 / 1360 (0.22%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Spinal Osteoarthritis                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Spinal Pain                                     |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Spinal Stenosis                                 |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Infections and infestations                     |                  |                  |                  |
| Abscess Soft Tissue                             |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Appendicitis                                    |                  |                  |                  |
| subjects affected / exposed                     | 3 / 1355 (0.22%) | 1 / 1360 (0.07%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Arthritis Bacterial                             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 2 / 1360 (0.15%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0            |
| Atypical Pneumonia                              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Bronchitis                                      |                  |                  |                  |
| subjects affected / exposed                     | 4 / 1355 (0.30%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Bronchitis Bacterial                            |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0            |
| Covid-19  |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 5 / 1355 (0.37%) | 1 / 1360 (0.07%) | 5 / 1358 (0.37%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 1            | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            | 0 / 2            |
| Covid-19 Pneumonia                              |                  |                  |                  |
| subjects affected / exposed                     | 5 / 1355 (0.37%) | 7 / 1360 (0.51%) | 6 / 1358 (0.44%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 7            | 0 / 6            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 2            | 0 / 3            |
| Campylobacter Gastroenteritis                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cellulitis                                      |                  |                  |                  |
| subjects affected / exposed                     | 6 / 1355 (0.44%) | 3 / 1360 (0.22%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 3            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cholangitis Infective                           |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0            |
| Chronic Sinusitis                               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Cystitis  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 2 / 1360 (0.15%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Dermatitis Infected                             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Diabetic Foot Infection                         |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Diabetic Gangrene                               |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 1 / 1360 (0.07%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Disseminated Tuberculosis                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Diverticulitis                                  |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 3 / 1360 (0.22%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Enterococcal Bacteraemia                        |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Escherichia Bacteraemia                         |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Escherichia Sepsis                              |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Escherichia Urinary Tract Infection             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gangrene  |                  |                  |                  |



|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 3 / 1355 (0.22%) | 1 / 1360 (0.07%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gastroenteritis                                 |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 0 / 1360 (0.00%) | 6 / 1358 (0.44%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 1 / 7            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gastroenteritis Salmonella                      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gastroenteritis Viral                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gastrointestinal Infection                      |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Groin Abscess                                   |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| H1n1 Influenza                                  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hepatitis C                                     |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hepatitis E                                     |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Herpes Zoster Infection Neurological            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Influenza                                       |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 4 / 1360 (0.29%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Joint Abscess                                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Klebsiella Sepsis                               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Large Intestine Infection                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Laryngitis                                      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Localised Infection                             |                  |                  |                  |
| subjects affected / exposed                     | 4 / 1355 (0.30%) | 2 / 1360 (0.15%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Mastoiditis                                     |                  |                  |                  |

|   |                   |                   |                  |
|---|-------------------|-------------------|------------------|
| subjects affected / exposed                     | 0 / 1355 (0.00%)  | 1 / 1360 (0.07%)  | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0            |
| Mediastinitis                                   |                   |                   |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%)  | 0 / 1360 (0.00%)  | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0            |
| Oesophageal Abscess                             |                   |                   |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%)  | 1 / 1360 (0.07%)  | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0            |
| Osteomyelitis                                   |                   |                   |                  |
| subjects affected / exposed                     | 5 / 1355 (0.37%)  | 2 / 1360 (0.15%)  | 3 / 1358 (0.22%) |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 2             | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0            |
| Peritonitis                                     |                   |                   |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%)  | 2 / 1360 (0.15%)  | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0            |
| Pilonidal Cyst                                  |                   |                   |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%)  | 1 / 1360 (0.07%)  | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0            |
| Pneumonia                                       |                   |                   |                  |
| subjects affected / exposed                     | 15 / 1355 (1.11%) | 14 / 1360 (1.03%) | 9 / 1358 (0.66%) |
| occurrences causally related to treatment / all | 0 / 16            | 0 / 14            | 0 / 9            |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 1             | 0 / 2            |
| Pneumonia Bacterial                             |                   |                   |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%)  | 0 / 1360 (0.00%)  | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0             | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0            |
| Pneumonia Influenzal                            |                   |                   |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pneumonia Klebsiella                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pneumonia Mycoplasmal                           |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pneumonia Staphylococcal                        |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pneumonia Viral                                 |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Postoperative Wound Infection                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 5 / 1360 (0.37%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 5            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pulmonary Tuberculosis                          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pyelonephritis                                  |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pyelonephritis Acute                            |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pyelonephritis Chronic                          |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Renal Cyst Infection                            |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Salpingitis                                     |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Scrub Typhus                                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Sepsis  |                  |                  |                  |
| subjects affected / exposed                     | 9 / 1355 (0.66%) | 4 / 1360 (0.29%) | 4 / 1358 (0.29%) |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 4            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 1            |
| Septic Shock                                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 2 / 1360 (0.15%) | 3 / 1358 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 1            |
| Sinusitis                                       |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Skin Infection                                  |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Soft Tissue Infection                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Staphylococcal Bacteraemia                      |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Staphylococcal Sepsis                           |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0            |
| Subcutaneous Abscess                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Suspected Covid-19                              |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 0            |
| Tuberculosis                                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Tuberculosis Gastrointestinal                   |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Upper Respiratory Tract Infection               |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Urinary Tract Infection                         |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 7 / 1360 (0.51%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 7            | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Urinary Tract Infection Enterococcal            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Urosepsis                                       |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Vulval Abscess                                  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Wound Infection                                 |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Wound Sepsis                                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Metabolism and nutrition disorders              |                  |                  |                  |
| Dehydration                                     |                  |                  |                  |
| subjects affected / exposed                     | 5 / 1355 (0.37%) | 3 / 1360 (0.22%) | 6 / 1358 (0.44%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 3            | 1 / 6            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Diabetes Mellitus                               |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 3 / 1355 (0.22%) | 0 / 1360 (0.00%) | 3 / 1358 (0.22%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Diabetes Mellitus Inadequate Control            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 3 / 1360 (0.22%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 5            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Diabetic Ketoacidosis                           |                  |                  |                  |
| subjects affected / exposed                     | 3 / 1355 (0.22%) | 2 / 1360 (0.15%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 3            | 1 / 2            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0            |
| Diabetic Metabolic Decompensation               |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 2 / 1360 (0.15%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Food Intolerance                                |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Gout  |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 1 / 1360 (0.07%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hyperglycaemia                                  |                  |                  |                  |
| subjects affected / exposed                     | 5 / 1355 (0.37%) | 8 / 1360 (0.59%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 9            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hyperglycaemic Hyperosmolar Nonketotic Syndrome |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hyperkalaemia                                   |                  |                  |                  |



|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hypoalbuminaemia                                |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hypoglycaemia                                   |                  |                  |                  |
| subjects affected / exposed                     | 3 / 1355 (0.22%) | 8 / 1360 (0.59%) | 4 / 1358 (0.29%) |
| occurrences causally related to treatment / all | 0 / 3            | 1 / 8            | 0 / 6            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hypokalaemia                                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 1 / 1360 (0.07%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hypomagnesaemia                                 |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Hyponatraemia                                   |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 0            |
| Hypovolaemia                                    |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Lactic Acidosis                                 |                  |                  |                  |
| subjects affected / exposed                     | 1 / 1355 (0.07%) | 0 / 1360 (0.00%) | 1 / 1358 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Metabolic Acidosis                              |                  |                  |                  |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 0 / 1355 (0.00%) | 0 / 1360 (0.00%) | 2 / 1358 (0.15%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Type 2 Diabetes Mellitus                        |                  |                  |                  |
| subjects affected / exposed                     | 2 / 1355 (0.15%) | 0 / 1360 (0.00%) | 0 / 1358 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |

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

| <b>Non-serious adverse events</b>                     | Placebo             | Efpeglenatide 4 mg  | Efpeglenatide 6 mg  |
|---|---------------------|---------------------|---------------------|
| Total subjects affected by non-serious adverse events |                     |                     |                     |
| subjects affected / exposed                           | 151 / 1355 (11.14%) | 348 / 1360 (25.59%) | 342 / 1358 (25.18%) |
| Gastrointestinal disorders                            |                     |                     |                     |
| Diarrhoea   |                     |                     |                     |
| subjects affected / exposed                           | 64 / 1355 (4.72%)   | 116 / 1360 (8.53%)  | 117 / 1358 (8.62%)  |
| occurrences (all)                                     | 69                  | 139                 | 153                 |
| Nausea  |                     |                     |                     |
| subjects affected / exposed                           | 51 / 1355 (3.76%)   | 196 / 1360 (14.41%) | 167 / 1358 (12.30%) |
| occurrences (all)                                     | 60                  | 282                 | 194                 |
| Vomiting  |                     |                     |                     |
| subjects affected / exposed                           | 18 / 1355 (1.33%)   | 85 / 1360 (6.25%)   | 75 / 1358 (5.52%)   |
| occurrences (all)                                     | 19                  | 106                 | 95                  |
| Metabolism and nutrition disorders                    |                     |                     |                     |
| Decreased Appetite                                    |                     |                     |                     |
| subjects affected / exposed                           | 15 / 1355 (1.11%)   | 68 / 1360 (5.00%)   | 77 / 1358 (5.67%)   |
| occurrences (all)                                     | 16                  | 74                  | 80                  |
| Hypoglycaemia   |                     |                     |                     |
| subjects affected / exposed                           | 37 / 1355 (2.73%)   | 73 / 1360 (5.37%)   | 53 / 1358 (3.90%)   |
| occurrences (all)                                     | 81                  | 159                 | 97                  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date         | Amendment   |
|--------------|---|
| 28 May 2018  | The following substantial amendment was done - Clarified the contraception requirements for male and woman of childbearing potential (WOCBP): contraception for male subjects not required, ova donation restrictions added, change in contraceptive methods to be used for WOCBP, follow-up of pregnancy extended to one year. |
| 30 July 2018 | The following substantial amendment was done - Added an electrocardiogram assessment at Week 12, when steady state had been achieved, to allow Investigators to assess the effects of efpeglenatide on the heart earlier in the study.  |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated early by the Sponsor but not due to any safety concerns.

Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/34215025>