



## Clinical trial results:

### A MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY AND EFFICACY OF INTRAVENOUS CR845 IN HEMODIALYSIS PATIENTS WITH MODERATE-TO-SEVERE PRURITUS, WITH A 52-WEEK OPEN-LABEL EXTENSION

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2018-001930-17 |
| Trial protocol           | HU CZ GB       |
| Global end of trial date | 30 March 2020  |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 10 October 2021 |
| First version publication date | 10 October 2021 |

#### Trial information

##### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | CR845-CLIN3103 |
|-----------------------|----------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03636269 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Cara Therapeutics, Inc.   |
| Sponsor organisation address | 107 Elm Street, 9th Floor, Stamford, United States, 06902   |
| Public contact               | Regulatory Affairs, Icon clinical Research Ltd, 44 07831653684, markas.marriott@iconplc.com             |
| Scientific contact           | Regulatory Affairs, Icon clinical Research Ltd, 44 07831653684, markas.marriott@iconplc.com             |
| Sponsor organisation name    | Cara Therapeutics, Inc.   |
| Sponsor organisation address | 107 Elm Street, 9th Floor, Stamford, United States, 06902   |
| Public contact               | Cara Clinical Trials, Cara Therapeutics, Inc., 1 203-406-3700, Cara Therapeutics, Inc., 1 203-406-3700, |
| Scientific contact           | Cara Clinical Trials, Cara Therapeutics, Inc., 1 203-406-3700, Cara Therapeutics, Inc., 1 203-406-3700, |

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                       | 30 March 2020 |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 30 March 2020 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 30 March 2020 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of IV CR845 at a dose of 0.5 mcg/kg compared to placebo in reducing the intensity of itch in hemodialysis patients with moderate-to-severe pruritus.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 17 July 2018 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Canada: 3              |
| Country: Number of subjects enrolled | Korea, Republic of: 18 |
| Country: Number of subjects enrolled | New Zealand: 3         |
| Country: Number of subjects enrolled | Taiwan: 2              |
| Country: Number of subjects enrolled | United States: 279     |
| Country: Number of subjects enrolled | Poland: 69             |
| Country: Number of subjects enrolled | United Kingdom: 20     |
| Country: Number of subjects enrolled | Czechia: 3             |
| Country: Number of subjects enrolled | Germany: 5             |
| Country: Number of subjects enrolled | Hungary: 42            |
| Country: Number of subjects enrolled | Australia: 29          |
| Worldwide total number of subjects   | 473                    |
| EEA total number of subjects         | 119                    |

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)                      | 300 |
| From 65 to 84 years                       | 167 |
| 85 years and over                         | 6   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

The Screening Visit will occur within 7 to 28 days prior to randomization to assess eligibility.

### Period 1

|                              |  |
|------------------------------|--|
| Period 1 title               | Double-blind Period                      |
| Is this the baseline period? | Yes                                      |
| Allocation method            | Randomised - controlled                  |
| Blinding used                | Double blind                             |
| Roles blinded                | Subject, Investigator, Monitor, Assessor |

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |       |
|------------------|-------|
| <b>Arm title</b> | CR845 |
|------------------|-------|

Arm description:

The ITT Population consisted of 473 subjects randomized to study treatment, 237 to difelikefalin and 236 to placebo. The Double-blind Safety Population consisted of 471 randomized subjects who received at least 1 dose of double-blind study drug during the Double-blind Treatment Period; 235 of these subjects were treated with difelikefalin, and 236 were treated with placebo. Two subjects were randomized to difelikefalin but did not receive any study drug.

|  |                        |
|--|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | CR845                  |
| Investigational medicinal product code |                        |
| Other name                             | Difelikefalin          |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

Dosage and administration details:

IV CR845 0.5 mcg/kg administered after each dialysis session (3 times/week)

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

Arm description: -

|  |                        |
|--|------------------------|
| Arm type                               | Placebo                |
| Investigational medicinal product name | Placebo                |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

Dosage and administration details:

IV Placebo administered after each dialysis session (3 times/week)

| Number of subjects in period 1             | CR845 | Placebo |
|--|-------|---------|
| Started                                    | 237   | 236     |
| Completed                                  | 206   | 223     |
| Not completed                              | 31    | 13      |
| Adverse event, serious fatal               | 2     | 1       |
| Consent withdrawn by subject               | 5     | 1       |
| Subject non-compliance                     | 1     | 2       |
| Adverse event, non-fatal                   | 11    | 6       |
| Eligibility (inclusion/exclusion criteria) | 2     | -       |
| other                                      | 8     | 3       |
| Lost to follow-up                          | 1     | -       |
| Lack of efficacy                           | 1     | -       |

