



## Clinical trial results:

**A trial comparing the efficacy and safety of insulin degludec and insulin glargine 300 units/mL in subjects with type 2 diabetes mellitus inadequately treated with basal insulin with or without oral antidiabetic drugs**

### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2016-002801-20    |
| Trial protocol           | DE HU DK EE GR PL |
| Global end of trial date | 04 March 2019     |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 26 February 2020 |
| First version publication date | 26 February 2020 |

### Trial information

#### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | NN1250-4252 |
|-----------------------|-------------|

#### Additional study identifiers

|                                    |                 |
|------------------------------------|-----------------|
| ISRCTN number                      | -               |
| ClinicalTrials.gov id (NCT number) | NCT03078478     |
| WHO universal trial number (UTN)   | U1111-1184-8175 |

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                       | 10 July 2019     |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 13 February 2019 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 04 March 2019    |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To compare the effects of insulin degludec once daily and insulin glargine 300 units/mL once daily on hypoglycaemia in subjects with type 2 diabetes mellitus, inadequately treated with basal insulin with or without oral anti-diabetic drugs.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (64th WMA General Assembly, October 2013) and ICH Good Clinical Practice, including archiving of essential documents, (June 1996) and 21 CFR 312.120.

Background therapy:

The participants were previously treated with basal insulin once daily or twice daily  $\pm$  oral anti-diabetic drugs excluding sulfonylureas/glinides. Pre-trial insulin was discontinued and the subjects continued their pre-trial OADs.

Evidence for comparator:

Not applicable.

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 13 March 2017 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Canada: 87         |
| Country: Number of subjects enrolled | Germany: 100       |
| Country: Number of subjects enrolled | Denmark: 32        |
| Country: Number of subjects enrolled | Estonia: 40        |
| Country: Number of subjects enrolled | Greece: 58         |
| Country: Number of subjects enrolled | Hungary: 62        |
| Country: Number of subjects enrolled | Norway: 20         |
| Country: Number of subjects enrolled | Poland: 145        |
| Country: Number of subjects enrolled | Romania: 21        |
| Country: Number of subjects enrolled | Serbia: 60         |
| Country: Number of subjects enrolled | United States: 984 |
| Worldwide total number of subjects   | 1609               |
| EEA total number of subjects         | 478                |

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)                      | 836 |
| From 65 to 84 years                       | 764 |
| 85 years and over                         | 9   |

## Subject disposition

### Recruitment

#### Recruitment details:

The trial was conducted at 230 sites in 11 countries as follows. Number of sites that screened and randomised participants to treatment are given in parenthesis. Canada: (9/9), Denmark: (6/6), Estonia: (5/5), Germany: (11 /11), Greece: (7/7), Hungary: (9/9), Norway: (4/4), Poland: (9/9), Romania: (5/4), Serbia: (8/8), United States: (157/153).

### Pre-assignment

#### Screening details:

The participants were previously treated with basal insulin once daily or twice daily  $\pm$  oral anti-diabetic drugs excluding sulfonylureas/glinides. Pre-trial insulin was discontinued and the subjects continued their pre-trial OADs.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Not blinded                    |

### Arms

|                              |                       |
|------------------------------|-----------------------|
| Are arms mutually exclusive? | Yes                   |
| <b>Arm title</b>             | Insulin degludec U200 |

#### Arm description:

Participants received insulin degludec 200 units/mL once daily as subcutaneous injections (in the thigh, upper arm or abdomen)  $\pm$  oral anti-diabetic drugs. The treatment duration was up to 88 weeks divided into; a 16-week titration period, an up to 36-week maintenance period 1 (variable length) and a 36-week maintenance period 2.

|  |  |
|--|--|
| Arm type                               | Experimental                             |
| Investigational medicinal product name | INSULIN DEGLUDEC                         |
| Investigational medicinal product code |  |
| Other name                             | Tresiba® 200 units/ml                    |
| Pharmaceutical forms                   | Solution for injection in pre-filled pen |
| Routes of administration               | Subcutaneous use                         |

#### Dosage and administration details:

Insulin degludec 200 units/mL was administered once daily as subcutaneous injections in the thigh, upper arm or abdomen. The daily basal insulin dose was reduced by 20% from their pre-trial dose. Insulin dose was adjusted once weekly by the investigator, based on the mean of three fasting SMPG values, to reach a SMPG of 4.0-5.0 mmol/L (71-90 mg/dL).

|                  |                       |
|------------------|-----------------------|
| <b>Arm title</b> | Insulin glargine U300 |
|------------------|-----------------------|

#### Arm description:

Participants received insulin glargine 300 units/mL once daily as subcutaneous injections (in the thigh, upper arm or abdomen)  $\pm$  pre-trial oral anti-diabetic drugs. The treatment duration was up to 88 weeks divided into; a 16-week titration period, an up to 36-week maintenance period 1 (variable length) and a 36-week maintenance period 2.

|  |  |
|--|--|
| Arm type                               | Active comparator                        |
| Investigational medicinal product name | INSULIN GLARGINE                         |
| Investigational medicinal product code |  |
| Other name                             | Toujeo® 300 units/ml                     |
| Pharmaceutical forms                   | Solution for injection in pre-filled pen |
| Routes of administration               | Subcutaneous use                         |

#### Dosage and administration details:

Insulin glargine (IGlar) 300 units/mL was administered once daily as subcutaneous injections in the thigh, upper arm or abdomen. The dose of IGlar U300 corresponded to the pre-trial daily basal insulin dose. Insulin dose was adjusted once weekly by the investigator, based on the mean of three fasting

SMPG values, to reach a SMPG of 4.0-5.0 mmol/L (71-90 mg/dL).

| <b>Number of subjects in period 1</b> | Insulin degludec<br>U200 | Insulin glargine<br>U300 |
|---------------------------------------|--------------------------|--------------------------|
| Started                               | 805                      | 804                      |
| Completed                             | 733                      | 734                      |
| Not completed                         | 72                       | 70                       |
| Consent withdrawn by subject          | 54                       | 49                       |
| Death                                 | 7                        | 9                        |
| Unclassified                          | 1                        | 2                        |
| Lost to follow-up                     | 10                       | 10                       |

## Baseline characteristics

### Reporting groups

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | Insulin degludec U200 |
|-----------------------|-----------------------|

Reporting group description:

Participants received insulin degludec 200 units/mL once daily as subcutaneous injections (in the thigh, upper arm or abdomen) ± oral anti-diabetic drugs. The treatment duration was up to 88 weeks divided into; a 16-week titration period, an up to 36-week maintenance period 1 (variable length) and a 36-week maintenance period 2.

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | Insulin glargine U300 |
|-----------------------|-----------------------|

Reporting group description:

Participants received insulin glargine 300 units/mL once daily as subcutaneous injections (in the thigh, upper arm or abdomen) ± pre-trial oral anti-diabetic drugs. The treatment duration was up to 88 weeks divided into; a 16-week titration period, an up to 36-week maintenance period 1 (variable length) and a 36-week maintenance period 2.

| Reporting group values                | Insulin degludec U200 | Insulin glargine U300 | Total |
|---------------------------------------|-----------------------|-----------------------|-------|
| Number of subjects                    | 805                   | 804                   | 1609  |
| Age Categorical<br>Units: Subjects    |                       |                       |       |
| Adults (18-64 years)                  | 418                   | 418                   | 836   |
| Adults (65-74 years)                  | 301                   | 308                   | 609   |
| From 75-84 years                      | 82                    | 73                    | 155   |
| 85 years and over                     | 4                     | 5                     | 9     |
| Age Continuous<br>Units: years        |                       |                       |       |
| arithmetic mean                       | 62.9                  | 62.8                  |       |
| standard deviation                    | ± 10                  | ± 10                  | -     |
| Gender Categorical<br>Units: Subjects |                       |                       |       |
| Female                                | 333                   | 368                   | 701   |
| Male                                  | 472                   | 436                   | 908   |

## End points

### End points reporting groups

|  |                       |
|--|-----------------------|
| Reporting group title  | Insulin degludec U200 |
| Reporting group description:<br>Participants received insulin degludec 200 units/mL once daily as subcutaneous injections (in the thigh, upper arm or abdomen) ± oral anti-diabetic drugs. The treatment duration was up to 88 weeks divided into; a 16-week titration period, an up to 36-week maintenance period 1 (variable length) and a 36-week maintenance period 2.           |                       |
| Reporting group title  | Insulin glargine U300 |
| Reporting group description:<br>Participants received insulin glargine 300 units/mL once daily as subcutaneous injections (in the thigh, upper arm or abdomen) ± pre-trial oral anti-diabetic drugs. The treatment duration was up to 88 weeks divided into; a 16-week titration period, an up to 36-week maintenance period 1 (variable length) and a 36-week maintenance period 2. |                       |

### Primary: Number of severe or blood glucose confirmed symptomatic hypoglycaemic episodes

|  |  |
|--|--|
| End point title  | Number of severe or blood glucose confirmed symptomatic hypoglycaemic episodes |
| End point description:<br>Severe or BG confirmed symptomatic hypoglycaemia was evaluated during maintenance 2 (36 weeks) period. Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA 2013 classification or blood glucose (BG) confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia. The observed rates (number of episodes divided by patient years of exposure multiplied by 100) of severe or BG-confirmed symptomatic hypoglycaemic episodes per patient years of exposure (PYE) is presented in this endpoint results. |  |
| End point type   | Primary  |
| End point timeframe:<br>During maintenance 2 (36 weeks)  |  |

| End point values                      | Insulin degludec U200 | Insulin glargine U300 |  |  |
|---------------------------------------|-----------------------|-----------------------|--|--|
| Subject group type                    | Reporting group       | Reporting group       |  |  |
| Number of subjects analysed           | 742                   | 741                   |  |  |
| Units: Rate of hypoglycaemic episodes |                       |                       |  |  |
| number (not applicable)               | 216.8                 | 243.9                 |  |  |

### Statistical analyses

|  |   |
|--|---|
| Statistical analysis title   | Analysis 1                                    |
| Statistical analysis description:<br>The number of episodes is analysed using a negative binomial regression model (log link) with the logarithm of the time period in which a hypoglycaemic episode was considered treatment emergent as offset. The model includes treatment, number of OADs, region, sex and dosing time as fixed factors, and age as a covariate. Missing values are imputed through multiple imputation by treatment arm, based on a Poisson model. |   |
| Comparison groups  | Insulin degludec U200 v Insulin glargine U300 |

|   |                              |
|---|------------------------------|
| Number of subjects included in analysis | 1483                         |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| P-value                                 | = 0.1715                     |
| Method                                  | Negative binomial regression |
| Parameter estimate                      | Treatment rate ratio         |
| Point estimate                          | 0.88                         |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 0.73                         |
| upper limit                             | 1.06                         |

### Secondary: Basal insulin dose (units)

|                        |   |
|------------------------|---|
| End point title        | Basal insulin dose (units)  |
| End point description: | The observed mean daily basal insulin doses was evaluated at the end of trial (88 weeks). |
| End point type         | Secondary   |
| End point timeframe:   | At end of treatment (up to 88 weeks)  |

| End point values                     | Insulin degludec U200 | Insulin glargine U300 |  |  |
|--------------------------------------|-----------------------|-----------------------|--|--|
| Subject group type                   | Reporting group       | Reporting group       |  |  |
| Number of subjects analysed          | 703                   | 704                   |  |  |
| Units: Units                         |                       |                       |  |  |
| arithmetic mean (standard deviation) | 66.6 (± 48.54)        | 73.0 (± 48.48)        |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of nocturnal, severe or blood glucose confirmed symptomatic hypoglycaemic episodes

|                        |  |
|------------------------|--|
| End point title        | Number of nocturnal, severe or blood glucose confirmed symptomatic hypoglycaemic episodes  |
| End point description: | Nocturnal severe or BG confirmed symptomatic hypoglycaemia was evaluated at the end of trial (88 weeks). The nocturnal period defined as the period between 00:01 and 05:59 a.m. (both inclusive). Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA 2013 classification or blood glucose (BG) confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia. The observed rates (number of episodes divided by patient years of exposure multiplied by 100) of severe or BG-confirmed symptomatic hypoglycaemic episodes per patient years of exposure (PYE) is presented in this endpoint results. |
| End point type         | Secondary  |



End point timeframe:  
During maintenance 2 (36 weeks)

| End point values                      | Insulin<br>degludec U200 | Insulin glargine<br>U300 |  |  |
|---------------------------------------|--------------------------|--------------------------|--|--|
| Subject group type                    | Reporting group          | Reporting group          |  |  |
| Number of subjects analysed           | 742                      | 741                      |  |  |
| Units: Rate of hypoglycaemic episodes |                          |                          |  |  |
| number (not applicable)               | 62.30                    | 93.75                    |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of severe hypoglycaemic episodes

|   |   |
|---|---|
| End point title   | Number of severe hypoglycaemic episodes |
| End point description:<br>Severe hypoglycaemia are those episodes positively adjudicated by the event adjudication committee according to the ADA definition of a severe hypoglycaemic episode. This was evaluated for maintenance 2 period. The observed rates (number of episodes divided by patient years of exposure multiplied by 100) of severe hypoglycaemic episodes per patient years of exposure (PYE) is presented in this endpoint results. |   |
| End point type  | Secondary                               |
| End point timeframe:<br>During maintenance 2 (36 weeks)   |   |

| End point values                      | Insulin<br>degludec U200 | Insulin glargine<br>U300 |  |  |
|---------------------------------------|--------------------------|--------------------------|--|--|
| Subject group type                    | Reporting group          | Reporting group          |  |  |
| Number of subjects analysed           | 742                      | 741                      |  |  |
| Units: Rate of hypoglycaemic episodes |                          |                          |  |  |
| number (not applicable)               | 0.98                     | 4.88                     |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in HbA1c

|  |                 |
|--|-----------------|
| End point title  | Change in HbA1c |
| End point description:<br>Change in glycosylated haemoglobin (HbA1c) was evaluated from baseline to end of treatment period (week 88). |                 |
| End point type   | Secondary       |

End point timeframe:

From baseline to end of treatment (up to 88 weeks)

| End point values                     | Insulin<br>degludec U200 | Insulin glargine<br>U300 |  |  |
|--------------------------------------|--------------------------|--------------------------|--|--|
| Subject group type                   | Reporting group          | Reporting group          |  |  |
| Number of subjects analysed          | 694                      | 700                      |  |  |
| Units: Percentage of HbA1c           |                          |                          |  |  |
| arithmetic mean (standard deviation) | -0.54 (± 0.91)           | -0.46 (± 0.90)           |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Hypoglycaemia: Number of severe or blood glucose confirmed symptomatic hypoglycaemic episodes

|                 |   |
|-----------------|---|
| End point title | Hypoglycaemia: Number of severe or blood glucose confirmed symptomatic hypoglycaemic episodes |
|-----------------|---|

End point description:

Severe or BG confirmed symptomatic hypoglycaemia was evaluated during treatment (up to 88 weeks). Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA 2013 classification or blood glucose (BG) confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia. The observed rates (number of episodes divided by patient years of exposure multiplied by 100) of severe or BG-confirmed symptomatic hypoglycaemic episodes per patient years of exposure (PYE) is presented in this endpoint results.

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

End point timeframe:

During treatment (up to 88 weeks)

| End point values                      | Insulin<br>degludec U200 | Insulin glargine<br>U300 |  |  |
|---------------------------------------|--------------------------|--------------------------|--|--|
| Subject group type                    | Reporting group          | Reporting group          |  |  |
| Number of subjects analysed           | 802                      | 798                      |  |  |
| Units: Rate of hypoglycaemic episodes |                          |                          |  |  |
| number (not applicable)               | 137.8                    | 163.7                    |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Hypoglycaemia: Number of nocturnal, severe or blood glucose confirmed symptomatic hypoglycaemic episodes

|                 |  |
|-----------------|--|
| End point title | Hypoglycaemia: Number of nocturnal, severe or blood glucose confirmed symptomatic hypoglycaemic episodes |
|-----------------|--|

**End point description:**

Nocturnal severe or BG confirmed symptomatic hypoglycaemia was evaluated at the end of trial (88 weeks). The nocturnal period defined as the period between 00:01 and 05:59 a.m. (both inclusive). Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA 2013 classification or blood glucose (BG) confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia. The observed rates (number of episodes divided by patient years of exposure multiplied by 100) of severe or BG-confirmed symptomatic hypoglycaemic episodes per patient years of exposure (PYE) is presented in this endpoint results.

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

End point timeframe:

During treatment (up to 88 weeks)

| End point values                      | Insulin<br>degludec U200 | Insulin glargine<br>U300 |  |  |
|---------------------------------------|--------------------------|--------------------------|--|--|
| Subject group type                    | Reporting group          | Reporting group          |  |  |
| Number of subjects analysed           | 802                      | 798                      |  |  |
| Units: Rate of hypoglycaemic episodes |                          |                          |  |  |
| number (not applicable)               | 36.93                    | 60.03                    |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Hypoglycaemia: Number of severe hypoglycaemic episodes**

|                 |  |
|-----------------|--|
| End point title | Hypoglycaemia: Number of severe hypoglycaemic episodes |
|-----------------|--|

**End point description:**

Severe hypoglycaemia are those episodes positively adjudicated by the event adjudication committee according to the ADA definition of a severe hypoglycaemic episode. This was evaluated for the total trial period (88 weeks). The observed rates (number of episodes divided by patient years of exposure multiplied by 100) of severe hypoglycaemic episodes per patient years of exposure (PYE) is presented in this endpoint results.

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

End point timeframe:

During treatment (up to 88 weeks)

| End point values                      | Insulin<br>degludec U200 | Insulin glargine<br>U300 |  |  |
|---------------------------------------|--------------------------|--------------------------|--|--|
| Subject group type                    | Reporting group          | Reporting group          |  |  |
| Number of subjects analysed           | 802                      | 798                      |  |  |
| Units: Rate of hypoglycaemic episodes |                          |                          |  |  |
| number (not applicable)               | 2.06                     | 5.21                     |  |  |

**Statistical analyses**

No statistical analyses for this end point

## Secondary: Number of adverse events

|                 |                          |
|-----------------|--------------------------|
| End point title | Number of adverse events |
|-----------------|--------------------------|

End point description:

The adverse events presented are treatment emergent. A treatment-emergent AE (TEAE) was defined as an event that had onset date on or after the first day of exposure to randomised treatment and no later than 7 days after the last days of randomised treatment or had onset date before the first day of exposure on randomised treatment and increased in severity during the treatment period and until 7 days after the last date of randomised treatment. Number of adverse events expressed in rates, from randomisation to end of maintenance period 2 (up to 88 weeks) is presented. Rate = number of events divided by patient years of exposure multiplied by 100.

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

End point timeframe:

During treatment (up to 88 weeks)

| End point values              | Insulin<br>degludec U200 | Insulin glargine<br>U300 |  |  |
|-------------------------------|--------------------------|--------------------------|--|--|
| Subject group type            | Reporting group          | Reporting group          |  |  |
| Number of subjects analysed   | 802                      | 798                      |  |  |
| Units: Rate of adverse events |                          |                          |  |  |
| number (not applicable)       | 367.32                   | 365.42                   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first trial-related activity after the subject had signed the informed consent until the End of Trial (week 88) + 7 days follow-up period.

Adverse event reporting additional description:

A treatment-emergent adverse event was defined as one which had onset date on or after the 1st day of exposure to treatment and no later than 7 days after the last days of treatment or had onset date before the 1st day of exposure to treatment and increased in severity during the treatment period and until 7 days after the last date of treatment.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 21     |

### Reporting groups

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | Insulin degludec U200 |
|-----------------------|-----------------------|

Reporting group description:

Participants received insulin degludec 200 units/mL once daily as subcutaneous injections (in the thigh, upper arm or abdomen) ± oral anti-diabetic drugs. The treatment duration was up to 88 weeks divided into; a 16-week titration period, an up to 36-week maintenance period 1 (variable length) and a 36-week maintenance period 2.

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | Insulin Glargine U300 |
|-----------------------|-----------------------|

Reporting group description:

Participants received insulin glargine 300 units/mL once daily as subcutaneous injections (in the thigh, upper arm or abdomen) ± pre-trial oral anti-diabetic drugs. The treatment duration was up to 88 weeks divided into; a 16-week titration period, an up to 36-week maintenance period 1 (variable length) and a 36-week maintenance period 2.

| Serious adverse events  | Insulin degludec U200 | Insulin Glargine U300 |  |
|---|-----------------------|-----------------------|--|
| Total subjects affected by serious adverse events                   |                       |                       |  |
| subjects affected / exposed   | 167 / 802 (20.82%)    | 141 / 798 (17.67%)    |  |
| number of deaths (all causes)                                       | 7                     | 6                     |  |
| number of deaths resulting from adverse events                      | 0                     | 0                     |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                       |                       |  |
| Adenocarcinoma of colon   |                       |                       |  |
| subjects affected / exposed   | 2 / 802 (0.25%)       | 0 / 798 (0.00%)       |  |
| occurrences causally related to treatment / all                     | 0 / 2                 | 0 / 0                 |  |
| deaths causally related to treatment / all                          | 0 / 0                 | 0 / 0                 |  |
| Bladder transitional cell carcinoma                                 |                       |                       |  |
| subjects affected / exposed   | 2 / 802 (0.25%)       | 0 / 798 (0.00%)       |  |
| occurrences causally related to treatment / all                     | 0 / 2                 | 0 / 0                 |  |
| deaths causally related to treatment / all                          | 0 / 0                 | 0 / 0                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Bladder transitional cell carcinoma stage I     |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Breast cancer                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colon adenoma                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colorectal adenocarcinoma                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (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 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endometrial adenocarcinoma                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic cancer metastatic                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| 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                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intraductal proliferative breast lesion         |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Invasive ductal breast carcinoma                |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Malignant melanoma                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Malignant melanoma stage IV                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neoplasm malignant                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neuroendocrine carcinoma of the skin            |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophageal cancer metastatic                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophageal squamous cell carcinoma stage 0     |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatic carcinoma stage IV                   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Prostate cancer                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Prostate cancer metastatic                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Rectal cancer stage I                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Squamous cell carcinoma of skin                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular disorders                              |                 |                 |  |
| Deep vein thrombosis                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 2 / 798 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Embolism venous                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematoma                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypertension                                    |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 802 (0.12%) | 1 / 798 (0.13%) |  |
| 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                     | 1 / 802 (0.12%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypertensive emergency                          |                 |                 |  |
| subjects affected / exposed                     | 2 / 802 (0.25%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Internal haemorrhage                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (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 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral arterial occlusive disease           |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral artery occlusion                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (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                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral artery thrombosis                    |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral vascular disorder                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral venous disease                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Steal syndrome                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thrombophlebitis superficial                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Varicose vein                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Surgical and medical procedures                 |                 |                 |  |
| Abdominal wall operation                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac ablation                                |                 |                 |  |
| subjects affected / exposed                     | 2 / 802 (0.25%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac pacemaker insertion                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric bypass                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenterostomy                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intervertebral disc operation                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Large intestinal polypectomy                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Medical device removal                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolic surgery                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Multiple drug therapy                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rehabilitation therapy                          |                 |                 |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| 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                          | 2 / 802 (0.25%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Capsular contracture associated with breast implant  |                 |                 |  |
| subjects affected / exposed                          | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Chest discomfort                                     |                 |                 |  |
| subjects affected / exposed                          | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Chest pain   |                 |                 |  |
| subjects affected / exposed                          | 2 / 802 (0.25%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Gait disturbance                                     |                 |                 |  |
| subjects affected / exposed                          | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Multiple organ dysfunction syndrome                  |                 |                 |  |
| subjects affected / exposed                          | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0           |  |
| Non-cardiac chest pain                               |                 |                 |  |
| subjects affected / exposed                          | 3 / 802 (0.37%) | 2 / 798 (0.25%) |  |
| occurrences causally related to treatment / all      | 0 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Pyrexia  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sudden death                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Immune system disorders                         |                 |                 |  |
| Anaphylactic reaction                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sarcoidosis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Reproductive system and breast disorders        |                 |                 |  |
| Benign prostatic hyperplasia                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Uterine prolapse                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Acute interstitial pneumonitis                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (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                     | 3 / 802 (0.37%) | 2 / 798 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Chronic obstructive pulmonary disease           |                 |                 |  |
| subjects affected / exposed                     | 2 / 802 (0.25%) | 4 / 798 (0.50%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspnoea  |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Emphysema                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Epistaxis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoxia   |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Interstitial lung disease                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (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 / 802 (0.12%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary embolism                              |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary mass                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary oedema                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 2 / 798 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Respiratory failure                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 2 / 798 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sinus polyp                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                           |                 |                 |  |
| Alcohol withdrawal syndrome                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Confusional state                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Delirium  |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (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                     | 0 / 802 (0.00%) | 2 / 798 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Suicidal ideation                               |                 |                 |  |
| subjects affected / exposed                     | 2 / 802 (0.25%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Blood lactic acid increased                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemoglobin decreased                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lipase increased                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Weight decreased                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Acetabulum fracture                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (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 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Arterial bypass occlusion                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cartilage injury                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (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                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Craniocerebral injury                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Drug administered in wrong device               |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fall  |                 |                 |  |
| subjects affected / exposed                     | 3 / 802 (0.37%) | 3 / 798 (0.38%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Femur fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 2 / 798 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Gastrointestinal procedural complication        |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| 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                     | 0 / 802 (0.00%) | 2 / 798 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Incision site haemorrhage                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intentional product misuse                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Jaw fracture                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| 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 / 802 (0.12%) | 0 / 798 (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                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ligament rupture                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post procedural haemorrhage                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post procedural oedema                          |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post procedural pulmonary embolism              |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post-traumatic pain                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Postoperative respiratory failure               |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Procedural hypertension                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Procedural nausea                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Radiation oesophagitis                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (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                     | 1 / 802 (0.12%) | 2 / 798 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal column injury                            |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tibia fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 2 / 798 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Toxicity to various agents                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Vascular graft thrombosis                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Congenital, familial and genetic disorders      |                 |                 |  |
| Vitello-intestinal duct remnant                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Acute left ventricular failure                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute myocardial infarction                     |                 |                 |  |
| subjects affected / exposed                     | 6 / 802 (0.75%) | 2 / 798 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| Angina pectoris                                 |                 |                 |  |
| subjects affected / exposed                     | 3 / 802 (0.37%) | 2 / 798 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Angina unstable                                 |                 |                 |  |
| subjects affected / exposed                     | 6 / 802 (0.75%) | 4 / 798 (0.50%) |  |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aortic valve stenosis                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arteriosclerosis coronary artery                |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 9 / 802 (1.12%) | 5 / 798 (0.63%) |  |
| occurrences causally related to treatment / all | 1 / 9           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial flutter                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial tachycardia                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (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                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bradycardia                                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 802 (0.25%) | 2 / 798 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bundle branch block left                        |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bundle branch block right                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (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                     | 0 / 802 (0.00%) | 2 / 798 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 2 / 798 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure acute                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 2 / 798 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure congestive                      |                 |                 |  |
| subjects affected / exposed                     | 6 / 802 (0.75%) | 3 / 798 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardio-respiratory arrest                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Cardiogenic shock                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Cardiomyopathy                                  |                 |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 2 / 802 (0.25%)  | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Coronary artery disease                         |                  |                 |  |
| subjects affected / exposed                     | 10 / 802 (1.25%) | 5 / 798 (0.63%) |  |
| occurrences causally related to treatment / all | 0 / 10           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Coronary artery occlusion                       |                  |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%)  | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Coronary artery stenosis                        |                  |                 |  |
| subjects affected / exposed                     | 2 / 802 (0.25%)  | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hypertensive heart disease                      |                  |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%)  | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Intracardiac thrombus                           |                  |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%)  | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Myocardial infarction                           |                  |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%)  | 4 / 798 (0.50%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Myocardial ischaemia                            |                  |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%)  | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Sinus bradycardia                               |                  |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sinus node dysfunction                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sinus tachycardia                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ventricular hypokinesia                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Ataxia  |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Carotid artery disease                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Carotid artery occlusion                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Carotid artery stenosis                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebral infarction                             |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 802 (0.00%) | 2 / 798 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebrovascular disorder                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Cervical radiculopathy                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dementia Alzheimer's type                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dizziness                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dysarthria                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Embolic stroke                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Encephalopathy                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 802 (0.25%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhagic stroke                             |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Headache  |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoaesthesia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoglycaemic coma                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (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                     | 3 / 802 (0.37%) | 9 / 798 (1.13%) |  |
| occurrences causally related to treatment / all | 4 / 4           | 8 / 11          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypotonia                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ischaemic stroke                                |                 |                 |  |
| subjects affected / exposed                     | 5 / 802 (0.62%) | 4 / 798 (0.50%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lacunar stroke                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Loss of consciousness                           |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lumbar radiculopathy                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolic encephalopathy                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Presyncope                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sciatica  |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Seizure   |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subarachnoid haemorrhage                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Syncope   |                 |                 |  |
| subjects affected / exposed                     | 3 / 802 (0.37%) | 2 / 798 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transient ischaemic attack                      |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 3 / 802 (0.37%) | 5 / 798 (0.63%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Blood and lymphatic system disorders</b>     |                 |                 |  |
| <b>Anaemia</b>                                  |                 |                 |  |
| subjects affected / exposed                     | 3 / 802 (0.37%) | 4 / 798 (0.50%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Iron deficiency anaemia</b>                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 802 (0.25%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Leukocytosis</b>                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Lymphadenopathy</b>                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Thrombocytopenia</b>                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Ear and labyrinth disorders</b>              |                 |                 |  |
| <b>Vertigo</b>                                  |                 |                 |  |
| subjects affected / exposed                     | 3 / 802 (0.37%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Vertigo positional</b>                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Eye disorders</b>                            |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Blindness unilateral                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetic retinopathy                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eye haematoma                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Macular degeneration                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Retinal detachment                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Retinal tear                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Retinopathy proliferative                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rhegmatogenous retinal detachment               |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vitreous adhesions                              |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vitreous haemorrhage                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal pain upper                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diverticulum                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diverticulum intestinal haemorrhagic            |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Duodenal ulcer                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| 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 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enteritis                                       |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Faecaloma                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (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                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastritis erosive                               |                 |                 |  |
| subjects affected / exposed                     | 3 / 802 (0.37%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal angiodysplasia                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (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 / 802 (0.12%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrooesophageal reflux disease                |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematemesis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (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                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hiatus hernia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ileus   |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal obstruction                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (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                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatic cyst                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatic duct dilatation                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis necrotising                        |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Peptic ulcer perforation                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Small intestinal obstruction                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 802 (0.25%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Volvulus  |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Cholecystitis                                   |                 |                 |  |
| subjects affected / exposed                     | 2 / 802 (0.25%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholelithiasis                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 802 (0.25%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cirrhosis alcoholic                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (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          |                 |                 |  |
| Diabetic foot                                   |                 |                 |  |
| subjects affected / exposed                     | 2 / 802 (0.25%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Erythema  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hidradenitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin ulcer                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Stasis dermatitis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Acute kidney injury                             |                 |                 |  |
| subjects affected / exposed                     | 4 / 802 (0.50%) | 8 / 798 (1.00%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 1 / 9           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bladder prolapse                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nephrolithiasis                                 |                 |                 |  |
| subjects affected / exposed                     | 2 / 802 (0.25%) | 2 / 798 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Polyuria  |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal failure                                   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal mass                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endocrine disorders                             |                 |                 |  |
| Goitre  |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| 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 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Arthralgia                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Back pain                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cervical spinal stenosis                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intervertebral disc degeneration                |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Intervertebral disc protrusion                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lumbar spinal stenosis                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 2 / 798 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal chest pain                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 802 (0.25%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myofascial pain syndrome                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neuropathic arthropathy                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteoarthritis                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 802 (0.25%) | 5 / 798 (0.63%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteochondrosis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteopenia                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (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                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rhabdomyolysis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rotator cuff syndrome                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal osteoarthritis                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vertebral foraminal stenosis                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Abscess limb                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Appendicitis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Appendicitis perforated                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchitis                                      |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 802 (0.25%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchitis bacterial                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 802 (0.25%) | 3 / 798 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic tonsillitis                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetic foot infection                         |                 |                 |  |
| subjects affected / exposed                     | 3 / 802 (0.37%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diverticulitis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 3 / 798 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endocarditis staphylococcal                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Escherichia urinary tract infection             |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (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 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis viral                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Helicobacter infection                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatitis A                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatitis C                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Influenza                                       |                 |                 |  |
| subjects affected / exposed                     | 3 / 802 (0.37%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Joint abscess                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Localised infection                             |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 802 (0.00%) | 2 / 798 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lyme disease                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteomyelitis                                   |                 |                 |  |
| subjects affected / exposed                     | 2 / 802 (0.25%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteomyelitis acute                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Otitis externa                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Otitis media                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Parametritis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peritonitis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 6 / 802 (0.75%) | 9 / 798 (1.13%) |  |
| occurrences causally related to treatment / all | 0 / 8           | 0 / 9           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia fungal                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post procedural cellulitis                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| 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                     | 1 / 802 (0.12%) | 2 / 798 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Postoperative wound infection                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyelonephritis acute                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sepsis  |                 |                 |  |
| subjects affected / exposed                     | 2 / 802 (0.25%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Staphylococcal sepsis                           |                 |                 |  |
| subjects affected / exposed                     | 2 / 802 (0.25%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Streptococcal sepsis                            |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tooth abscess                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tuberculosis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 802 (0.25%) | 5 / 798 (0.63%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urosepsis                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 802 (0.25%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vestibular neuronitis                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Viral infection                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Viral pharyngitis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound infection                                 |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound infection staphylococcal                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 3 / 802 (0.37%) | 0 / 798 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetes mellitus                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetic ketoacidosis                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperammonaemia                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperglycaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperkalaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoglycaemia                                   |                 |                 |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 8 / 802 (1.00%) | 19 / 798 (2.38%) |  |
| occurrences causally related to treatment / all | 7 / 8           | 18 / 21          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| <b>Hypokalaemia</b>                             |                 |                  |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| <b>Hyponatraemia</b>                            |                 |                  |  |
| subjects affected / exposed                     | 1 / 802 (0.12%) | 1 / 798 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| <b>Metabolic acidosis</b>                       |                 |                  |  |
| subjects affected / exposed                     | 0 / 802 (0.00%) | 1 / 798 (0.13%)  |  |
| 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>                     | Insulin degludec U200 | Insulin Glargine U300 |  |
|---|-----------------------|-----------------------|--|
| Total subjects affected by non-serious adverse events |                       |                       |  |
| subjects affected / exposed                           | 496 / 802 (61.85%)    | 476 / 798 (59.65%)    |  |
| <b>Nervous system disorders</b>                       |                       |                       |  |
| Headache  |                       |                       |  |
| subjects affected / exposed                           | 51 / 802 (6.36%)      | 62 / 798 (7.77%)      |  |
| occurrences (all)                                     | 61                    | 70                    |  |
| <b>Gastrointestinal disorders</b>                     |                       |                       |  |
| Diarrhoea   |                       |                       |  |
| subjects affected / exposed                           | 72 / 802 (8.98%)      | 79 / 798 (9.90%)      |  |
| occurrences (all)                                     | 90                    | 97                    |  |
| Nausea  |                       |                       |  |
| subjects affected / exposed                           | 43 / 802 (5.36%)      | 50 / 798 (6.27%)      |  |
| occurrences (all)                                     | 53                    | 56                    |  |
| Vomiting  |                       |                       |  |
| subjects affected / exposed                           | 26 / 802 (3.24%)      | 40 / 798 (5.01%)      |  |
| occurrences (all)                                     | 30                    | 52                    |  |

|   |                    |                    |  |
|---|--------------------|--------------------|--|
| Respiratory, thoracic and mediastinal disorders |                    |                    |  |
| Cough   |                    |                    |  |
| subjects affected / exposed                     | 48 / 802 (5.99%)   | 46 / 798 (5.76%)   |  |
| occurrences (all)                               | 60                 | 53                 |  |
| Musculoskeletal and connective tissue disorders |                    |                    |  |
| Arthralgia                                      |                    |                    |  |
| subjects affected / exposed                     | 51 / 802 (6.36%)   | 65 / 798 (8.15%)   |  |
| occurrences (all)                               | 59                 | 84                 |  |
| Back pain                                       |                    |                    |  |
| subjects affected / exposed                     | 59 / 802 (7.36%)   | 62 / 798 (7.77%)   |  |
| occurrences (all)                               | 73                 | 70                 |  |
| Pain in extremity                               |                    |                    |  |
| subjects affected / exposed                     | 45 / 802 (5.61%)   | 43 / 798 (5.39%)   |  |
| occurrences (all)                               | 49                 | 49                 |  |
| Infections and infestations                     |                    |                    |  |
| Bronchitis                                      |                    |                    |  |
| subjects affected / exposed                     | 48 / 802 (5.99%)   | 46 / 798 (5.76%)   |  |
| occurrences (all)                               | 54                 | 46                 |  |
| Influenza                                       |                    |                    |  |
| subjects affected / exposed                     | 59 / 802 (7.36%)   | 41 / 798 (5.14%)   |  |
| occurrences (all)                               | 64                 | 44                 |  |
| Nasopharyngitis                                 |                    |                    |  |
| subjects affected / exposed                     | 152 / 802 (18.95%) | 161 / 798 (20.18%) |  |
| occurrences (all)                               | 253                | 265                |  |
| Sinusitis                                       |                    |                    |  |
| subjects affected / exposed                     | 45 / 802 (5.61%)   | 40 / 798 (5.01%)   |  |
| occurrences (all)                               | 58                 | 53                 |  |
| Upper respiratory tract infection               |                    |                    |  |
| subjects affected / exposed                     | 145 / 802 (18.08%) | 122 / 798 (15.29%) |  |
| occurrences (all)                               | 199                | 177                |  |
| Urinary tract infection                         |                    |                    |  |
| subjects affected / exposed                     | 49 / 802 (6.11%)   | 47 / 798 (5.89%)   |  |
| occurrences (all)                               | 58                 | 65                 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment  |
|---------------|--|
| 07 March 2018 | Due to an unusual data reporting pattern of hypoglycaemia and glycaemic values being linked to the glycaemic data collection system (the combined use of MyGlucoHealth with the eDiary) it was decided on 13-Feb-2018 to apply a new data collecting system consisting of an Abbott BGM and paper diary. To accommodate changes in the data collection system and to ensure sufficient data collection with respect to the confirmatory endpoints a new maintenance period (maintenance 2) of 36 weeks duration was included in the trial. |

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/30974986>