



## Clinical trial results:

### A trial investigating the cardiovascular safety of oral semaglutide in subjects with type 2 diabetes.

#### Summary

|                          |                         |
|--------------------------|-------------------------|
| EudraCT number           | 2015-003563-10          |
| Trial protocol           | GB NL DK DE ES PL RO IT |
| Global end of trial date | 25 September 2018       |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 05 October 2019 |
| First version publication date | 05 October 2019 |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | NN9924-4221 |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |                 |
|------------------------------------|-----------------|
| ISRCTN number                      | -               |
| ClinicalTrials.gov id (NCT number) | NCT02692716     |
| WHO universal trial number (UTN)   | U1111-1173-0750 |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Novo Nordisk A/S  |
| Sponsor organisation address | Novo Allé, Bagsvaerd, Denmark, 2880   |
| Public contact               | Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com |
| Scientific contact           | Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, clinicaltrials@novonordisk.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 February 2019  |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 25 September 2018 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 25 September 2018 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective is to confirm that treatment with oral semaglutide does not result in an unacceptable increase in cardiovascular risk compared to placebo (rule out 80% excess risk) in subjects with type 2 diabetes at high risk of cardiovascular events.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2013), ICH Good Clinical Practice, including archiving of essential documents, (1996) and 21 CFR 312.120.

Background therapy:

During the trial, all subjects were to receive standard-of-care with regards to glycaemic control, management of complications, comorbidities and cardiovascular (CV) risk factors at the investigator's discretion and according to local practices and guidelines.

Evidence for comparator:

Not applicable

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 17 January 2017 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | Yes             |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Algeria: 75       |
| Country: Number of subjects enrolled | Argentina: 150    |
| Country: Number of subjects enrolled | Brazil: 101       |
| Country: Number of subjects enrolled | Canada: 76        |
| Country: Number of subjects enrolled | Denmark: 71       |
| Country: Number of subjects enrolled | Germany: 110      |
| Country: Number of subjects enrolled | India: 201        |
| Country: Number of subjects enrolled | Israel: 75        |
| Country: Number of subjects enrolled | Italy: 81         |
| Country: Number of subjects enrolled | Malaysia: 151     |
| Country: Number of subjects enrolled | Mexico: 150       |
| Country: Number of subjects enrolled | Netherlands: 80   |
| Country: Number of subjects enrolled | Poland: 120       |
| Country: Number of subjects enrolled | Romania: 100      |
| Country: Number of subjects enrolled | South Africa: 120 |
| Country: Number of subjects enrolled | Spain: 110        |
| Country: Number of subjects enrolled | Taiwan: 75        |

|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | Thailand: 95        |
| Country: Number of subjects enrolled | Turkey: 101         |
| Country: Number of subjects enrolled | United Kingdom: 111 |
| Country: Number of subjects enrolled | United States: 1030 |
| Worldwide total number of subjects   | 3183                |
| EEA total number of subjects         | 783                 |

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)                      | 1334 |
| From 65 to 84 years                       | 1835 |
| 85 years and over                         | 14   |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 214 sites in 21 countries: Algeria (4), Argentina (6), Brazil (1), Canada (7), Denmark (5), Germany (10), India (16), Israel (8), Italy (7), Malaysia (10), Mexico (6), Netherlands (5), Poland (5), Romania (8), South Africa (9), Spain (9), Taiwan (4), Thailand (7), Turkey (9) and United Kingdom (9), United States (69).

### Pre-assignment

Screening details:

Reporting of AEs: Assessment of non-SAEs was unsystematic for the majority of AEs. Non-SAEs were only collected systematically for: 1) AEs leading to discontinuation of trial product; 2) Diabetic retinopathy and related complications; 3) Episodes of severe hypoglycaemia; 4) Hepatic events; 5) Pregnancies and 6) Medication errors.

### 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          |

Blinding implementation details:

All tablets containing oral semaglutide or placebo (irrespective of strength) were identical with regards to visual appearance to maintain the blinding of the trial.

### Arms

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

Arm description:

Subjects received once-daily semaglutide tablets in a dose escalation manner for up to 82 weeks: 3 mg from weeks 1-4, 7 mg from weeks 5-8 and 14 mg from weeks 9 to up to 82.

|  |                  |
|--|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Semaglutide 3 mg |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Tablet           |
| Routes of administration               | Oral use         |

Dosage and administration details:

Semaglutide 3 mg tablets were to be taken from week 1 to 4, once daily in the morning in a fasting state and at least 30 minutes before the first meal of the day. The trial product could be taken with up to half a glass of water (approximately 120 mL/4 fluid ounces) and was to be swallowed whole and not broken or chewed. Oral medication other than trial product could only be taken 30 minutes after administration of trial product. If treatment with the trial product was associated with unacceptable AEs, dose reductions, treatment pauses and extension of dose escalation periods was allowed as per the investigator's discretion.

|  |                  |
|--|------------------|
| Investigational medicinal product name | Semaglutide 7 mg |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Tablet           |
| Routes of administration               | Oral use         |

Dosage and administration details:

Semaglutide 7 mg tablets were to be taken from week 5 to 8, once daily in the morning in a fasting state and at least 30 minutes before the first meal of the day. The trial product could be taken with up to half a glass of water (approximately 120 mL/4 fluid ounces) and was to be swallowed whole and not broken or chewed. Oral medication other than trial product could only be taken 30 minutes after administration of trial product. If treatment with the trial product was associated with unacceptable AEs,

dose reductions, treatment pauses and extension of dose escalation periods was allowed as per the investigator's discretion.

|  |                   |
|--|-------------------|
| Investigational medicinal product name | Semaglutide 14 mg |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Tablet            |
| Routes of administration               | Oral use          |

Dosage and administration details:

Semaglutide 14 mg tablets were to be taken from week 9 to 82, once daily in the morning in a fasting state and at least 30 minutes before the first meal of the day. The trial product could be taken with up to half a glass of water (approximately 120 mL/4 fluid ounces) and was to be swallowed whole and not broken or chewed. Oral medication other than trial product could only be taken 30 minutes after administration of trial product. If treatment with the trial product was associated with unacceptable AEs, dose reductions, treatment pauses and extension of dose escalation periods was allowed as per the investigator's discretion.

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

Arm description:

Subjects received once-daily placebo (for semaglutide) tablets for a period of upto 82 weeks.

|  |          |
|--|----------|
| Arm type                               | Placebo  |
| Investigational medicinal product name | Placebo  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

Subjects took the placebo tablets once daily in the morning in a fasting state for 82 weeks. Subjects took the tablet with about half a glass (120 mL/4 fluid ounces) of water. Subjects had to swallow the tablet as a whole and not break or chew it. Oral medication other than trial product could only be taken 30 minutes after administration of trial product. If treatment with the trial product was associated with unacceptable AEs, dose reductions, treatment pauses and extension of dose escalation periods was allowed as per the investigator's discretion.

| <b>Number of subjects in period 1</b> | Oral Semaglutide | Placebo |
|---------------------------------------|------------------|---------|
| Started                               | 1591             | 1592    |
| Exposed                               | 1591             | 1591    |
| Completed                             | 1586             | 1586    |
| Not completed                         | 5                | 6       |
| Consent withdrawn by subject          | 3                | 1       |
| Lost to follow-up                     | 2                | 5       |

## Baseline characteristics

### Reporting groups

|   |                  |
|---|------------------|
| Reporting group title   | Oral Semaglutide |
| Reporting group description:  |                  |
| Subjects received once-daily semaglutide tablets in a dose escalation manner for upto 82 weeks: 3 mg from weeks 1-4, 7 mg from weeks 5-8 and 14 mg from weeks 9 to upto 82. |                  |
| Reporting group title   | Placebo          |
| Reporting group description:  |                  |
| Subjects received once-daily placebo (for semaglutide) tablets for a period of upto 82 weeks.   |                  |

| Reporting group values  | Oral Semaglutide | Placebo | Total |
|---|------------------|---------|-------|
| Number of subjects  | 1591             | 1592    | 3183  |
| Age Categorical   |                  |         |       |
| Units: Subjects   |                  |         |       |
| Adults (18-64 years)  | 700              | 634     | 1334  |
| From 65-84 years  | 887              | 948     | 1835  |
| 85 years and over   | 4                | 10      | 14    |
| Age Continuous  |                  |         |       |
| Units: years  |                  |         |       |
| arithmetic mean   | 66               | 66      |       |
| standard deviation  | ± 7              | ± 7     | -     |
| Gender Categorical  |                  |         |       |
| Units: Subjects   |                  |         |       |
| Female  | 507              | 500     | 1007  |
| Male  | 1084             | 1092    | 2176  |
| Baseline cardiovascular disease (CVD)/chronic kidney disease (CKD) risk details                     |                  |         |       |
| This table describes the baseline details of subjects in the study with the risk of CVD and/or CKD. |                  |         |       |
| Units: Subjects   |                  |         |       |
| Established CVD and/or CKD, age ≥ 50 years  | 1350             | 1345    | 2695  |
| Evidence of CV risk factors, age ≥ 50 years   | 241              | 247     | 488   |

## End points

### End points reporting groups

|   |                  |
|---|------------------|
| Reporting group title   | Oral Semaglutide |
| Reporting group description:<br>Subjects received once-daily semaglutide tablets in a dose escalation manner for upto 82 weeks: 3 mg from weeks 1-4, 7 mg from weeks 5-8 and 14 mg from weeks 9 to upto 82. |                  |
| Reporting group title   | Placebo          |
| Reporting group description:<br>Subjects received once-daily placebo (for semaglutide) tablets for a period of upto 82 weeks.   |                  |

### Primary: Time from randomisation to first occurrence of a major adverse cardiovascular event (MACE) composite endpoint consisting of: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke

|  |  |
|--|--|
| End point title  | Time from randomisation to first occurrence of a major adverse cardiovascular event (MACE) composite endpoint consisting of: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke |
| End point description:<br>Number of subjects experiencing a first event of a MACE, defined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. Results are based on the in-trial observation period which started at the date of randomisation, included the period after permanent trial product discontinuation, if any and ended at the date of the follow-up visit regardless of adherence to treatment. Population analysed was the full analysis set (FAS), which comprised of all randomised subjects. Number of subjects analysed = number of subjects with available data. |  |
| End point type   | Primary  |
| End point timeframe:<br>Maximum treatment duration is dependent on event rates and is estimated to be no longer than 19 months   |  |

| End point values            | Oral Semaglutide | Placebo         |  |  |
|-----------------------------|------------------|-----------------|--|--|
| Subject group type          | Reporting group  | Reporting group |  |  |
| Number of subjects analysed | 1591             | 1592            |  |  |
| Units: Subjects             | 61               | 76              |  |  |

### Statistical analyses

|   |                            |
|---|----------------------------|
| Statistical analysis title  | Non-inferiority analysis   |
| Statistical analysis description:<br>Data from the in-trial observation period. Time from randomisation to first EAC-confirmed MACE was analysed using a Cox proportional hazards model with treatment as categorical fixed factor and stratified by evidence of cardiovascular disease at screening. Subjects were censored at the end of their in-trial observation period. |                            |
| Comparison groups   | Oral Semaglutide v Placebo |

|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 3183                           |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | non-inferiority <sup>[1]</sup> |
| P-value                                 | < 0.0001 <sup>[2]</sup>        |
| Method                                  | Regression, Cox                |
| Parameter estimate                      | Hazard ratio (HR)              |
| Point estimate                          | 0.79                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 0.57                           |
| upper limit                             | 1.11                           |

Notes:

[1] - Non-inferiority of oral semaglutide versus placebo was considered confirmed if the upper limit of the two-sided 95% confidence interval for the HR was strictly below 1.8.

[2] - Unadjusted two-sided p-value for test of no difference from the non-inferiority margin (non-inferiority).

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

Statistical analysis description:

Data from the in-trial observation period. Time from randomisation to first EAC-confirmed MACE was analysed using a Cox proportional hazards model with treatment as categorical fixed factor and stratified by evidence of cardiovascular disease at screening. Subjects were censored at the end of their in-trial observation period.

|   |                            |
|---|----------------------------|
| Comparison groups                       | Oral Semaglutide v Placebo |
| Number of subjects included in analysis | 3183                       |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.1749 <sup>[3]</sup>    |
| Method                                  | Regression, Cox            |
| Parameter estimate                      | Hazard ratio (HR)          |
| Point estimate                          | 0.79                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 0.57                       |
| upper limit                             | 1.11                       |

Notes:

[3] - Unadjusted two-sided p-value from test of no difference from 1 (superiority)

### **Secondary: Time from randomisation to first occurrence of an expanded composite cardiovascular endpoint consisting of: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, UAP requiring hospitalisation or hospitalisation for heart failure**

|                 |   |
|-----------------|---|
| End point title | Time from randomisation to first occurrence of an expanded composite cardiovascular endpoint consisting of: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, UAP requiring hospitalisation or hospitalisation for heart failure |
|-----------------|---|

End point description:

Subjects experiencing first occurrence of an expanded composite CV endpoint [defined as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, UAP (unstable angina pectoris) requiring hospitalisation or heart failure requiring hospitalisation]. Results are based on the in-trial observation period which started at the date of randomisation, included the period after permanent trial product discontinuation, if any and ended at the date of the follow-up visit regardless of adherence to treatment. Population analysed was the full analysis set (FAS), which comprised of all randomised subjects. Number of subjects analysed = number of subjects with available data.



|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Maximum treatment duration is dependent on event rates and is estimated to be no longer than 19 months |           |

| End point values            | Oral Semaglutide | Placebo         |  |  |
|-----------------------------|------------------|-----------------|--|--|
| Subject group type          | Reporting group  | Reporting group |  |  |
| Number of subjects analysed | 1591             | 1592            |  |  |
| Units: Subjects             | 83               | 100             |  |  |

## Statistical analyses

| Statistical analysis title  | Oral Semaglutide vs Placebo |
|---|-----------------------------|
| Statistical analysis description:   |                             |
| Data from the in-trial observation period. Time from randomisation to first EAC-confirmed expanded cardiovascular outcome was analysed using a Cox proportional hazards model with treatment as categorical fixed factor and stratified by evidence of cardiovascular disease at screening. Subjects were censored at the end of their in-trial observation period. |                             |
| Comparison groups   | Oral Semaglutide v Placebo  |
| Number of subjects included in analysis   | 3183                        |
| Analysis specification  | Pre-specified               |
| Analysis type   | other <sup>[4]</sup>        |
| P-value   | = 0.1827 <sup>[5]</sup>     |
| Method  | Regression, Cox             |
| Parameter estimate  | Hazard ratio (HR)           |
| Point estimate  | 0.82                        |
| Confidence interval   |                             |
| level   | 95 %                        |
| sides   | 2-sided                     |
| lower limit   | 0.61                        |
| upper limit   | 1.1                         |

Notes:

[4] - Analysis population - Full analysis set; Number of subjects analysed = Number of subjects with available data

[5] - Unadjusted two-sided p-value for test of no difference from 1.

## Secondary: Time from randomisation to first occurrence of each of the individual components in the expanded composite cardiovascular endpoint

|                 |  |
|-----------------|--|
| End point title | Time from randomisation to first occurrence of each of the individual components in the expanded composite cardiovascular endpoint |
|-----------------|--|

End point description:

Subjects experiencing an event onset for each individual component of the expanded composite cardiovascular outcomes (defined as defined as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, unstable angina requiring hospitalisation or heart failure requiring hospitalisation). Results are based on the in-trial observation period which started at the date of randomisation, included the period after permanent trial product discontinuation, if any and ended at the date of the follow-up visit regardless of adherence to treatment. Population analysed was the full analysis set (FAS), which comprised of all randomised subjects. Number of subjects analysed = number of subjects with available data.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Maximum treatment duration is dependent on event rates and is estimated to be no longer than 19 months |           |

| End point values                          | Oral Semaglutide | Placebo         |  |  |
|---|------------------|-----------------|--|--|
| Subject group type                        | Reporting group  | Reporting group |  |  |
| Number of subjects analysed               | 1591             | 1592            |  |  |
| Units: Subjects                           |                  |                 |  |  |
| Cardiovascular death                      | 15               | 30              |  |  |
| Non-fatal myocardial infarction           | 37               | 31              |  |  |
| Non-fatal stroke                          | 12               | 16              |  |  |
| Unstable angina requiring hospitalisation | 11               | 7               |  |  |
| Heart failure requiring hospitalisation   | 21               | 24              |  |  |

## Statistical analyses

| Statistical analysis title   | Analysis for Cardiovascular death |
|--|-----------------------------------|
| Statistical analysis description:  |                                   |
| Data from the in-trial observation period. Time from randomisation to first EAC-confirmed cardiovascular death (including undetermined cause of death) was analysed using a Cox proportional hazards model with treatment as categorical fixed factor and stratified by evidence of cardiovascular disease at screening. Subjects were censored at the end of their in-trial observation period. |                                   |
| Comparison groups  | Oral Semaglutide v Placebo        |
| Number of subjects included in analysis  | 3183                              |
| Analysis specification   | Pre-specified                     |
| Analysis type  | other                             |
| P-value  | = 0.0261 <sup>[6]</sup>           |
| Method   | Regression, Cox                   |
| Parameter estimate   | Hazard ratio (HR)                 |
| Point estimate   | 0.49                              |
| Confidence interval  |                                   |
| level  | 95 %                              |
| sides  | 2-sided                           |
| lower limit  | 0.27                              |
| upper limit  | 0.92                              |

Notes:

[6] - Unadjusted two-sided p-value for test of no difference from 1.

| Statistical analysis title  | Analysis of non-fatal myocardial infarction |
|---|---|
| Statistical analysis description:   |   |
| Data from the in-trial observation period. Time from randomisation to first EAC-confirmed non-fatal myocardial infarction was analysed using a Cox proportional hazards model with treatment as categorical fixed factor and stratified by evidence of cardiovascular disease at screening. Subjects were censored at the end of their in-trial observation period. |   |
| Comparison groups   | Oral Semaglutide v Placebo                  |

|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 3183                    |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | other                   |
| P-value                                 | = 0.5044 <sup>[7]</sup> |
| Method                                  | Regression, Cox         |
| Parameter estimate                      | Hazard ratio (HR)       |
| Point estimate                          | 1.18                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 0.73                    |
| upper limit                             | 1.9                     |

Notes:

[7] - Unadjusted two-sided p-value for test of no difference from 1.

|                                   |                               |
|-----------------------------------|-------------------------------|
| <b>Statistical analysis title</b> | Analysis for non-fatal stroke |
|-----------------------------------|-------------------------------|

Statistical analysis description:

Data from the in-trial observation period. Time from randomisation to first EAC-confirmed non-fatal stroke was analysed using a Cox proportional hazards model with treatment as categorical fixed factor and stratified by evidence of cardiovascular disease at screening. Subjects were censored at the end of their in-trial observation period.

|   |                            |
|---|----------------------------|
| Comparison groups                       | Oral Semaglutide v Placebo |
| Number of subjects included in analysis | 3183                       |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | other                      |
| P-value                                 | = 0.435 <sup>[8]</sup>     |
| Method                                  | Regression, Cox            |
| Parameter estimate                      | Hazard ratio (HR)          |
| Point estimate                          | 0.74                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 0.35                       |
| upper limit                             | 1.57                       |

Notes:

[8] - Unadjusted two-sided p-value for test of no difference from 1

|                                   |                                       |
|-----------------------------------|---------------------------------------|
| <b>Statistical analysis title</b> | Analysis for unstable angina pectoris |
|-----------------------------------|---------------------------------------|

Statistical analysis description:

Data from the in-trial observation period. Time from randomisation to first EAC-confirmed unstable angina pectoris requiring hospitalisation was analysed using a Cox proportional hazards model with treatment as categorical fixed factor and stratified by evidence of cardiovascular disease at screening. Subjects were censored at the end of their in-trial observation period.

|   |                            |
|---|----------------------------|
| Comparison groups                       | Oral Semaglutide v Placebo |
| Number of subjects included in analysis | 3183                       |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | other                      |
| P-value                                 | = 0.3605 <sup>[9]</sup>    |
| Method                                  | Regression, Cox            |
| Parameter estimate                      | Hazard ratio (HR)          |
| Point estimate                          | 1.56                       |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.6     |
| upper limit         | 4.01    |

Notes:

[9] - Unadjusted two-sided p-value for test of no difference from 1.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Analysis for heart failure with hospitalisation |
|-----------------------------------|---|

Statistical analysis description:

Data from the in-trial observation period. Time from randomisation to first EAC-confirmed hospitalisation for heart failure was analysed using a Cox proportional hazards model with treatment as categorical fixed factor and stratified by evidence of cardiovascular disease at screening. Subjects were censored at the end of their in-trial observation period.

|   |                            |
|---|----------------------------|
| Comparison groups                       | Oral Semaglutide v Placebo |
| Number of subjects included in analysis | 3183                       |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | other                      |
| P-value                                 | = 0.6227 <sup>[10]</sup>   |
| Method                                  | Regression, Cox            |
| Parameter estimate                      | Hazard ratio (HR)          |
| Point estimate                          | 0.86                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 0.48                       |
| upper limit                             | 1.55                       |

Notes:

[10] - Unadjusted two-sided p-value for test of no difference from 1.

### **Secondary: Time from randomisation to first occurrence of a composite endpoint consisting of: all-cause death, non-fatal myocardial infarction or nonfatal stroke**

|                 |  |
|-----------------|--|
| End point title | Time from randomisation to first occurrence of a composite endpoint consisting of: all-cause death, non-fatal myocardial infarction or nonfatal stroke |
|-----------------|--|

End point description:

Subjects experiencing first occurrence of an expanded composite CV endpoint (defined as all-cause death, non-fatal myocardial infarction or nonfatal stroke). Results are based on the in-trial observation period which started at the date of randomisation, included the period after permanent trial product discontinuation, if any and ended at the date of the follow-up visit regardless of adherence to treatment. Population analysed was the full analysis set (FAS), which comprised of all randomised subjects. Number of subjects analysed = number of subjects with available data.

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

End point timeframe:

Maximum treatment duration is dependent on event rates and is estimated to be no longer than 19 months

| <b>End point values</b>     | Oral Semaglutide | Placebo         |  |  |
|-----------------------------|------------------|-----------------|--|--|
| Subject group type          | Reporting group  | Reporting group |  |  |
| Number of subjects analysed | 1591             | 1592            |  |  |
| Units: Subjects             | 69               | 89              |  |  |

## Statistical analyses

| <b>Statistical analysis title</b>  | Analysis for the composite endpoint |
|--|-------------------------------------|
| Statistical analysis description:  |                                     |
| Data from the in-trial observation period. Time from randomisation to first EAC-confirmed all-cause death, non-fatal myocardial infarction or non-fatal stroke was analysed using a Cox proportional hazards model with treatment as categorical fixed factor and stratified by evidence of cardiovascular disease at screening. Subjects were censored at the end of their in-trial observation period. |                                     |
| Comparison groups  | Oral Semaglutide v Placebo          |
| Number of subjects included in analysis  | 3183                                |
| Analysis specification   | Pre-specified                       |
| Analysis type  | other                               |
| P-value  | = 0.0952 <sup>[11]</sup>            |
| Method   | Regression, Cox                     |
| Parameter estimate   | Hazard ratio (HR)                   |
| Point estimate   | 0.77                                |
| Confidence interval  |                                     |
| level  | 95 %                                |
| sides  | 2-sided                             |
| lower limit  | 0.56                                |
| upper limit  | 1.05                                |

Notes:

[11] - Unadjusted two-sided p-value for test of no difference from 1.

## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

From the date of first dose of trial product (week 0) to end of treatment (week 82) + 5 weeks of follow-up (until week 87).

Adverse event reporting additional description:

All presented AEs are TEAEs which were recorded during the exposure to trial products. AEs with onset during the on-treatment observation period were considered treatment-emergent. 'Number of deaths causally related to treatment' is the data considered to present under 'total number of deaths resulting from AEs.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 20     |

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Oral Semaglutide |
|-----------------------|------------------|

Reporting group description:

Subjects received once-daily semaglutide tablets in a dose escalation manner for 82 weeks: 3 mg from weeks 1-4, 7 mg from weeks 5-8 and 14 mg from 9 to upto 82 weeks.

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

Reporting group description:

Subjects received once-daily placebo tablets for a period of upto 82 weeks.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Systematic collection of AEs was limited to SAEs, AEs leading to permanent discontinuation of IMP, medication errors leading to SAEs and AEs related to technical complaints and were summarised. Non-serious AEs not fulfilling the above criteria as they were not systematically collected.

| Serious adverse events  | Oral Semaglutide       | Placebo                |  |
|---|------------------------|------------------------|--|
| Total subjects affected by serious adverse events                   |                        |                        |  |
| subjects affected / exposed   | 301 / 1591<br>(18.92%) | 358 / 1591<br>(22.50%) |  |
| number of deaths (all causes)                                       | 20                     | 38                     |  |
| number of deaths resulting from adverse events                      | 3                      | 1                      |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                        |                        |  |
| Adenocarcinoma gastric  |                        |                        |  |
| subjects affected / exposed   | 1 / 1591 (0.06%)       | 2 / 1591 (0.13%)       |  |
| occurrences causally related to treatment / all                     | 0 / 1                  | 1 / 2                  |  |
| deaths causally related to treatment / all                          | 0 / 1                  | 0 / 1                  |  |
| Adenocarcinoma of colon   |                        |                        |  |
| subjects affected / exposed   | 4 / 1591 (0.25%)       | 1 / 1591 (0.06%)       |  |
| occurrences causally related to treatment / all                     | 0 / 4                  | 0 / 1                  |  |
| deaths causally related to treatment / all                          | 0 / 0                  | 0 / 0                  |  |
| Adenocarcinoma pancreas   |                        |                        |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| B-cell lymphoma                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Basal cell carcinoma                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bladder cancer                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bladder transitional cell carcinoma             |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Breast cancer                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Carcinoid tumour of the appendix                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholangiocarcinoma                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Choroid melanoma                                |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chronic myelomonocytic leukaemia                |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colon cancer                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diffuse large B-cell lymphoma                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Endometrial adenocarcinoma                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemangioma                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatic cancer                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Hepatocellular carcinoma                        |                  |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 1 / 2            | 0 / 1            |  |
| Light chain disease                             |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lip squamous cell carcinoma                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lung adenocarcinoma                             |                  |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lung cancer metastatic                          |                  |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lymphoma  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Malignant peritoneal neoplasm                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Medullary thyroid cancer                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mesothelioma malignant                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Metastases to liver                             |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Metastases to lung                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastatic malignant melanoma                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Non-Hodgkin's lymphoma                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatic carcinoma                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatic carcinoma metastatic                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Pancreatic neuroendocrine tumour metastatic     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Papillary renal cell carcinoma                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Penile squamous cell carcinoma                  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pituitary tumour benign                         |                  |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Plasma cell myeloma                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Polycythaemia vera                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Prostate cancer                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 4 / 1591 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Prostate cancer metastatic                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Prostate cancer stage III                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Prostate cancer stage IV                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectal adenocarcinoma                           |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal neoplasm                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Small cell carcinoma                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Squamous cell carcinoma of lung                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Squamous cell carcinoma of the tongue           |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Thyroid cancer metastatic                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vascular disorders                              |                  |                  |  |
| Aortic aneurysm                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Aortic dissection                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Aortic stenosis                                 |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arteriosclerosis                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Deep vein thrombosis                            |                  |                  |  |
| subjects affected / exposed                     | 3 / 1591 (0.19%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypertension                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypertensive crisis                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypertensive emergency                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypotension                                     |                  |                  |  |
| subjects affected / exposed                     | 5 / 1591 (0.31%) | 3 / 1591 (0.19%) |  |
| occurrences causally related to treatment / all | 1 / 5            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Malignant hypertension                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Orthostatic hypotension                         |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 3 / 1591 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral arterial occlusive disease           |                  |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 7 / 1591 (0.44%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral artery dissection                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral artery occlusion                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral artery stenosis                      |                  |                  |  |
| subjects affected / exposed                     | 3 / 1591 (0.19%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral ischaemia                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 3 / 1591 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral vascular disorder                    |                  |                  |  |
| subjects affected / exposed                     | 3 / 1591 (0.19%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thrombosis                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Surgical and medical procedures                 |                  |                  |  |
| Aortic aneurysm repair                          |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiac pacemaker insertion                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cataract operation                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholecystectomy                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Finger repair operation                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric bypass                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Glaucoma surgery                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hip arthroplasty                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Implantable defibrillator insertion             |                  |                  |  |

|  |                  |                  |  |
|--|------------------|------------------|--|
| subjects affected / exposed                          | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Joint arthroplasty                                   |                  |                  |  |
| subjects affected / exposed                          | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Knee arthroplasty                                    |                  |                  |  |
| subjects affected / exposed                          | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Spinal fusion surgery                                |                  |                  |  |
| subjects affected / exposed                          | 0 / 1591 (0.00%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Subdural haematoma evacuation                        |                  |                  |  |
| subjects affected / exposed                          | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Transurethral prostatectomy                          |                  |                  |  |
| subjects affected / exposed                          | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Trapeziectomy  |                  |                  |  |
| subjects affected / exposed                          | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| General disorders and administration site conditions |                  |                  |  |
| Asthenia   |                  |                  |  |
| subjects affected / exposed                          | 3 / 1591 (0.19%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Chest pain   |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Death   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 3 / 1591 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 3            |  |
| Drowning  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 1 / 1            |  |
| Fatigue   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hernia pain                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Non-cardiac chest pain                          |                  |                  |  |
| subjects affected / exposed                     | 9 / 1591 (0.57%) | 7 / 1591 (0.44%) |  |
| occurrences causally related to treatment / all | 1 / 11           | 0 / 9            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oedema peripheral                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral swelling                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pyrexia   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sudden cardiac death                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| Systemic inflammatory response syndrome         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vascular stent restenosis                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Immune system disorders                         |                  |                  |  |
| Anaphylactic reaction                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Reproductive system and breast disorders        |                  |                  |  |
| Benign prostatic hyperplasia                    |                  |                  |  |
| subjects affected / exposed                     | 3 / 1591 (0.19%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Respiratory, thoracic and mediastinal disorders |                  |                  |  |
| Acute pulmonary oedema                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Acute respiratory failure                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Aspiration                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Asthma  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bronchial hyperreactivity                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bronchospasm                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chronic obstructive pulmonary disease           |                  |                  |  |
| subjects affected / exposed                     | 8 / 1591 (0.50%) | 4 / 1591 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 11           | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Dyspnoea  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemothorax                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypoxia   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Idiopathic pulmonary fibrosis                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lung disorder                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Obstructive airways disorder                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Organising pneumonia                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pharyngeal oedema                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pleural effusion                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumonitis                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pulmonary embolism                              |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pulmonary oedema                                |                  |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Respiratory failure                             |                  |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Sleep apnoea syndrome                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Psychiatric disorders                           |                  |                  |  |
| Alcoholism                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bipolar disorder                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Confusional state                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Depression                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Drug dependence                                 |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mania   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mental status changes                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Product issues                                  |                  |                  |  |
| Device malfunction                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Investigations                                  |                  |                  |  |
| Blood creatinine increased                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood potassium increased                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Clostridium test positive                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ejection fraction decreased                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatic enzyme increased                        |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Troponin increased                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Injury, poisoning and procedural complications  |                  |                  |  |
| Accidental overdose                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ankle fracture                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Brain contusion                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cervical vertebral fracture                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chemical peritonitis                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Comminuted fracture                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Coronary artery restenosis                      |                  |                  |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Ear injury                                      |                  |                   |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Facial bones fracture                           |                  |                   |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Fall  |                  |                   |  |
| subjects affected / exposed                     | 5 / 1591 (0.31%) | 11 / 1591 (0.69%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 11            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Femoral neck fracture                           |                  |                   |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 2 / 1591 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Femur fracture                                  |                  |                   |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Foot fracture                                   |                  |                   |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Forearm fracture                                |                  |                   |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Foreign body in ear                             |                  |                   |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Graft haemorrhage                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hip fracture                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Humerus fracture                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Injury corneal                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Joint dislocation                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Joint injury                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Laceration                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Limb injury                                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Open globe injury                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Patella fracture                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pelvic fracture                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural bile leak                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural complication                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural haematuria                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Postoperative thoracic procedure complication   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Radius fracture                                 |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rib fracture                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Road traffic accident                           |                  |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal compression fracture                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subdural haematoma                              |                  |                  |  |
| subjects affected / exposed                     | 3 / 1591 (0.19%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Subdural haemorrhage                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tendon injury                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tendon rupture                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thermal burn                                    |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 1591 (0.00%)  | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Upper limb fracture                             |                   |                   |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%)  | 0 / 1591 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Vascular pseudoaneurysm                         |                   |                   |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%)  | 2 / 1591 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cardiac disorders                               |                   |                   |  |
| Acute coronary syndrome                         |                   |                   |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%)  | 0 / 1591 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Acute left ventricular failure                  |                   |                   |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%)  | 2 / 1591 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Acute myocardial infarction                     |                   |                   |  |
| subjects affected / exposed                     | 21 / 1591 (1.32%) | 22 / 1591 (1.38%) |  |
| occurrences causally related to treatment / all | 4 / 25            | 1 / 25            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 3             |  |
| Angina pectoris                                 |                   |                   |  |
| subjects affected / exposed                     | 8 / 1591 (0.50%)  | 7 / 1591 (0.44%)  |  |
| occurrences causally related to treatment / all | 0 / 9             | 0 / 7             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Angina unstable                                 |                   |                   |  |
| subjects affected / exposed                     | 19 / 1591 (1.19%) | 15 / 1591 (0.94%) |  |
| occurrences causally related to treatment / all | 0 / 20            | 0 / 18            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Arrhythmia                                      |                   |                   |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Arteriosclerosis coronary artery                |                  |                   |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Arteriospasm coronary                           |                  |                   |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Atrial fibrillation                             |                  |                   |  |
| subjects affected / exposed                     | 6 / 1591 (0.38%) | 14 / 1591 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 3 / 14            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Atrial flutter                                  |                  |                   |  |
| subjects affected / exposed                     | 3 / 1591 (0.19%) | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Atrioventricular block complete                 |                  |                   |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Atrioventricular block first degree             |                  |                   |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Atrioventricular block second degree            |                  |                   |  |
| subjects affected / exposed                     | 3 / 1591 (0.19%) | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Bradycardia                                     |                  |                   |  |

|   |                  |                  |
|---|------------------|------------------|
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| Cardiac arrest                                  |                  |                  |
| subjects affected / exposed                     | 5 / 1591 (0.31%) | 0 / 1591 (0.00%) |
| occurrences causally related to treatment / all | 1 / 6            | 0 / 0            |
| deaths causally related to treatment / all      | 1 / 3            | 0 / 0            |
| Cardiac failure                                 |                  |                  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 7 / 1591 (0.44%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 8            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |
| Cardiac failure acute                           |                  |                  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 2 / 1591 (0.13%) |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| Cardiac failure chronic                         |                  |                  |
| subjects affected / exposed                     | 5 / 1591 (0.31%) | 8 / 1591 (0.50%) |
| occurrences causally related to treatment / all | 0 / 5            | 1 / 9            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 3            |
| Cardiac failure congestive                      |                  |                  |
| subjects affected / exposed                     | 9 / 1591 (0.57%) | 9 / 1591 (0.57%) |
| occurrences causally related to treatment / all | 1 / 12           | 1 / 11           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| Cardiac flutter                                 |                  |                  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| Cardio-respiratory arrest                       |                  |                  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 3 / 1591 (0.19%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 3            |
| Cardiogenic shock                               |                  |                  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1             |  |
| Cardiomyopathy                                  |                  |                   |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Cardiopulmonary failure                         |                  |                   |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1             |  |
| Cardiorenal syndrome                            |                  |                   |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1             |  |
| Coronary artery disease                         |                  |                   |  |
| subjects affected / exposed                     | 9 / 1591 (0.57%) | 13 / 1591 (0.82%) |  |
| occurrences causally related to treatment / all | 0 / 9            | 2 / 13            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1             |  |
| Coronary artery stenosis                        |                  |                   |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 3 / 1591 (0.19%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Coronary artery thrombosis                      |                  |                   |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 1 / 1             |  |
| Degenerative aortic valve disease               |                  |                   |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Hypertensive heart disease                      |                  |                   |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1591 (0.00%)  | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1            |  |
| Ischaemic cardiomyopathy                        |                   |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%)  | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Left ventricular failure                        |                   |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%)  | 4 / 1591 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Mitral valve incompetence                       |                   |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%)  | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Myocardial infarction                           |                   |                  |  |
| subjects affected / exposed                     | 11 / 1591 (0.69%) | 9 / 1591 (0.57%) |  |
| occurrences causally related to treatment / all | 0 / 11            | 0 / 9            |  |
| deaths causally related to treatment / all      | 0 / 4             | 0 / 5            |  |
| Myocardial ischaemia                            |                   |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%)  | 3 / 1591 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 2            |  |
| Myocarditis                                     |                   |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%)  | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Prinzmetal angina                               |                   |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%)  | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Pulseless electrical activity                   |                   |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sinus node dysfunction                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Supraventricular tachycardia                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tachycardia                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ventricular fibrillation                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ventricular tachycardia                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nervous system disorders                        |                  |                  |  |
| Carotid artery occlusion                        |                  |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Carotid artery stenosis                         |                  |                  |  |
| subjects affected / exposed                     | 4 / 1591 (0.25%) | 4 / 1591 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebellar infarction                           |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebral infarction                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebral ischaemia                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebrovascular accident                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dementia with Lewy bodies                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic neuropathy                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dizziness                                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dyspraxia                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Encephalopathy                                  |                  |                  |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 0 / 1591 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Headache  |                  |                   |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Hemiparesis                                     |                  |                   |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 0 / 1591 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Hypoaesthesia                                   |                  |                   |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Hypoglycaemic seizure                           |                  |                   |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Hypoglycaemic unconsciousness                   |                  |                   |  |
| subjects affected / exposed                     | 9 / 1591 (0.57%) | 6 / 1591 (0.38%)  |  |
| occurrences causally related to treatment / all | 10 / 11          | 1 / 8             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Ischaemic cerebral infarction                   |                  |                   |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 2 / 1591 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Ischaemic stroke                                |                  |                   |  |
| subjects affected / exposed                     | 9 / 1591 (0.57%) | 11 / 1591 (0.69%) |  |
| occurrences causally related to treatment / all | 0 / 9            | 1 / 12            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0             |  |
| Lacunar infarction                              |                  |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lacunar stroke                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lumbosacral plexopathy                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Migraine  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Myasthenia gravis                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neuritis  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neurotoxicity                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Optic neuritis                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Parkinsonism                                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Seizure   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spondylitic myelopathy                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Syncope   |                  |                  |  |
| subjects affected / exposed                     | 7 / 1591 (0.44%) | 4 / 1591 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Transient ischaemic attack                      |                  |                  |  |
| subjects affected / exposed                     | 3 / 1591 (0.19%) | 6 / 1591 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 1 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vlth nerve paralysis                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vascular dementia                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood and lymphatic system disorders            |                  |                  |  |
| Anaemia   |                  |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Autoimmune haemolytic anaemia                   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Iron deficiency anaemia                         |                  |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Leukocytosis                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Splenic haemorrhage                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ear and labyrinth disorders                     |                  |                  |  |
| Vertigo   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Eye disorders                                   |                  |                  |  |
| Cataract  |                  |                  |  |
| subjects affected / exposed                     | 8 / 1591 (0.50%) | 5 / 1591 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Retinal tear                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Retinopathy proliferative                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal disorders                      |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| Abdominal pain                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal pain upper                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colitis   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colitis ischaemic                               |                  |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Constipation                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diarrhoea                                       |                  |                  |  |
| subjects affected / exposed                     | 4 / 1591 (0.25%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Duodenal ulcer                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Duodenal ulcer haemorrhage                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dyspepsia                                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric ulcer                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastritis                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastroduodenitis                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal haemorrhage                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal polyp haemorrhage              |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrooesophageal reflux disease                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haematochezia                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemorrhoids                                    |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Impaired gastric emptying                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Inguinal hernia                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intestinal ischaemia                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intestinal mass                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Large intestine polyp                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lower gastrointestinal haemorrhage              |                  |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nausea  |                  |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal haemorrhage                         |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal varices haemorrhage                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophagitis                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophagitis ulcerative                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatitis                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatitis acute                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatitis chronic                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peptic ulcer haemorrhage                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Salivary gland calculus                         |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Umbilical hernia                                |                  |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vomiting  |                  |                  |  |
| subjects affected / exposed                     | 4 / 1591 (0.25%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatobiliary disorders                         |                  |                  |  |
| Bile duct stone                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Biliary fistula                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholangitis acute                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholecystitis                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholecystitis acute                             |                  |                  |  |
| subjects affected / exposed                     | 3 / 1591 (0.19%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholecystitis chronic                           |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholelithiasis                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 4 / 1591 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 2 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Drug-induced liver injury                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gallbladder polyp                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatic cirrhosis                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatic steatosis                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatitis                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Liver disorder                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin and subcutaneous tissue disorders          |                  |                  |  |
| Angioedema                                      |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 1591 (0.00%)  | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 1 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| <b>Dermatomyositis</b>                          |                   |                   |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%)  | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| <b>Diabetic foot</b>                            |                   |                   |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%)  | 6 / 1591 (0.38%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 7             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| <b>Skin ulcer</b>                               |                   |                   |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%)  | 4 / 1591 (0.25%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| <b>Vasculitic ulcer</b>                         |                   |                   |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%)  | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| <b>Renal and urinary disorders</b>              |                   |                   |  |
| <b>Acute kidney injury</b>                      |                   |                   |  |
| subjects affected / exposed                     | 13 / 1591 (0.82%) | 14 / 1591 (0.88%) |  |
| occurrences causally related to treatment / all | 5 / 14            | 2 / 18            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| <b>Acute prerenal failure</b>                   |                   |                   |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%)  | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| <b>Azotaemia</b>                                |                   |                   |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%)  | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| <b>Bladder prolapse</b>                         |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chronic kidney disease                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 5 / 1591 (0.31%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic nephropathy                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haematuria                                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hydronephrosis                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| IgA nephropathy                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nephrolithiasis                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal failure                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal impairment                                |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 1 / 1            | 0 / 0            |  |
| Ureterolithiasis                                |                  |                  |  |
| subjects affected / exposed                     | 3 / 1591 (0.19%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urethral stenosis                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary incontinence                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endocrine disorders                             |                  |                  |  |
| Hyperthyroidism                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thyroid mass                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Musculoskeletal and connective tissue disorders |                  |                  |  |
| Arthritis                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arthropathy                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| Back pain                                       |                  |                   |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 2 / 1591 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Bursitis  |                  |                   |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Intervertebral disc protrusion                  |                  |                   |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Lumbar spinal stenosis                          |                  |                   |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 2 / 1591 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Muscular weakness                               |                  |                   |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Musculoskeletal chest pain                      |                  |                   |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Neck pain                                       |                  |                   |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Osteoarthritis                                  |                  |                   |  |
| subjects affected / exposed                     | 6 / 1591 (0.38%) | 10 / 1591 (0.63%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 10            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Pain in extremity                               |                  |                   |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pathological fracture                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Polymyalgia rheumatica                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rhabdomyolysis                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rotator cuff syndrome                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sacroiliitis                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal column stenosis                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal osteoarthritis                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Trigger finger                                  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infections and infestations                     |                  |                  |  |
| Abscess limb                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anal abscess                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Biliary sepsis                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bronchitis                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 3 / 1591 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Campylobacter gastroenteritis                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Carbuncle                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cellulitis                                      |                  |                  |  |
| subjects affected / exposed                     | 9 / 1591 (0.57%) | 7 / 1591 (0.44%) |  |
| occurrences causally related to treatment / all | 1 / 9            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholecystitis infective                         |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Device related infection                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic foot infection                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic gangrene                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diverticulitis                                  |                  |                  |  |
| subjects affected / exposed                     | 3 / 1591 (0.19%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Emphyema  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endocarditis bacterial                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Erysipelas                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 3 / 1591 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Escherichia pyelonephritis                      |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Folliculitis                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gallbladder empyema                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gangrene  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastroenteritis                                 |                  |                  |  |
| subjects affected / exposed                     | 5 / 1591 (0.31%) | 5 / 1591 (0.31%) |  |
| occurrences causally related to treatment / all | 4 / 5            | 1 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastroenteritis viral                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Herpes zoster                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infective tenosynovitis                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Influenza                                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Injection site abscess                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intervertebral discitis                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lower respiratory tract infection               |                  |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Ludwig angina                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Meningitis                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Murine typhus                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Myelitis  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oral infection                                  |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 1591 (0.00%)  | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Osteomyelitis                                   |                   |                   |  |
| subjects affected / exposed                     | 5 / 1591 (0.31%)  | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Periorbital cellulitis                          |                   |                   |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%)  | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia                                       |                   |                   |  |
| subjects affected / exposed                     | 12 / 1591 (0.75%) | 21 / 1591 (1.32%) |  |
| occurrences causally related to treatment / all | 1 / 13            | 0 / 21            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 4             |  |
| Pneumonia acinetobacter                         |                   |                   |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%)  | 0 / 1591 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia escherichia                           |                   |                   |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%)  | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia influenzal                            |                   |                   |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%)  | 0 / 1591 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia klebsiella                            |                   |                   |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%)  | 1 / 1591 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia streptococcal                         |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural cellulitis                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural infection                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural pneumonia                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Postoperative wound infection                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pulmonary tuberculosis                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pyelonephritis                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pyelonephritis acute                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectal abscess                                  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sepsis  |                  |                  |  |
| subjects affected / exposed                     | 3 / 1591 (0.19%) | 6 / 1591 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Septic shock                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 3 / 1591 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 3            |  |
| Sialoadenitis                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sinusitis                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Staphylococcal bacteraemia                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tinea pedis                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tonsillitis                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Upper respiratory tract infection               |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Upper respiratory tract infection bacterial     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary tract infection                         |                  |                  |  |
| subjects affected / exposed                     | 3 / 1591 (0.19%) | 5 / 1591 (0.31%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urosepsis                                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 3 / 1591 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Wound sepsis                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metabolism and nutrition disorders              |                  |                  |  |
| Dehydration                                     |                  |                  |  |
| subjects affected / exposed                     | 3 / 1591 (0.19%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetes mellitus                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetes mellitus inadequate control            |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 3 / 1591 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic ketoacidosis                           |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyperglycaemia                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 4 / 1591 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 2 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyperglycaemic hyperosmolar nonketotic syndrome |                  |                  |  |
| subjects affected / exposed                     | 2 / 1591 (0.13%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyperkalaemia                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypervolaemia                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypoglycaemia                                   |                  |                  |  |
| subjects affected / exposed                     | 5 / 1591 (0.31%) | 4 / 1591 (0.25%) |  |
| occurrences causally related to treatment / all | 3 / 5            | 1 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypokalaemia                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 0 / 1591 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyponatraemia                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1591 (0.06%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypovolaemia                                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lactic acidosis                                 |                  |                  |  |
| subjects affected / exposed                     | 3 / 1591 (0.19%) | 2 / 1591 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Latent autoimmune diabetes in adults            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1591 (0.00%) | 1 / 1591 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

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

| <b>Non-serious adverse events</b>                     | Oral Semaglutide | Placebo          |  |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                  |                  |  |
| subjects affected / exposed                           | 0 / 1591 (0.00%) | 0 / 1591 (0.00%) |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 09 August 2016   | Amendment created to incorporate an additional screening procedure and exclusion criterion related to diabetic retinopathy.   |
| 17 November 2016 | Additional eye examinations and additional data collection for events of diabetic retinopathy or related complications. Addition of bicarbonate as a part of the biochemistry laboratory assessments.<br>Clarification in relation to physical examination.<br>Minor corrections or clarifications. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30284349>