## Period 2

|                              |                             |
|------------------------------|-----------------------------|
| Period 2 title               | Open-label Period           |
| Is this the baseline period? | No                          |
| Allocation method            | Non-randomised - controlled |
| Blinding used                | Not blinded                 |

## Arms

|  |                        |
|--|------------------------|
| Arm title                              | CR845                  |
| Arm description: -                     |                        |
| Arm type                               | Experimental           |
| Investigational medicinal product name | CR845                  |
| Investigational medicinal product code |                        |
| Other name                             | Difelikefalin          |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

Dosage and administration details:

IV CR845 0.5 mcg/kg administered after each dialysis session (3 times/week)

| Number of subjects in period 2 <sup>[1]</sup> | CR845 |
|---|-------|
| Started                                       | 399   |
| Completed                                     | 5     |
| Not completed                                 | 394   |
| Adverse event, serious fatal                  | 13    |
| Consent withdrawn by subject                  | 11    |
| Administrative                                | 36    |

|   |     |
|---|-----|
| Adverse event, non-fatal                        | 8   |
| Eligibility (inclusion/exclusion criteria)      | 2   |
| other   | 9   |
| Stop-unrelated to safety or lack of drug effect | 313 |
| Lack of efficacy                                | 2   |

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Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: A total of 399 subjects out of 473 randomized in the Double-blind Treatment Phase continued to the Open-label Phase, of whom 210 were previously randomized to the placebo group and 189 were previously randomized to the difelikefalin, respectively.

## Baseline characteristics

### Reporting groups

|                       |       |
|-----------------------|-------|
| Reporting group title | CR845 |
|-----------------------|-------|

Reporting group description:

The ITT Population consisted of 473 subjects randomized to study treatment, 237 to difelikefalin and 236 to placebo. The Double-blind Safety Population consisted of 471 randomized subjects who received at least 1 dose of double-blind study drug during the Double-blind Treatment Period; 235 of these subjects were treated with difelikefalin, and 236 were treated with placebo. Two subjects were randomized to difelikefalin but did not receive any study drug.

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

Reporting group description: -

| Reporting group values             | CR845 | Placebo | Total |
|------------------------------------|-------|---------|-------|
| Number of subjects                 | 237   | 236     | 473   |
| Age categorical<br>Units: Subjects |       |         |       |

|   |                 |                 |     |
|---|-----------------|-----------------|-----|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 59.7<br>± 13.11 | 59.6<br>± 13.07 | -   |
| Gender categorical<br>Units: Subjects                                   |                 |                 |     |
| Female  | 100             | 97              | 197 |
| Male  | 137             | 139             | 276 |

## End points

### End points reporting groups

|  |         |
|--|---------|
| Reporting group title  | CR845   |
| Reporting group description:<br>The ITT Population consisted of 473 subjects randomized to study treatment, 237 to difelikefalin and 236 to placebo. The Double-blind Safety Population consisted of 471 randomized subjects who received at least 1 dose of double-blind study drug during the Double-blind Treatment Period; 235 of these subjects were treated with difelikefalin, and 236 were treated with placebo. Two subjects were randomized to difelikefalin but did not receive any study drug. |         |
| Reporting group title  | Placebo |
| Reporting group description: -   |         |
| Reporting group title  | CR845   |
| Reporting group description: -   |         |

### Primary: Reduction of itch intensity as assessed by the proportion of patients achieving an improvement from baseline $\geq 3$ points with respect to the weekly mean of the daily 24-hour Worst Itching Intensity Numerical Rating Scale (NRS) score at Week 12

|                                 |   |
|---------------------------------|---|
| End point title                 | Reduction of itch intensity as assessed by the proportion of patients achieving an improvement from baseline $\geq 3$ points with respect to the weekly mean of the daily 24-hour Worst Itching Intensity Numerical Rating Scale (NRS) score at Week 12 |
| End point description:          |   |
| End point type                  | Primary   |
| End point timeframe:<br>Week 12 |   |

| End point values                             | CR845               | Placebo             |  |  |
|--|---------------------|---------------------|--|--|
| Subject group type                           | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed                  | 237                 | 236                 |  |  |
| Units: Percentage                            |                     |                     |  |  |
| least squares mean (confidence interval 54%) | 54.0 (43.9 to 63.9) | 42.2 (32.5 to 52.5) |  |  |

### Statistical analyses

|   |   |
|---|---|
| Statistical analysis title  | LS means estimate of percent with improvement |
| Statistical analysis description:<br>Estimated percentage, odds ratio and P value used a logistic regression model with terms for treatment group, baseline NRS score, region, use of anti-itch medication during the week prior to randomization, and the presence of specific medical conditions. Missing values were imputed using MI under MAR missing data assumption for interim subjects and post-interim subjects separately. |   |



|   |                       |
|---|-----------------------|
| Comparison groups                       | CR845 v Placebo       |
| Number of subjects included in analysis | 473                   |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | superiority           |
| P-value                                 | = 0.02                |
| Method                                  | CHW = Cui, Hung, Wang |
| Parameter estimate                      | Odds ratio (OR)       |
| Point estimate                          | 1.61                  |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | 1.08                  |
| upper limit                             | 2.41                  |

**Secondary: Reduction of itch intensity as assessed by the proportion of patients achieving an improvement from baseline  $\geq 4$  points with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS score at Week 12**

|                        |  |
|------------------------|--|
| End point title        | Reduction of itch intensity as assessed by the proportion of patients achieving an improvement from baseline $\geq 4$ points with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS score at Week 12 |
| End point description: |  |
| End point type         | Secondary  |
| End point timeframe:   |  |
| Week 12                |  |

| End point values                               | CR845               | Placebo             |  |  |
|--|---------------------|---------------------|--|--|
| Subject group type                             | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed                    | 237 <sup>[1]</sup>  | 236                 |  |  |
| Units: Percentage                              |                     |                     |  |  |
| least squares mean (confidence interval 41.2%) | 41.2 (33.0 to 55.0) | 28.4 (21.3 to 36.7) |  |  |

Notes:

[1] - 2 Subjects were randomized to CR845 but did not receive CR845

**Statistical analyses**

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | LS means estimate of percent with improvement |
| Comparison groups                       | CR845 v Placebo                               |
| Number of subjects included in analysis | 473   |
| Analysis specification                  | Pre-specified                                 |
| Analysis type                           | superiority                                   |
| P-value                                 | = 0.01  |
| Method                                  | Cui, Hung, Wang                               |
| Parameter estimate                      | Odds ratio (OR)                               |
| Point estimate                          | 1.77  |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 1.14    |
| upper limit         | 2.74    |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The period of adverse event reporting started after the signing of the ICF through the study follow-up visit or early termination visit (or 7-10 days after the last dose if no early termination visit was conducted).

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 20.1   |

### Reporting groups

|                                |   |
|--------------------------------|---|
| Reporting group title          | Subjects in CR845 Group in Double-blind Portion   |
| Reporting group description: - |   |
| Reporting group title          | Subjects in Placebo Group in Double-blind Portion |
| Reporting group description: - |   |
| Reporting group title          | Subjects in CR845 Open-label Portion              |
| Reporting group description: - |   |

| Serious adverse events  | Subjects in CR845 Group in Double-blind Portion | Subjects in Placebo Group in Double-blind Portion | Subjects in CR845 Open-label Portion |
|---|---|---|--------------------------------------|
| Total subjects affected by serious adverse events                   |   |   |                                      |
| subjects affected / exposed   | 58 / 235 (24.68%)                               | 51 / 236 (21.61%)                                 | 130 / 399 (32.58%)                   |
| number of deaths (all causes)                                       | 2   | 2   | 15                                   |
| number of deaths resulting from adverse events                      | 0   | 0   | 0                                    |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |   |   |                                      |
| Lung adenocarcinoma   |   |   |                                      |
| subjects affected / exposed   | 0 / 235 (0.00%)                                 | 1 / 236 (0.42%)                                   | 0 / 399 (0.00%)                      |
| occurrences causally related to treatment / all                     | 0 / 0   | 0 / 1   | 0 / 0                                |
| deaths causally related to treatment / all                          | 0 / 0   | 0 / 0   | 0 / 0                                |
| Adenocarcinoma of colon   |   |   |                                      |
| subjects affected / exposed   | 0 / 235 (0.00%)                                 | 0 / 236 (0.00%)                                   | 1 / 399 (0.25%)                      |
| occurrences causally related to treatment / all                     | 0 / 0   | 0 / 0   | 0 / 1                                |
| deaths causally related to treatment / all                          | 0 / 0   | 0 / 0   | 0 / 0                                |
| Gastric neoplasm  |   |   |                                      |
| subjects affected / exposed   | 0 / 235 (0.00%)                                 | 0 / 236 (0.00%)                                   | 1 / 399 (0.25%)                      |
| occurrences causally related to treatment / all                     | 0 / 0   | 0 / 0   | 0 / 1                                |
| deaths causally related to treatment / all                          | 0 / 0   | 0 / 0   | 0 / 0                                |
| Lung neoplasm   |   |   |                                      |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lung neoplasm malignant                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Squamous cell carcinoma                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular disorders                              |                 |                 |                 |
| Hypotension                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 5 / 236 (2.12%) | 5 / 399 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 5           | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Peripheral ischaemia                            |                 |                 |                 |
| subjects affected / exposed                     | 3 / 235 (1.28%) | 1 / 236 (0.42%) | 2 / 399 (0.50%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Deep vein thrombosis                            |                 |                 |                 |
| subjects affected / exposed                     | 2 / 235 (0.85%) | 1 / 236 (0.42%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypertension                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 3 / 236 (1.27%) | 3 / 399 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypertensive crisis                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 2 / 236 (0.85%) | 3 / 399 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Jugular vein thrombosis                         |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Peripheral artery stenosis                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Shock haemorrhagic                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dry gangrene                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 2 / 399 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypertensive emergency                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 2 / 399 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Circulatory collapse                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haematoma                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Orthostatic hypotension                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Peripheral arterial occlusive disease           |                 |                 |                 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Temporal arteritis                                   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Thrombophlebitis                                     |                 |                 |                 |
| subjects affected / exposed                          | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Varicose vein  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Peripheral artery occlusion                          |                 |                 |                 |
| subjects affected / exposed                          | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Surgical and medical procedures                      |                 |                 |                 |
| Abdominal hernia repair                              |                 |                 |                 |
| subjects affected / exposed                          | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Catheter placement                                   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Multiple drug therapy                                |                 |                 |                 |
| subjects affected / exposed                          | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| General disorders and administration site conditions |                 |                 |                 |

|   |                 |                 |                  |
|---|-----------------|-----------------|------------------|
| Chest pain                                      |                 |                 |                  |
| subjects affected / exposed                     | 8 / 235 (3.40%) | 1 / 236 (0.42%) | 10 / 399 (2.51%) |
| occurrences causally related to treatment / all | 0 / 8           | 0 / 1           | 0 / 13           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Pyrexia   |                 |                 |                  |
| subjects affected / exposed                     | 2 / 235 (0.85%) | 0 / 236 (0.00%) | 2 / 399 (0.50%)  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Asthenia  |                 |                 |                  |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 5 / 399 (1.25%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1            |
| Multiple organ dysfunction syndrome             |                 |                 |                  |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1            |
| Peripheral swelling                             |                 |                 |                  |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Immune system disorders                         |                 |                 |                  |
| Hypersensitivity                                |                 |                 |                  |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 0 / 399 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                  |
| Dyspnoea  |                 |                 |                  |
| subjects affected / exposed                     | 4 / 235 (1.70%) | 2 / 236 (0.85%) | 5 / 399 (1.25%)  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 2           | 0 / 7            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Chronic obstructive pulmonary disease           |                 |                 |                  |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 235 (0.85%) | 1 / 236 (0.42%) | 5 / 399 (1.25%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pleural effusion                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 1 / 236 (0.42%) | 3 / 399 (0.75%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory failure                             |                 |                 |                 |
| subjects affected / exposed                     | 2 / 235 (0.85%) | 0 / 236 (0.00%) | 7 / 399 (1.75%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 8           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary mass                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary oedema                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Asthma  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chronic respiratory failure                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cough   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Epistaxis                                       |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemothorax                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypoxia   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary embolism                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory distress                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Psychiatric disorders                           |                 |                 |                 |
| Mental status changes                           |                 |                 |                 |
| subjects affected / exposed                     | 3 / 235 (1.28%) | 0 / 236 (0.00%) | 5 / 399 (1.25%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0           | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Confusional state                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Delirium  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Anxiety   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Product issues                                  |                 |                 |                 |
| Device malfunction                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Investigations                                  |                 |                 |                 |
| Blood pressure increased                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chest X-ray abnormal                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Paracentesis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Weight decreased                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemoglobin decreased                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 2 / 399 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bleeding time prolonged                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| C-reactive protein increased                    |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural complications  |                 |                 |                 |
| Arteriovenous fistula thrombosis                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 3 / 236 (1.27%) | 5 / 399 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 5           | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Fall  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 235 (0.85%) | 1 / 236 (0.42%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular access malfunction                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 2 / 236 (0.85%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Arteriovenous fistula site complication         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 6 / 399 (1.50%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 6           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Arteriovenous graft site haemorrhage            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Arteriovenous graft thrombosis                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Femur fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Fibula fracture                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hip fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Post procedural haemorrhage                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subdural haemorrhage                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Thermal burn                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular access complication                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 3 / 399 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular graft complication                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Arteriovenous fistula aneurysm                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 2 / 399 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Arteriovenous fistula site haemorrhage          |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 2 / 399 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Abdominal wall wound                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Femoral neck fracture                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Fractured ischium                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemodialysis complication                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Head injury                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ligament rupture                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Overdose  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular access site thrombosis                 |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hand fracture                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |                 |                 |                 |
| Bradycardia                                     |                 |                 |                 |
| subjects affected / exposed                     | 2 / 235 (0.85%) | 1 / 236 (0.42%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac failure congestive                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 2 / 236 (0.85%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Acute myocardial infarction                     |                 |                 |                 |
| subjects affected / exposed                     | 2 / 235 (0.85%) | 0 / 236 (0.00%) | 5 / 399 (1.25%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac arrest                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 1 / 236 (0.42%) | 3 / 399 (0.75%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 2           |
| Cardiac failure                                 |                 |                 |                 |
| subjects affected / exposed                     | 2 / 235 (0.85%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 1           |
| Acute coronary syndrome                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrial fibrillation                             |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrioventricular block                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrioventricular block second degree            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiogenic shock                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Coronary artery stenosis                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial infarction                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Palpitations                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardio-respiratory arrest                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 3 / 399 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 3           |
| Acute left ventricular failure                  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Angina pectoris                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Angina unstable                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Aortic valve stenosis                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Coronary artery disease                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial ischaemia                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                        |                 |                 |                 |
| Syncope   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 1 / 236 (0.42%) | 3 / 399 (0.75%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dizziness                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatic encephalopathy                          |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypertensive encephalopathy                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypoaesthesia                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Loss of consciousness                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metabolic encephalopathy                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 2 / 399 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Somnolence                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Toxic encephalopathy                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Amnesia   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebrovascular accident                        |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Delayed ischaemic neurological deficit          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dementia  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Encephalopathy                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Epilepsy  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lethargy  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lumbar radiculopathy                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Posterior reversible encephalopathy syndrome    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vertebrobasilar insufficiency                   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Blood and lymphatic system disorders</b>     |                 |                 |                 |
| Anaemia   |                 |                 |                 |
| subjects affected / exposed                     | 2 / 235 (0.85%) | 4 / 236 (1.69%) | 6 / 399 (1.50%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 5           | 0 / 6           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 1           |
| <b>Ear and labyrinth disorders</b>              |                 |                 |                 |
| Vertigo   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Gastrointestinal disorders</b>               |                 |                 |                 |
| Diarrhoea                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 2 / 236 (0.85%) | 3 / 399 (0.75%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal haemorrhage                    |                 |                 |                 |
| subjects affected / exposed                     | 2 / 235 (0.85%) | 1 / 236 (0.42%) | 4 / 399 (1.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Abdominal pain                                  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 235 (0.85%) | 0 / 236 (0.00%) | 3 / 399 (0.75%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Abdominal pain upper                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Constipation                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Impaired gastric emptying                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pancreatitis acute                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Small intestinal obstruction                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Upper gastrointestinal haemorrhage              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vomiting  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haematochezia                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 3 / 399 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lower gastrointestinal haemorrhage              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 2 / 399 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 2           |
| Alcoholic pancreatitis                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Colitis   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Colitis ischaemic                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diabetic gastroparesis                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Duodenal ulcer perforation                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dysphagia                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastric polyps                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haematemesis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Incarcerated inguinal hernia                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intestinal ischaemia                            |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Melaena   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pancreatitis chronic                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumoperitoneum                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rectal polyp                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatobiliary disorders                         |                 |                 |                 |
| Pneumobilia                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Acute hepatic failure                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cholelithiasis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Diabetic foot                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Angioedema                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |
| End stage renal disease                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 3 / 399 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Nephrolithiasis                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 2 / 399 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haematuria                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary retention                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Flank pain                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Osteoarthritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                  |
|---|-----------------|-----------------|------------------|
| Back pain                                       |                 |                 |                  |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 2 / 399 (0.50%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Arthralgia                                      |                 |                 |                  |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Infections and infestations                     |                 |                 |                  |
| Sepsis  |                 |                 |                  |
| subjects affected / exposed                     | 3 / 235 (1.28%) | 4 / 236 (1.69%) | 14 / 399 (3.51%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 4           | 0 / 14           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 3            |
| Cellulitis                                      |                 |                 |                  |
| subjects affected / exposed                     | 2 / 235 (0.85%) | 1 / 236 (0.42%) | 1 / 399 (0.25%)  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Device related infection                        |                 |                 |                  |
| subjects affected / exposed                     | 2 / 235 (0.85%) | 1 / 236 (0.42%) | 4 / 399 (1.00%)  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Osteomyelitis                                   |                 |                 |                  |
| subjects affected / exposed                     | 2 / 235 (0.85%) | 1 / 236 (0.42%) | 1 / 399 (0.25%)  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Urinary tract infection                         |                 |                 |                  |
| subjects affected / exposed                     | 2 / 235 (0.85%) | 1 / 236 (0.42%) | 3 / 399 (0.75%)  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Bronchitis                                      |                 |                 |                  |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 2 / 236 (0.85%) | 2 / 399 (0.50%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Influenza                                       |                 |                 |                  |



|   |                 |                 |                  |
|---|-----------------|-----------------|------------------|
| subjects affected / exposed                     | 2 / 235 (0.85%) | 0 / 236 (0.00%) | 2 / 399 (0.50%)  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Pneumonia                                       |                 |                 |                  |
| subjects affected / exposed                     | 3 / 235 (1.28%) | 0 / 236 (0.00%) | 22 / 399 (5.51%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 24           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1            |
| Abscess limb                                    |                 |                 |                  |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 1 / 399 (0.25%)  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Arteriovenous fistula site infection            |                 |                 |                  |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 1 / 399 (0.25%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Bacterial sepsis                                |                 |                 |                  |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 0 / 399 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Catheter site cellulitis                        |                 |                 |                  |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Endocarditis                                    |                 |                 |                  |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Gangrene  |                 |                 |                  |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 3 / 399 (0.75%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Hepatic cyst infection                          |                 |                 |                  |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Incision site cellulitis                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infectious mononucleosis                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Localised infection                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Necrotising fasciitis                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia viral                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Septic shock                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 4 / 399 (1.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Skin infection                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Staphylococcal bacteraemia                      |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Staphylococcal sepsis                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 2 / 399 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Streptococcal bacteraemia                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subcutaneous abscess                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urosepsis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 1 / 236 (0.42%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Wound infection                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Abdominal wall abscess                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bacteraemia                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Clostridium difficile colitis                   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diabetic foot infection                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diverticulitis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Emphysematous cystitis                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastroenteritis                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastroenteritis Escherichia coli                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Groin abscess                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infection                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lower respiratory tract infection               |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Mastoiditis                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Perirectal abscess                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Peritonitis                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Peritonitis bacterial                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory tract infection                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Tooth abscess                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Catheter site infection                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 0 / 399 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia escherichia                           |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Hyperkalaemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 4 / 235 (1.70%) | 3 / 236 (1.27%) | 4 / 399 (1.00%) |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 3           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Fluid overload                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 2 / 236 (0.85%) | 6 / 399 (1.50%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 6           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypoglycaemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 235 (0.43%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Calciphylaxis                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Decreased appetite                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diabetes mellitus inadequate control            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diabetic ketoacidosis                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diabetic ketosis                                |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Hypervolaemia</b>                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Metabolic acidosis</b>                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 235 (0.00%) | 0 / 236 (0.00%) | 1 / 399 (0.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

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

| <b>Non-serious adverse events</b>                            | Subjects in CR845 Group in Double-blind Portion | Subjects in Placebo Group in Double-blind Portion | Subjects in CR845 Open-label Portion |
|--|---|---|--------------------------------------|
| <b>Total subjects affected by non-serious adverse events</b> |   |   |                                      |
| subjects affected / exposed                                  | 56 / 235 (23.83%)                               | 43 / 236 (18.22%)                                 | 204 / 399 (51.13%)                   |
| <b>Injury, poisoning and procedural complications</b>        |   |   |                                      |
| <b>Fall</b>  |   |   |                                      |
| subjects affected / exposed                                  | 14 / 235 (5.96%)                                | 11 / 236 (4.66%)                                  | 52 / 399 (13.03%)                    |
| occurrences (all)  | 15  | 11  | 61                                   |
| <b>Vascular disorders</b>                                    |   |   |                                      |
| <b>Hypotension</b>   |   |   |                                      |
| subjects affected / exposed                                  | 9 / 235 (3.83%)                                 | 4 / 236 (1.69%)                                   | 25 / 399 (6.27%)                     |
| occurrences (all)  | 10  | 4   | 40                                   |
| <b>Hypertension</b>  |   |   |                                      |
| subjects affected / exposed                                  | 6 / 235 (2.55%)                                 | 10 / 236 (4.24%)                                  | 24 / 399 (6.02%)                     |
| occurrences (all)  | 11  | 17  | 40                                   |
| <b>Nervous system disorders</b>                              |   |   |                                      |
| <b>Dizziness</b>   |   |   |                                      |
| subjects affected / exposed                                  | 12 / 235 (5.11%)                                | 12 / 236 (5.08%)                                  | 31 / 399 (7.77%)                     |
| occurrences (all)  | 13  | 14  | 36                                   |
| <b>Headache</b>  |   |   |                                      |

|  |                        |                      |                        |
|--|------------------------|----------------------|------------------------|
| subjects affected / exposed<br>occurrences (all) | 10 / 235 (4.26%)<br>10 | 6 / 236 (2.54%)<br>6 | 20 / 399 (5.01%)<br>21 |
| Gastrointestinal disorders                       |                        |                      |                        |
| Diarrhoea  |                        |                      |                        |
| subjects affected / exposed                      | 18 / 235 (7.66%)       | 12 / 236 (5.08%)     | 45 / 399 (11.28%)      |
| occurrences (all)                                | 22                     | 13                   | 55                     |
| Vomiting   |                        |                      |                        |
| subjects affected / exposed                      | 15 / 235 (6.38%)       | 13 / 236 (5.51%)     | 36 / 399 (9.02%)       |
| occurrences (all)                                | 19                     | 14                   | 45                     |
| Nausea   |                        |                      |                        |
| subjects affected / exposed                      | 15 / 235 (6.38%)       | 10 / 236 (4.24%)     | 37 / 399 (9.27%)       |
| occurrences (all)                                | 19                     | 11                   | 43                     |
| Musculoskeletal and connective tissue disorders  |                        |                      |                        |
| Pain in extremity                                |                        |                      |                        |
| subjects affected / exposed                      | 8 / 235 (3.40%)        | 5 / 236 (2.12%)      | 20 / 399 (5.01%)       |
| occurrences (all)                                | 9                      | 5                    | 26                     |
| Infections and infestations                      |                        |                      |                        |
| Nasopharyngitis                                  |                        |                      |                        |
| subjects affected / exposed                      | 3 / 235 (1.28%)        | 5 / 236 (2.12%)      | 22 / 399 (5.51%)       |
| occurrences (all)                                | 3                      | 5                    | 26                     |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 28 February 2019  | Update protocol to global amendment  |
| 12 July 2019      | Modify the order of the secondary endpoints  |
| 10 September 2019 | <p>Analysis of treatment effect at specific early timepoints, Week 4 and Week 8, has been added as secondary efficacy endpoints, and an adjustment for multiplicity will be implemented to protect the overall Type 1 error.</p> <p>Change from baseline at Week 12 for the Skindex-10 Scale total score and the 5-D Itch Scale total score will be analyzed using an analysis of covariance (ANCOVA) model.</p> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported