

**Clinical trial results:****Phase 3b, Randomized, Open-label, Active-controlled Trial Evaluating the Efficacy and Safety of Oral Vadadustat Once Daily (QD) and Three Times Weekly (TIW) for the Maintenance Treatment of Anemia in Hemodialysis Subjects Converting from Erythropoiesis-Stimulating Agents (ESAs)****Summary**

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2019-004851-36 |
| Trial protocol           | HU PL CZ IT    |
| Global end of trial date | 22 June 2022   |

**Results information**

|                                |                   |
|--------------------------------|-------------------|
| Result version number          | v1 (current)      |
| This version publication date  | 19 September 2024 |
| First version publication date | 19 September 2024 |

**Trial information****Trial identification**

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | 404-201-00012 |
|-----------------------|---------------|

**Additional study identifiers**

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT04313153 |
| WHO universal trial number (UTN)   | -           |

Notes:

**Sponsors**

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Akebia Therapeutics  |
| Sponsor organisation address | 245 First St #1400, Cambridge, Massachusetts, United States, 02142   |
| Public contact               | Clinical Trial Information Desk,<br>Akebia Therapeutics, Inc., Akebia Therapeutics<br>245 First St #1400, Cambridge<br>Massachusetts<br>02142<br>United States, +1 6178446128, trials@akebia.com |
| Scientific contact           | Clinical Trial Information Desk,<br>Akebia Therapeutics, Inc., Akebia Therapeutics<br>245 First St #1400, Cambridge<br>Massachusetts<br>02142<br>United States, +1 6178446128, trials@akebia.com |

Notes:

**Paediatric regulatory details**

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

|  |    |
|--|----|
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
|--|----|

Notes:

## Results analysis stage

|  |              |
|--|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 22 June 2022 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 22 June 2022 |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate the efficacy and safety of vadadustat compared to darbepoetin alfa for the maintenance treatment of anemia in hemodialysis participants after conversion from current erythropoiesis-stimulating agent (ESA) therapy.

Protection of trial subjects:

At the first visit, prior to initiation of any study-related procedures, the parent(s) or legal guardian(s) of the participants gave their written consent to participate in the study after having been informed about the nature and purpose of the study, participation / termination conditions, and risks and benefits.

Before the informed consent document was signed, the investigator, or a person designated by the investigator, provided the participant or the participant's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial were answered to the satisfaction of the subject or the participant's legally acceptable representative.

Background therapy: -

Evidence for comparator: -

|   |             |
|---|-------------|
| Actual start date of recruitment                          | 27 May 2020 |
| 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 | Czechia: 26        |
| Country: Number of subjects enrolled | Hungary: 33        |
| Country: Number of subjects enrolled | Italy: 4           |
| Country: Number of subjects enrolled | Poland: 26         |
| Country: Number of subjects enrolled | Spain: 1           |
| Country: Number of subjects enrolled | United States: 229 |
| Worldwide total number of subjects   | 319                |
| EEA total number of subjects         | 90                 |

Notes:

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**Subjects enrolled per age group**

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|   |     |
|---|-----|
| 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)                      | 193 |
| From 65 to 84 years                       | 126 |
| 85 years and over                         | 0   |

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## Subject disposition

### Recruitment

Recruitment details:

This was a randomized, open-label, active-controlled study of vadadustat versus darbepoetin alfa for the maintenance treatment of anemia in hemodialysis participants, after conversion from erythropoiesis-stimulating agent (ESA therapy).

### Pre-assignment

Screening details:

A total of 319 participants were enrolled in the study. Participants were randomized 1:1:1 to vadadustat once daily (QD), vadadustat three times weekly (TIW), or darbepoetin alfa, stratified with respect to geographic region and mean weekly darbepoetin alfa dose (or ESA equivalent) calculated over a period of 8 weeks prior to Screening Visit 2.

### Period 1

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

### Arms

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

Arm description:

Participants were randomized to receive vadadustat QD orally. Vadadustat starting daily dose was determined by pre-Baseline mean weekly darbepoetin alfa dose (or ESA equivalent). In the low darbepoetin alfa dose group (less than or equal to [ $\leq$ ] 0.45 micrograms per kilograms per week [mcg/kg/week]), participants received an initial vadadustat daily dose of 300 milligrams (mg) daily. In the high darbepoetin alfa dose group ( $>$  0.45 and  $\leq$  1.5 mcg/kg/week), participants received an initial vadadustat daily dose of 450 mg daily. Vadadustat was titrated to achieve and maintain target hemoglobin (Hb) levels. The dose range for titration was 150 to 900 mg vadadustat QD.

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Vadadustat         |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

One 150 mg or 450 mg vadadustat tablet was to be taken each day.

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Vadadustat TIW |
|------------------|----------------|

Arm description:

Participants were randomized to receive vadadustat TIW orally. Vadadustat starting daily dose was determined by pre-Baseline mean weekly darbepoetin alfa dose (or ESA equivalent). In the low darbepoetin alfa dose group ( $\leq$  0.45 mcg/kg/week), participants received an initial vadadustat dose of 600 mg TIW. In the high darbepoetin alfa dose group ( $>$  0.45 and  $\leq$  1.5 mcg/kg/week), participants received an initial vadadustat dose of 750 mg TIW. Vadadustat was titrated to achieve and maintain target Hb levels. The dose range for titration was 150 to 1200 mg vadadustat TIW.

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Vadadustat         |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

One 150 mg or 450 mg vadadustat tablet was to be taken three times weekly.

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | Darbepoetin alfa |
|------------------|------------------|

Arm description:

Participants were randomized to receive darbepoetin alfa as a solution in single-dose prefilled syringes via intravenous (IV) injection through dialysis vascular access. For participants who had received darbepoetin alfa during screening, the initial dosing regimen was approximately the same weekly dose that they were receiving prior to randomization. For participants who had received darbepoetin alfa for the first time, the initial dosing regimen was determined by the United States Package Insert (USPI) or European Union Summary of product characteristics (EU SmPC), per the medical judgment of the investigator.

|  |  |
|--|--|
| Arm type                               | Experimental                                 |
| Investigational medicinal product name | Darbepoetin alfa                             |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Intravenous use                              |

Dosage and administration details:

One single-dose prefilled syringes was given by IV injection through dialysis vascular access.

| <b>Number of subjects in period 1</b>            | Vadadustat QD | Vadadustat TIW | Darbepoetin alfa |
|--|---------------|----------------|------------------|
| Started  | 105           | 106            | 108              |
| Completed  | 54            | 50             | 67               |
| Not completed                                    | 51            | 56             | 41               |
| Adverse Event (Includes Death)                   | 14            | 19             | 10               |
| Consent withdrawn by subject                     | 7             | 6              | 2                |
| Physician decision                               | 4             | 2              | 1                |
| Change In Dialysis Modality                      | -             | 1              | 2                |
| Unspecified                                      | 5             | 3              | 2                |
| Change Of In-Center Hemodialysis From TIW        | 1             | -              | -                |
| Lost to follow-up                                | 1             | -              | 2                |
| Met Criteria For Trial Medication Stopping Rules | 16            | 20             | 19               |
| Receipt Of Any Transplantation                   | -             | 2              | 3                |
| Lack of efficacy                                 | 3             | 3              | -                |

## Baseline characteristics

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Vadadustat QD |
|-----------------------|---------------|

Reporting group description:

Participants were randomized to receive vadadustat QD orally. Vadadustat starting daily dose was determined by pre-Baseline mean weekly darbepoetin alfa dose (or ESA equivalent). In the low darbepoetin alfa dose group (less than or equal to [ $\leq$ ] 0.45 micrograms per kilograms per week [mcg/kg/week]), participants received an initial vadadustat daily dose of 300 milligrams (mg) daily. In the high darbepoetin alfa dose group ( $> 0.45$  and  $\leq 1.5$  mcg/kg/week), participants received an initial vadadustat daily dose of 450 mg daily. Vadadustat was titrated to achieve and maintain target hemoglobin (Hb) levels. The dose range for titration was 150 to 900 mg vadadustat QD.

|                       |                |
|-----------------------|----------------|
| Reporting group title | Vadadustat TIW |
|-----------------------|----------------|

Reporting group description:

Participants were randomized to receive vadadustat TIW orally. Vadadustat starting daily dose was determined by pre-Baseline mean weekly darbepoetin alfa dose (or ESA equivalent). In the low darbepoetin alfa dose group ( $\leq 0.45$  mcg/kg/week), participants received an initial vadadustat dose of 600 mg TIW. In the high darbepoetin alfa dose group ( $> 0.45$  and  $\leq 1.5$  mcg/kg/week), participants received an initial vadadustat dose of 750 mg TIW. Vadadustat was titrated to achieve and maintain target Hb levels. The dose range for titration was 150 to 1200 mg vadadustat TIW.

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Darbepoetin alfa |
|-----------------------|------------------|

Reporting group description:

Participants were randomized to receive darbepoetin alfa as a solution in single-dose prefilled syringes via intravenous (IV) injection through dialysis vascular access. For participants who had received darbepoetin alfa during screening, the initial dosing regimen was approximately the same weekly dose that they were receiving prior to randomization. For participants who had received darbepoetin alfa for the first time, the initial dosing regimen was determined by the United States Package Insert (USPI) or European Union Summary of product characteristics (EU SmPC), per the medical judgment of the investigator.

| Reporting group values                    | Vadadustat QD | Vadadustat TIW | Darbepoetin alfa |
|---|---------------|----------------|------------------|
| Number of subjects                        | 105           | 106            | 108              |
| Age categorical                           |               |                |                  |
| Units:                                    |               |                |                  |
| <65 years                                 | 59            | 65             | 69               |
| $\geq 65$ years                           | 46            | 41             | 39               |
| Age continuous                            |               |                |                  |
| Units: years                              |               |                |                  |
| arithmetic mean                           | 60.9          | 61.2           | 60.8             |
| standard deviation                        | $\pm 13.4$    | $\pm 12.5$     | $\pm 12.8$       |
| Gender categorical                        |               |                |                  |
| Units: Subjects                           |               |                |                  |
| Female                                    | 47            | 46             | 43               |
| Male                                      | 58            | 60             | 65               |
| Race/Ethnicity, Customized                |               |                |                  |
| Units: Subjects                           |               |                |                  |
| American Indian or Alaska Native          | 1             | 2              | 0                |
| Asian                                     | 4             | 1              | 3                |
| Black Or African American                 | 31            | 30             | 33               |
| Native Hawaiian or Other Pacific Islander | 0             | 2              | 1                |
| White                                     | 68            | 67             | 71               |
| Not Reported                              | 1             | 3              | 0                |
| Reported as Other                         | 0             | 1              | 0                |

| <b>Reporting group values</b>   | Total |  |  |
|---|-------|--|--|
| Number of subjects  | 319   |  |  |
| Age categorical<br>Units:   |       |  |  |
| <65 years   | 193   |  |  |
| ≥65 years   | 126   |  |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | -     |  |  |
| Gender categorical<br>Units: Subjects                                   |       |  |  |
| Female  | 136   |  |  |
| Male  | 183   |  |  |
| Race/Ethnicity, Customized<br>Units: Subjects                           |       |  |  |
| American Indian or Alaska Native  | 3     |  |  |
| Asian   | 8     |  |  |
| Black Or African American   | 94    |  |  |
| Native Hawaiian or Other Pacific Islander                               | 3     |  |  |
| White   | 206   |  |  |
| Not Reported  | 4     |  |  |
| Reported as Other   | 1     |  |  |

## End points

### End points reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Vadadustat QD |
|-----------------------|---------------|

Reporting group description:

Participants were randomized to receive vadadustat QD orally. Vadadustat starting daily dose was determined by pre-Baseline mean weekly darbepoetin alfa dose (or ESA equivalent). In the low darbepoetin alfa dose group (less than or equal to [ $\leq$ ] 0.45 micrograms per kilograms per week [mcg/kg/week]), participants received an initial vadadustat daily dose of 300 milligrams (mg) daily. In the high darbepoetin alfa dose group ( $> 0.45$  and  $\leq 1.5$  mcg/kg/week), participants received an initial vadadustat daily dose of 450 mg daily. Vadadustat was titrated to achieve and maintain target hemoglobin (Hb) levels. The dose range for titration was 150 to 900 mg vadadustat QD.

|                       |                |
|-----------------------|----------------|
| Reporting group title | Vadadustat TIW |
|-----------------------|----------------|

Reporting group description:

Participants were randomized to receive vadadustat TIW orally. Vadadustat starting daily dose was determined by pre-Baseline mean weekly darbepoetin alfa dose (or ESA equivalent). In the low darbepoetin alfa dose group ( $\leq 0.45$  mcg/kg/week), participants received an initial vadadustat dose of 600 mg TIW. In the high darbepoetin alfa dose group ( $> 0.45$  and  $\leq 1.5$  mcg/kg/week), participants received an initial vadadustat dose of 750 mg TIW. Vadadustat was titrated to achieve and maintain target Hb levels. The dose range for titration was 150 to 1200 mg vadadustat TIW.

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Darbepoetin alfa |
|-----------------------|------------------|

Reporting group description:

Participants were randomized to receive darbepoetin alfa as a solution in single-dose prefilled syringes via intravenous (IV) injection through dialysis vascular access. For participants who had received darbepoetin alfa during screening, the initial dosing regimen was approximately the same weekly dose that they were receiving prior to randomization. For participants who had received darbepoetin alfa for the first time, the initial dosing regimen was determined by the United States Package Insert (USPI) or European Union Summary of product characteristics (EU SmPC), per the medical judgment of the investigator.

### Primary: Change from Baseline in Hb to the average over the Primary evaluation period (PEP) (Weeks 20 to 26)

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in Hb to the average over the Primary evaluation period (PEP) (Weeks 20 to 26) <sup>[1]</sup> |
|-----------------|--|

End point description:

The Baseline Hb was defined as the average of the last 2 central laboratory Hb values taken on or prior to the first dose date. The average for the PEP was calculated as the average of all Hb measurements from the central laboratory within the three visit windows during Weeks 20 through 26, regardless of intercurrent events. Analysis was conducted using an analysis of covariance (ANCOVA) model with multiple imputation for missing data with randomization stratification factors and Baseline Hb as covariates. Change from Baseline was calculated as PEP value minus the Baseline value.

Randomized population was defined as all participants randomized.

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

End point timeframe:

Baseline; Weeks 20 to 26

Notes:

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

Justification: Per protocol, statistical analysis was not planned for this endpoint

| <b>End point values</b>             | Vadadustat QD   | Vadadustat TIW  | Darbepoetin alfa |  |
|-------------------------------------|-----------------|-----------------|------------------|--|
| Subject group type                  | Reporting group | Reporting group | Reporting group  |  |
| Number of subjects analysed         | 105             | 106             | 108              |  |
| Units: Grams per deciliter (g/dL)   |                 |                 |                  |  |
| least squares mean (standard error) | 0.07 (± 0.12)   | -0.19 (± 0.12)  | 0.34 (± 0.12)    |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Hb to the average over the Secondary evaluation period (SEP) (Weeks 46 to 52)

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in Hb to the average over the Secondary evaluation period (SEP) (Weeks 46 to 52) |
|-----------------|---|

End point description:

The Baseline Hb was defined as the average of the last 2 central laboratory Hb values taken on or prior to the first dose date. The average for the SEP was calculated as the average of all Hb measurements from the central laboratory within the three visit windows during Weeks 46 through 52, regardless of intercurrent events. Analysis was conducted using an ANCOVA model with multiple imputation for missing data with randomization stratification factors and Baseline Hb as covariates. Change from Baseline was calculated as SEP value minus the Baseline value.

Randomized population.

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

End point timeframe:

Baseline; Weeks 46 to 52

| <b>End point values</b>             | Vadadustat QD   | Vadadustat TIW  | Darbepoetin alfa |  |
|-------------------------------------|-----------------|-----------------|------------------|--|
| Subject group type                  | Reporting group | Reporting group | Reporting group  |  |
| Number of subjects analysed         | 105             | 106             | 108              |  |
| Units: g/dL                         |                 |                 |                  |  |
| least squares mean (standard error) | 0.04 (± 0.15)   | 0.03 (± 0.15)   | 0.44 (± 0.15)    |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug (Day 1) up to Week 56 (from first dose of study drug to last dose + 4 weeks of follow-up)

Adverse event reporting additional description:

Treatment-emergent adverse events (TEAEs) are defined as those adverse events (AEs) that began or worsened after treatment initiation and are reported for the Safety Population which consisted of all participants in the randomized population who received at least 1 dose of study drug.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 25.0 |
|--------------------|------|

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Vadadustat QD |
|-----------------------|---------------|

Reporting group description:

Participants were randomized to receive vadadustat QD orally. Vadadustat starting daily dose was determined by pre-Baseline mean weekly darbepoetin alfa dose (or ESA equivalent). In the low darbepoetin alfa dose group (less than or equal to [ $\leq$ ] 0.45 micrograms per kilograms per week [mcg/kg/week]), participants received an initial vadadustat daily dose of 300 milligrams (mg) daily. In the high darbepoetin alfa dose group ( $>$  0.45 and  $\leq$  1.5 mcg/kg/week), participants received an initial vadadustat daily dose of 450 mg daily. Vadadustat was titrated to achieve and maintain target hemoglobin (Hb) levels. The dose range for titration was 150 to 900 mg vadadustat QD.

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Darbepoetin alfa |
|-----------------------|------------------|

Reporting group description:

Participants were randomized to receive darbepoetin alfa as a solution in single-dose prefilled syringes via intravenous (IV) injection through dialysis vascular access. For participants who had received darbepoetin alfa during screening, the initial dosing regimen was approximately the same weekly dose that they were receiving prior to randomization. For participants who had received darbepoetin alfa for the first time, the initial dosing regimen was determined by the United States Package Insert (USPI) or European Union Summary of product characteristics (EU SmPC), per the medical judgment of the investigator.

|                       |                |
|-----------------------|----------------|
| Reporting group title | Vadadustat TIW |
|-----------------------|----------------|

Reporting group description:

Participants were randomized to receive vadadustat TIW orally. Vadadustat starting daily dose was determined by pre-Baseline mean weekly darbepoetin alfa dose (or ESA equivalent). In the low darbepoetin alfa dose group ( $\leq$  0.45 mcg/kg/week), participants received an initial vadadustat dose of 600 mg TIW. In the high darbepoetin alfa dose group ( $>$  0.45 and  $\leq$  1.5 mcg/kg/week), participants received an initial vadadustat dose of 750 mg TIW. Vadadustat was titrated to achieve and maintain target Hb levels. The dose range for titration was 150 to 1200 mg vadadustat TIW.

| <b>Serious adverse events</b>                                       | Vadadustat QD     | Darbepoetin alfa  | Vadadustat TIW    |
|---|-------------------|-------------------|-------------------|
| Total subjects affected by serious adverse events                   |                   |                   |                   |
| subjects affected / exposed   | 47 / 105 (44.76%) | 47 / 108 (43.52%) | 47 / 104 (45.19%) |
| number of deaths (all causes)                                       | 12                | 7                 | 9                 |
| number of deaths resulting from adverse events                      | 0                 | 0                 | 0                 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                   |                   |
| Adenocarcinoma of appendix  |                   |                   |                   |
| alternative dictionary used:<br>MedDRA 25                           |                   |                   |                   |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Prostate cancer                                 |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 0 / 104 (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           |
| Liposarcoma                                     |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Invasive ductal breast carcinoma                |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Glioblastoma                                    |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal adenocarcinoma                 |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular disorders                              |                 |                 |                 |
| Hypertensive crisis                             |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 2 / 104 (1.92%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Hypertensive emergency                          |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypertensive urgency                            |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 1 / 108 (0.93%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Jugular vein thrombosis                         |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (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           |
| Steal syndrome                                  |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Peripheral arterial occlusive disease           |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 2 / 104 (1.92%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Peripheral vascular disorder                    |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                                   |                                   |                                   |
|---|-----------------------------------|-----------------------------------|-----------------------------------|
| Orthostatic hypotension<br>alternative dictionary used:<br>MedDRA 25<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all  | 0 / 105 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 108 (0.93%)<br>0 / 1<br>0 / 0 | 1 / 104 (0.96%)<br>0 / 1<br>0 / 0 |
| Surgical and medical procedures<br>Arteriovenous fistula operation<br>alternative dictionary used:<br>MedDRA 25<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                   | 0 / 105 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 108 (0.93%)<br>0 / 1<br>0 / 0 | 0 / 104 (0.00%)<br>0 / 0<br>0 / 0 |
| General disorders and administration<br>site conditions<br>Asthenia<br>alternative dictionary used:<br>MedDRA 25<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                  | 0 / 105 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 108 (0.93%)<br>0 / 1<br>0 / 0 | 0 / 104 (0.00%)<br>0 / 0<br>0 / 0 |
| Non-cardiac chest pain<br>alternative dictionary used:<br>MedDRA 25<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all   | 3 / 105 (2.86%)<br>0 / 3<br>0 / 0 | 0 / 108 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 104 (0.96%)<br>0 / 1<br>0 / 0 |
| Sudden cardiac death<br>alternative dictionary used:<br>MedDRA 25<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all   | 1 / 105 (0.95%)<br>0 / 1<br>0 / 1 | 0 / 108 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 104 (0.00%)<br>0 / 0<br>0 / 0 |
| Immune system disorders<br>Contrast media allergy<br>alternative dictionary used:<br>MedDRA 25<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all<br><br>Kidney transplant rejection | 0 / 105 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 108 (0.93%)<br>0 / 1<br>0 / 0 | 0 / 104 (0.00%)<br>0 / 0<br>0 / 0 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| alternative dictionary used:<br>MedDRA 25   |                 |                 |                 |
| subjects affected / exposed   | 0 / 105 (0.00%) | 2 / 108 (1.85%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all                                    | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to<br>treatment / all   | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Reproductive system and breast disorders</b>                                       |                 |                 |                 |
| Postmenopausal haemorrhage<br>alternative dictionary used:<br>MedDRA 25               |                 |                 |                 |
| subjects affected / exposed   | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all                                    | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all   | 0 / 0           | 0 / 0           | 0 / 0           |
| Uterine haemorrhage<br>alternative dictionary used:<br>MedDRA 25                      |                 |                 |                 |
| subjects affected / exposed   | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to<br>treatment / all                                    | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all   | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Respiratory, thoracic and mediastinal disorders</b>                                |                 |                 |                 |
| Acute pulmonary oedema<br>alternative dictionary used:<br>MedDRA 25                   |                 |                 |                 |
| subjects affected / exposed   | 2 / 105 (1.90%) | 0 / 108 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all                                    | 0 / 3           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all   | 0 / 0           | 0 / 0           | 0 / 0           |
| Dyspnoea<br>alternative dictionary used:<br>MedDRA 25                                 |                 |                 |                 |
| subjects affected / exposed   | 2 / 105 (1.90%) | 0 / 108 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all                                    | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all   | 0 / 0           | 0 / 0           | 0 / 0           |
| Chronic obstructive pulmonary<br>disease<br>alternative dictionary used:<br>MedDRA 25 |                 |                 |                 |
| subjects affected / exposed   | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all                                    | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all   | 0 / 0           | 0 / 0           | 0 / 0           |
| Acute respiratory failure   |                 |                 |                 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| alternative dictionary used:<br>MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                        | 3 / 105 (2.86%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to<br>treatment / all | 0 / 3           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pleural effusion                                   |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                        | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary hypertension                             |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                        | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to<br>treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary oedema                                   |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                        | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 2 / 104 (1.92%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           | 0 / 2           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory arrest                                 |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                        | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory failure                                |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                        | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Investigations                                     |                 |                 |                 |
| Aspartate aminotransferase<br>increased            |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25          |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (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           |
| Anticoagulation drug level above therapeutic    |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 0 / 104 (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           |
| Alanine aminotransferase increased              |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (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           |
| Troponin increased                              |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 0 / 104 (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           |
| Transaminases increased                         |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 0 / 104 (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           |
| Liver function test increased                   |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatic enzyme increased                        |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                           | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 0 / 104 (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           |
| <b>Injury, poisoning and procedural complications</b> |                 |                 |                 |
| Ankle fracture  |                 |                 |                 |
| alternative dictionary used: MedDRA 25                |                 |                 |                 |
| subjects affected / exposed                           | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| Arteriovenous fistula site complication               |                 |                 |                 |
| alternative dictionary used: MedDRA 25                |                 |                 |                 |
| subjects affected / exposed                           | 2 / 105 (1.90%) | 0 / 108 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all       | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| Arteriovenous fistula site haemorrhage                |                 |                 |                 |
| alternative dictionary used: MedDRA 25                |                 |                 |                 |
| subjects affected / exposed                           | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (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 fistula thrombosis                      |                 |                 |                 |
| alternative dictionary used: MedDRA 25                |                 |                 |                 |
| subjects affected / exposed                           | 0 / 105 (0.00%) | 3 / 108 (2.78%) | 2 / 104 (1.92%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 3           | 0 / 2           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| Arteriovenous graft thrombosis                        |                 |                 |                 |
| alternative dictionary used: MedDRA 25                |                 |                 |                 |
| subjects affected / exposed                           | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all       | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| Femur fracture  |                 |                 |                 |
| alternative dictionary used: MedDRA 25                |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| 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 sacrum                                |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (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           |
| Humerus fracture                                |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subdural haemorrhage                            |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subdural haematoma                              |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Wrist fracture                                  |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| 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 haemorrhage                |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (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           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Traumatic haemothorax<br>alternative dictionary used:<br>MedDRA 25<br>subjects affected / exposed   | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all  | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all   | 0 / 0           | 0 / 0           | 0 / 0           |
| Traumatic haematoma<br>alternative dictionary used:<br>MedDRA 25<br>subjects affected / exposed   | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to<br>treatment / all  | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all   | 0 / 0           | 0 / 0           | 0 / 1           |
| Post procedural haemorrhage<br>alternative dictionary used:<br>MedDRA 25<br>subjects affected / exposed   | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all  | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all   | 0 / 0           | 0 / 0           | 0 / 0           |
| Rib fracture<br>alternative dictionary used:<br>MedDRA 25<br>subjects affected / exposed  | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all  | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all   | 0 / 0           | 0 / 0           | 0 / 0           |
| Spinal compression fracture<br>alternative dictionary used:<br>MedDRA 25<br>subjects affected / exposed   | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all  | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all   | 0 / 0           | 0 / 0           | 0 / 0           |
| Congenital, familial and genetic<br>disorders<br>Haemorrhagic arteriovenous<br>malformation<br>alternative dictionary used:<br>MedDRA 25<br>subjects affected / exposed | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all  | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all   | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders   |                 |                 |                 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| Angina pectoris<br>alternative dictionary used:<br>MedDRA 25                 |                 |                 |                 |
| subjects affected / exposed  | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 1 / 104 (0.96%) |
| occurrences causally related to<br>treatment / all                           | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to<br>treatment / all                                | 0 / 0           | 0 / 0           | 0 / 0           |
| Acute left ventricular failure<br>alternative dictionary used:<br>MedDRA 25  |                 |                 |                 |
| subjects affected / exposed  | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to<br>treatment / all                           | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                                | 0 / 0           | 0 / 0           | 0 / 0           |
| Acute myocardial infarction<br>alternative dictionary used:<br>MedDRA 25     |                 |                 |                 |
| subjects affected / exposed  | 2 / 105 (1.90%) | 0 / 108 (0.00%) | 6 / 104 (5.77%) |
| occurrences causally related to<br>treatment / all                           | 0 / 3           | 0 / 0           | 0 / 6           |
| deaths causally related to<br>treatment / all                                | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrial fibrillation<br>alternative dictionary used:<br>MedDRA 25             |                 |                 |                 |
| subjects affected / exposed  | 1 / 105 (0.95%) | 1 / 108 (0.93%) | 2 / 104 (1.92%) |
| occurrences causally related to<br>treatment / all                           | 0 / 1           | 0 / 1           | 0 / 4           |
| deaths causally related to<br>treatment / all                                | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrial flutter<br>alternative dictionary used:<br>MedDRA 25                  |                 |                 |                 |
| subjects affected / exposed  | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all                           | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all                                | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrioventricular block complete<br>alternative dictionary used:<br>MedDRA 25 |                 |                 |                 |
| subjects affected / exposed  | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to<br>treatment / all                           | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                                | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac arrest<br>alternative dictionary used:<br>MedDRA 25                  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 105 (0.95%) | 1 / 108 (0.93%) | 2 / 104 (1.92%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 2           |
| Cardiac failure                                 |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 2 / 105 (1.90%) | 1 / 108 (0.93%) | 0 / 104 (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           |
| Pericardial effusion                            |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac failure congestive                      |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 2 / 105 (1.90%) | 1 / 108 (0.93%) | 2 / 104 (1.92%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardio-respiratory arrest                       |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 1 / 108 (0.93%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| Coronary artery disease                         |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial infarction                           |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 3 / 104 (2.88%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| Cardiac failure acute<br>alternative dictionary used:<br>MedDRA 25<br>subjects affected / exposed              | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all   | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all  | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders<br>Ataxia<br>alternative dictionary used:<br>MedDRA 25<br>subjects affected / exposed | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all   | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all  | 0 / 0           | 0 / 0           | 0 / 0           |
| Bell's palsy<br>alternative dictionary used:<br>MedDRA 25<br>subjects affected / exposed                       | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all   | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all  | 0 / 0           | 0 / 0           | 0 / 0           |
| Embolic stroke<br>alternative dictionary used:<br>MedDRA 25<br>subjects affected / exposed                     | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all   | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all  | 0 / 0           | 0 / 0           | 0 / 0           |
| Syncope<br>alternative dictionary used:<br>MedDRA 25<br>subjects affected / exposed                            | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all   | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all  | 0 / 0           | 0 / 0           | 0 / 0           |
| Seizure<br>alternative dictionary used:<br>MedDRA 25<br>subjects affected / exposed                            | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all   | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all  | 0 / 0           | 0 / 0           | 0 / 0           |
| Presyncope<br>alternative dictionary used:<br>MedDRA 25  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (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           |
| Myelopathy                                      |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (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           |
| Ischaemic stroke                                |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ischaemic cerebral infarction                   |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 1 / 108 (0.93%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemorrhagic stroke                             |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Generalised tonic-clonic seizure                |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (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           |
| Encephalopathy                                  |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| Toxic encephalopathy<br>alternative dictionary used:<br>MedDRA 25<br>subjects affected / exposed       | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to<br>treatment / all   | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all  | 0 / 0           | 0 / 0           | 0 / 0           |
| Transient ischaemic attack<br>alternative dictionary used:<br>MedDRA 25<br>subjects affected / exposed | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to<br>treatment / all   | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all  | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood and lymphatic system disorders   |                 |                 |                 |
| Anaemia<br>alternative dictionary used:<br>MedDRA 25<br>subjects affected / exposed                    | 3 / 105 (2.86%) | 5 / 108 (4.63%) | 5 / 104 (4.81%) |
| occurrences causally related to<br>treatment / all   | 0 / 3           | 0 / 6           | 0 / 5           |
| deaths causally related to<br>treatment / all  | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood loss anaemia<br>alternative dictionary used:<br>MedDRA 25<br>subjects affected / exposed         | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 2 / 104 (1.92%) |
| occurrences causally related to<br>treatment / all   | 0 / 1           | 0 / 0           | 0 / 2           |
| deaths causally related to<br>treatment / all  | 0 / 0           | 0 / 0           | 0 / 0           |
| Thrombocytopenia<br>alternative dictionary used:<br>MedDRA 25<br>subjects affected / exposed           | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to<br>treatment / all   | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all  | 0 / 0           | 0 / 0           | 0 / 0           |
| Eye disorders  |                 |                 |                 |
| Visual impairment<br>alternative dictionary used:<br>MedDRA 25<br>subjects affected / exposed          | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all   | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all  | 0 / 0           | 0 / 0           | 0 / 0           |
| Vitreous haemorrhage<br>alternative dictionary used:<br>MedDRA 25                                      |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed   | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all                           | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all                                | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Gastrointestinal disorders</b>   |                 |                 |                 |
| Gastrointestinal haemorrhage<br>alternative dictionary used:<br>MedDRA 25 |                 |                 |                 |
| subjects affected / exposed   | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 3 / 104 (2.88%) |
| occurrences causally related to treatment / all                           | 0 / 0           | 0 / 0           | 0 / 3           |
| deaths causally related to treatment / all                                | 0 / 0           | 0 / 0           | 0 / 1           |
| Duodenal ulcer haemorrhage<br>alternative dictionary used:<br>MedDRA 25   |                 |                 |                 |
| subjects affected / exposed   | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all                           | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all                                | 0 / 0           | 0 / 0           | 0 / 0           |
| Duodenitis<br>alternative dictionary used:<br>MedDRA 25                   |                 |                 |                 |
| subjects affected / exposed   | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all                           | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all                                | 0 / 0           | 0 / 0           | 0 / 0           |
| Food poisoning<br>alternative dictionary used:<br>MedDRA 25               |                 |                 |                 |
| subjects affected / exposed   | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 0 / 104 (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           |
| Gastritis haemorrhagic<br>alternative dictionary used:<br>MedDRA 25       |                 |                 |                 |
| subjects affected / exposed   | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all                           | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                                | 0 / 0           | 0 / 0           | 0 / 0           |
| Chronic gastritis<br>alternative dictionary used:<br>MedDRA 25            |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haematochezia                                   |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (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                       |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pancreatic duct obstruction                     |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 0 / 104 (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           |
| Pancreatitis acute                              |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 2 / 104 (1.92%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Small intestinal haemorrhage                    |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Upper gastrointestinal haemorrhage              |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 2 / 108 (1.85%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| Hepatobiliary disorders                            |                 |                 |                 |
| Cholecystitis acute                                |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                        | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bile duct stenosis                                 |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                        | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin and subcutaneous tissue disorders             |                 |                 |                 |
| Skin ulcer   |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                        | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diabetic foot                                      |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                        | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intertrigo   |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                        | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                        |                 |                 |                 |
| Renal cyst haemorrhage                             |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                        | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| End stage renal disease                            |                 |                 |                 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| alternative dictionary used:<br>MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                        | 2 / 105 (1.90%) | 0 / 108 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 2           | 0 / 0           | 0 / 0           |
| Azotaemia  |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                        | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Endocrine disorders                                |                 |                 |                 |
| Hyperparathyroidism secondary                      |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                        | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Parathyroid hyperplasia                            |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                        | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders    |                 |                 |                 |
| Osteoarthritis                                     |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                        | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intervertebral disc protrusion                     |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                        | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Fracture pain                                      |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25          |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cervical spinal stenosis                        |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 1 / 108 (0.93%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Back pain                                       |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 2 / 104 (1.92%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infections and infestations                     |                 |                 |                 |
| Arthritis bacterial                             |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (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           |
| Asymptomatic COVID-19                           |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| COVID-19  |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25       |                 |                 |                 |
| subjects affected / exposed                     | 2 / 105 (1.90%) | 4 / 108 (3.70%) | 2 / 104 (1.92%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 4           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Device related sepsis                           |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25       |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Candida pneumonia                               |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cellulitis                                      |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 2 / 105 (1.90%) | 2 / 108 (1.85%) | 2 / 104 (1.92%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cryptococcal fungaemia                          |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (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           |
| Device related bacteraemia                      |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| COVID-19 pneumonia                              |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 7 / 105 (6.67%) | 4 / 108 (3.70%) | 8 / 104 (7.69%) |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 4           | 0 / 8           |
| deaths causally related to treatment / all      | 0 / 3           | 0 / 2           | 0 / 3           |
| Diabetic foot infection                         |                 |                 |                 |
| alternative dictionary used: MedDRA 25          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (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           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Diverticulitis<br>alternative dictionary used:<br>MedDRA 25                         |                 |                 |                 |
| subjects affected / exposed   | 0 / 105 (0.00%) | 2 / 108 (1.85%) | 1 / 104 (0.96%) |
| occurrences causally related to<br>treatment / all                                  | 0 / 0           | 0 / 2           | 0 / 1           |
| deaths causally related to<br>treatment / all                                       | 0 / 0           | 0 / 0           | 0 / 0           |
| Diverticulitis intestinal haemorrhagic<br>alternative dictionary used:<br>MedDRA 25 |                 |                 |                 |
| subjects affected / exposed   | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all                                  | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all                                       | 0 / 0           | 0 / 0           | 0 / 0           |
| Endocarditis<br>alternative dictionary used:<br>MedDRA 25                           |                 |                 |                 |
| subjects affected / exposed   | 1 / 105 (0.95%) | 1 / 108 (0.93%) | 1 / 104 (0.96%) |
| occurrences causally related to<br>treatment / all                                  | 0 / 1           | 0 / 1           | 0 / 1           |
| deaths causally related to<br>treatment / all                                       | 0 / 0           | 0 / 0           | 0 / 0           |
| Enterococcal bacteraemia<br>alternative dictionary used:<br>MedDRA 25               |                 |                 |                 |
| subjects affected / exposed   | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to<br>treatment / all                                  | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                                       | 0 / 0           | 0 / 0           | 0 / 0           |
| Otitis media staphylococcal<br>alternative dictionary used:<br>MedDRA 25            |                 |                 |                 |
| subjects affected / exposed   | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to<br>treatment / all                                  | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                                       | 0 / 0           | 0 / 0           | 0 / 0           |
| Klebsiella sepsis<br>alternative dictionary used:<br>MedDRA 25                      |                 |                 |                 |
| subjects affected / exposed   | 0 / 105 (0.00%) | 2 / 108 (1.85%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all                                  | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to<br>treatment / all                                       | 0 / 0           | 0 / 0           | 0 / 0           |
| Muscle abscess<br>alternative dictionary used:<br>MedDRA 25                         |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Necrotising soft tissue infection               |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Osteomyelitis                                   |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 2 / 108 (1.85%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gangrene  |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 2 / 108 (1.85%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Peritonitis bacterial                           |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Pneumonia                                       |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25       |                 |                 |                 |
| subjects affected / exposed                     | 2 / 105 (1.90%) | 1 / 108 (0.93%) | 3 / 104 (2.88%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Pneumonia aspiration                            |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Pneumonia staphylococcal<br>alternative dictionary used:<br>MedDRA 25     |                 |                 |                 |
| subjects affected / exposed   | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to<br>treatment / all                        | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                             | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal abscess<br>alternative dictionary used:<br>MedDRA 25                |                 |                 |                 |
| subjects affected / exposed   | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to<br>treatment / all                        | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                             | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary tract infection<br>alternative dictionary used:<br>MedDRA 25      |                 |                 |                 |
| subjects affected / exposed   | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to<br>treatment / all                        | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                             | 0 / 0           | 0 / 0           | 0 / 0           |
| Sepsis<br>alternative dictionary used:<br>MedDRA 25                       |                 |                 |                 |
| subjects affected / exposed   | 1 / 105 (0.95%) | 3 / 108 (2.78%) | 3 / 104 (2.88%) |
| occurrences causally related to<br>treatment / all                        | 0 / 1           | 0 / 3           | 0 / 3           |
| deaths causally related to<br>treatment / all                             | 0 / 1           | 0 / 0           | 0 / 0           |
| Septic shock<br>alternative dictionary used:<br>MedDRA 25                 |                 |                 |                 |
| subjects affected / exposed   | 1 / 105 (0.95%) | 1 / 108 (0.93%) | 1 / 104 (0.96%) |
| occurrences causally related to<br>treatment / all                        | 0 / 1           | 0 / 1           | 0 / 1           |
| deaths causally related to<br>treatment / all                             | 0 / 1           | 0 / 1           | 0 / 1           |
| Staphylococcal osteomyelitis<br>alternative dictionary used:<br>MedDRA 25 |                 |                 |                 |
| subjects affected / exposed   | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to<br>treatment / all                        | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                             | 0 / 0           | 0 / 0           | 0 / 0           |
| Staphylococcal sepsis<br>alternative dictionary used:<br>MedDRA 25        |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 105 (0.00%) | 1 / 108 (0.93%) | 0 / 104 (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           |
| SARS-CoV-2 sepsis                               |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (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 graft infection                        |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (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           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Hypocalcaemia                                   |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 105 (0.00%) | 0 / 108 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypervolaemia                                   |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25       |                 |                 |                 |
| subjects affected / exposed                     | 2 / 105 (1.90%) | 4 / 108 (3.70%) | 4 / 104 (3.85%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 4           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyperkalaemia                                   |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 3 / 108 (2.78%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 5           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyperglycaemia                                  |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25       |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 105 (0.95%) | 1 / 108 (0.93%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Failure to thrive</b>                        |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| <b>Hypoglycaemia</b>                            |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 1 / 108 (0.93%) | 2 / 104 (1.92%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Diabetic ketoacidosis</b>                    |                 |                 |                 |
| alternative dictionary used:<br>MedDRA 25       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 105 (0.95%) | 0 / 108 (0.00%) | 0 / 104 (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           |

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

| <b>Non-serious adverse events</b>                     | Vadadustat QD     | Darbepoetin alfa  | Vadadustat TIW    |
|---|-------------------|-------------------|-------------------|
| Total subjects affected by non-serious adverse events |                   |                   |                   |
| subjects affected / exposed                           | 46 / 105 (43.81%) | 46 / 108 (42.59%) | 49 / 104 (47.12%) |
| <b>Injury, poisoning and procedural complications</b> |                   |                   |                   |
| Fall  |                   |                   |                   |
| alternative dictionary used:<br>MedDRA 25             |                   |                   |                   |
| subjects affected / exposed                           | 10 / 105 (9.52%)  | 5 / 108 (4.63%)   | 6 / 104 (5.77%)   |
| occurrences (all)                                     | 12                | 7                 | 7                 |
| <b>Vascular disorders</b>                             |                   |                   |                   |
| Hypertension  |                   |                   |                   |
| alternative dictionary used:<br>MedDRA 25             |                   |                   |                   |
| subjects affected / exposed                           | 6 / 105 (5.71%)   | 10 / 108 (9.26%)  | 11 / 104 (10.58%) |
| occurrences (all)                                     | 7                 | 10                | 14                |

|  |   |   |  |
|--|---|---|--|
| <p>Blood and lymphatic system disorders</p> <p>Anaemia</p> <p>alternative dictionary used:<br/>MedDRA 25</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>5 / 105 (4.76%)</p> <p>5</p>   | <p>7 / 108 (6.48%)</p> <p>9</p>   | <p>7 / 104 (6.73%)</p> <p>7</p>  |
| <p>General disorders and administration site conditions</p> <p>Oedema peripheral</p> <p>alternative dictionary used:<br/>MedDRA 25</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>6 / 105 (5.71%)</p> <p>6</p>   | <p>3 / 108 (2.78%)</p> <p>3</p>   | <p>0 / 104 (0.00%)</p> <p>0</p>  |
| <p>Gastrointestinal disorders</p> <p>Vomiting</p> <p>alternative dictionary used:<br/>MedDRA 25</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nausea</p> <p>alternative dictionary used:<br/>MedDRA 25</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Diarrhoea</p> <p>alternative dictionary used:<br/>MedDRA 25</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Abdominal pain</p> <p>alternative dictionary used:<br/>MedDRA 25</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>10 / 105 (9.52%)</p> <p>13</p> <p>12 / 105 (11.43%)</p> <p>14</p> <p>14 / 105 (13.33%)</p> <p>15</p> <p>4 / 105 (3.81%)</p> <p>4</p> | <p>6 / 108 (5.56%)</p> <p>6</p> <p>6 / 108 (5.56%)</p> <p>6</p> <p>6 / 108 (5.56%)</p> <p>8</p> <p>8 / 108 (7.41%)</p> <p>8</p> | <p>4 / 104 (3.85%)</p> <p>4</p> <p>6 / 104 (5.77%)</p> <p>7</p> <p>15 / 104 (14.42%)</p> <p>19</p> <p>4 / 104 (3.85%)</p> <p>4</p> |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Back pain</p> <p>alternative dictionary used:<br/>MedDRA 25</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>2 / 105 (1.90%)</p> <p>2</p>   | <p>2 / 108 (1.85%)</p> <p>2</p>   | <p>6 / 104 (5.77%)</p> <p>6</p>  |
| <p>Infections and infestations</p> <p>COVID-19</p> <p>alternative dictionary used:<br/>MedDRA 25</p>   |   |   |  |

|  |                         |                        |                         |
|--|-------------------------|------------------------|-------------------------|
| subjects affected / exposed<br>occurrences (all) | 12 / 105 (11.43%)<br>12 | 10 / 108 (9.26%)<br>10 | 11 / 104 (10.58%)<br>12 |
| Metabolism and nutrition disorders               |                         |                        |                         |
| Hypoglycaemia                                    |                         |                        |                         |
| alternative dictionary used:<br>MedDRA 25        |                         |                        |                         |
| subjects affected / exposed<br>occurrences (all) | 6 / 105 (5.71%)<br>7    | 3 / 108 (2.78%)<br>3   | 1 / 104 (0.96%)<br>1    |
| Hyperkalaemia                                    |                         |                        |                         |
| alternative dictionary used:<br>MedDRA 25        |                         |                        |                         |
| subjects affected / exposed<br>occurrences (all) | 4 / 105 (3.81%)<br>6    | 9 / 108 (8.33%)<br>13  | 5 / 104 (4.81%)<br>5    |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment   |
|---------------|---|
| 17 March 2021 | The amendment alters the trial design and/or increases the potential risk to the participant, the currently approved written ICF will require similar modification. In such cases, after approval/favorable opinion of the new ICF by the IRB/IEC, repeat written informed consent will be obtained from participants enrolled in the trial before expecting continued participation and before the amendment-specified changes in the trial are implemented. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

Per the protocol, all results data are summarized by the arm to which participants were randomized; no separate analysis was performed to report results for initial vadadustat dose received in either of the vadadustat QD or vadadustat TIW arms.

Notes: