



## Clinical trial results:

**A double-blind, randomised, placebo-controlled study to assess the effect of SNF472 on progression of cardiovascular calcification on top of standard of care in end-stage-renal-disease (ESRD) patients on haemodialysis (HD)**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2016-002834-59 |
| Trial protocol           | GB ES          |
| Global end of trial date | 14 August 2019 |

### Results information

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

### Trial information

#### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | SNFCT2015-05 |
|-----------------------|--------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02966028 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Sanifit Therapeutics S.A.  |
| Sponsor organisation address | PARC BIT. Europa Building. 2nd Floor, Palma , Spain, 07121               |
| Public contact               | Sanifit Information, Sanifit Therapeutics S.A, info@sanifit.com          |
| Scientific contact           | Regulatory Affairs, Sanifit Therapeutics S.A.,<br>lydie.yang@sanifit.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                       | 14 August 2019 |
| Is this the analysis of the primary completion data? | Yes            |
| Primary completion date                              | 14 August 2019 |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 14 August 2019 |
| Was the trial ended prematurely?                     | No             |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective is to assess the effect of 2 dose levels of SNF472 (300 mg and 600 mg) compared to placebo on the progression of absolute change in coronary artery calcium volume score over a 12 month (52 weeks) period in ESRD patients on HD.

Protection of trial subjects:

Written informed consent was obtained from each subject prior to evaluations being performed for eligibility. Subjects were given adequate time to review the information in the informed consent and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study. Through the informed consent process each subject was made aware of the purpose of the study, the procedures, the benefits and risks of the study, the discomforts and the precautions taken. Any side effects or other health issues occurring during the study were followed up by the study doctor. Subjects were able to stop taking part in the study at any time without giving any reason.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 01 November 2016 |
| 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 | United Kingdom: 14 |
| Country: Number of subjects enrolled | Spain: 94          |
| Country: Number of subjects enrolled | United States: 166 |
| Worldwide total number of subjects   | 274                |
| EEA total number of subjects         | 108                |

Notes:

### Subjects enrolled per age group

|   |   |
|---|---|
| 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)      | 160 |
| From 65 to 84 years       | 114 |
| 85 years and over         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Subjects were required to meet all of the inclusion criteria and none of the exclusion criteria to be enrolled in the study. Subjects with existing coronary artery calcification based on Agatston scores at screening were enrolled because they were more likely to show progressive calcification during the study.

### Pre-assignment

Screening details:

Screening was conducted in 2 steps:

- Step 1: After written informed consent was obtained, a CT scan of the coronary arteries was obtained and bone mineral density was measured by DXA.
- Step 2: If eligibility criterion in Step 1 was confirmed, then baseline data were collected at this visit.

### Period 1

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

Blinding implementation details:

Investigators, all clinical staff, study subjects, and study administrators remained blinded throughout the clinical trial, unless safety concerns or a regulatory requirement made unblinding necessary.

### Arms

|                              |               |
|------------------------------|---------------|
| Are arms mutually exclusive? | Yes           |
| <b>Arm title</b>             | SNF472 300 mg |

Arm description:

Subjects were assigned to receive 300 mg SNF472 administered 3 times per week in conjunction with the subject's hemodialysis sessions. All subjects received 2 identical vials of 10 mL each: 1 vial of SNF472 (300 mg/vial) and 1 vial of physiologic saline.

|  |                                       |
|--|---------------------------------------|
| Arm type                               | Experimental                          |
| Investigational medicinal product name | SNF472                                |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

SNF472 was provided as 10 mL of sterile liquid in transparent glass vials, containing either 300 mg of SNF472 for a concentration of 30 mg/mL. The full volume of the vial was injected into a bag of saline (0.9% sodium chloride) and administered as a constant rate intravenous (IV) infusion connected to an infusion pump, which was connected directly to the dialysis machine via an IV giving set and an accessory heparin line. The preferred physiologic saline bag size for dilution of the study drug was 100 mL.

The infusion was initiated approximately 30 minutes after the start of the hemodialysis procedure and was to be completed in 2.5 hours.

|  |                                       |
|--|---------------------------------------|
| Investigational medicinal product name | Physiologic saline                    |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Physiologic saline was provided as 10 mL of sterile liquid in transparent glass vials. The full volume of

the physiologic saline was injected into a bag of saline (0.9% sodium chloride) and administered as a constant rate intravenous (IV) infusion connected to an infusion pump, which was connected directly to the dialysis machine via an IV giving set and an accessory heparin line. The preferred physiologic saline bag size for dilution of the study drug was 100 mL.

The infusion was initiated approximately 30 minutes after the start of the hemodialysis procedure and was to be completed in 2.5 hours.

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | SNF472 600 mg |
|------------------|---------------|

Arm description:

Subjects were assigned to receive 600 mg SNF472 administered 3 times per week in conjunction with the subject's hemodialysis sessions. All subjects received 2 identical vials of 10 mL each: 2 vials of SNF472 (300 mg/vial).

|  |                                       |
|--|---------------------------------------|
| Arm type                               | Experimental                          |
| Investigational medicinal product name | SNF472                                |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

SNF472 was provided as 10 mL of sterile liquid in transparent glass vials, containing either 300 mg of SNF472 for a concentration of 30 mg/mL. The full volume of the vial was injected into a bag of saline (0.9% sodium chloride) and administered as a constant rate intravenous (IV) infusion connected to an infusion pump, which was connected directly to the dialysis machine via an IV giving set and an accessory heparin line. The preferred physiologic saline bag size for dilution of the study drug was 100 mL.

The infusion was initiated approximately 30 minutes after the start of the hemodialysis procedure and was to be completed in 2.5 hours.

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

Arm description:

Subjects were assigned to receive physiologic saline (0.9% sodium chloride) administered 3 times per week in conjunction with the subject's hemodialysis sessions. All subjects received 2 identical vials of 10 mL each: 2 vial of physiologic saline.

|  |                                       |
|--|---------------------------------------|
| Arm type                               | Placebo                               |
| Investigational medicinal product name | Physiologic saline                    |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Physiologic saline was provided as 10 mL of sterile liquid in transparent glass vials. The full volume of the physiologic saline was injected into a bag of saline (0.9% sodium chloride) and administered as a constant rate intravenous (IV) infusion connected to an infusion pump, which was connected directly to the dialysis machine via an IV giving set and an accessory heparin line. The preferred physiologic saline bag size for dilution of the study drug was 100 mL.

The infusion was initiated approximately 30 minutes after the start of the hemodialysis procedure and was to be completed in 2.5 hours.

| <b>Number of subjects in period 1</b> | SNF472 300 mg | SNF472 600 mg | Placebo |
|---------------------------------------|---------------|---------------|---------|
| Started                               | 92            | 91            | 91      |
| Received dose                         | 92            | 91            | 90      |
| Completed                             | 68            | 57            | 60      |
| Not completed                         | 24            | 34            | 31      |
| Adverse event, serious fatal          | 1             | 6             | 3       |
| Physician decision                    | 1             | -             | -       |
| Consent withdrawn by subject          | 7             | 5             | 5       |
| Transferred to other clinic           | 2             | -             | -       |
| Transfer to other clinic              | -             | 2             | 1       |
| Adverse event, non-fatal              | 6             | 7             | 7       |
| Subject determination                 | -             | -             | 1       |
| Physician decision Death              | -             | -             | 2       |
| Site/visit compliance                 | 1             | -             | -       |
| Kidney transplant                     | 6             | 12            | 8       |
| Site/visit non-compliance             | -             | 2             | 4       |

## Baseline characteristics

### Reporting groups

|  |               |
|--|---------------|
| Reporting group title  | SNF472 300 mg |
| Reporting group description:   |               |
| Subjects were assigned to receive 300 mg SNF472 administered 3 times per week in conjunction with the subject's hemodialysis sessions. All subjects received 2 identical vials of 10 mL each: 1 vial of SNF472 (300 mg/vial) and 1 vial of physiologic saline. |               |
| Reporting group title  | SNF472 600 mg |
| Reporting group description:   |               |
| Subjects were assigned to receive 600 mg SNF472 administered 3 times per week in conjunction with the subject's hemodialysis sessions. All subjects received 2 identical vials of 10 mL each: 2 vials of SNF472 (300 mg/vial).                                 |               |
| Reporting group title  | Placebo       |
| Reporting group description:   |               |
| Subjects were assigned to receive physiologic saline (0.9% sodium chloride) administered 3 times per week in conjunction with the subject's hemodialysis sessions. All subjects received 2 identical vials of 10 mL each: 2 vial of physiologic saline.        |               |

| Reporting group values  | SNF472 300 mg | SNF472 600 mg | Placebo |
|---|---------------|---------------|---------|
| Number of subjects  | 92            | 91            | 91      |
| Age categorical   |               |               |         |
| Units: Subjects   |               |               |         |
| In utero  | 0             | 0             | 0       |
| Preterm newborn infants (gestational age < 37 wks)                                  | 0             | 0             | 0       |
| Newborns (0-27 days)  | 0             | 0             | 0       |
| Infants and toddlers (28 days-23 months)  | 0             | 0             | 0       |
| Children (2-11 years)   | 0             | 0             | 0       |
| Adolescents (12-17 years)   | 0             | 0             | 0       |
| Adults (18-64 years)  | 54            | 51            | 40      |
| From 65-84 years  | 38            | 40            | 51      |
| 85 years and over   | 0             | 0             | 0       |
| Age continuous  |               |               |         |
| Units: years  |               |               |         |
| arithmetic mean   | 63.0          | 63.6          | 64.1    |
| standard deviation  | ± 9.48        | ± 8.94        | ± 8.18  |
| Gender categorical  |               |               |         |
| Units: Subjects   |               |               |         |
| Female  | 38            | 36            | 33      |
| Male  | 54            | 55            | 58      |
| Race  |               |               |         |
| Race was self reported by the subjects. Subjects could select more than one option. |               |               |         |
| Units: Subjects   |               |               |         |
| Asian   | 2             | 4             | 4       |
| American Indian or Alaska Native  | 2             | 0             | 0       |
| Black or African American   | 26            | 15            | 19      |
| Native Hawaiian or Other Pacific Islander   | 0             | 1             | 0       |
| White   | 59            | 67            | 63      |

|              |   |   |   |
|--------------|---|---|---|
| Not Reported | 3 | 4 | 5 |
|--------------|---|---|---|

| Reporting group values  | Total |  |  |
|---|-------|--|--|
| Number of subjects  | 274   |  |  |
| Age categorical<br>Units: Subjects  |       |  |  |
| In utero  | 0     |  |  |
| Preterm newborn infants (gestational age < 37 wks)                                  | 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)  | 145   |  |  |
| From 65-84 years  | 129   |  |  |
| 85 years and over   | 0     |  |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation             | -     |  |  |
| Gender categorical<br>Units: Subjects   |       |  |  |
| Female  | 107   |  |  |
| Male  | 167   |  |  |
| Race  |       |  |  |
| Race was self reported by the subjects. Subjects could select more than one option. |       |  |  |
| Units: Subjects   |       |  |  |
| Asian   | 10    |  |  |
| American Indian or Alaska Native  | 2     |  |  |
| Black or African American   | 60    |  |  |
| Native Hawaiian or Other Pacific Islander   | 1     |  |  |
| White   | 189   |  |  |
| Not Reported  | 12    |  |  |

### Subject analysis sets

|   |                                   |
|---|-----------------------------------|
| Subject analysis set title  | SNF472 300 mg - Safety Population |
| Subject analysis set type   | Safety analysis                   |
| Subject analysis set description:<br>The Safety Population included subjects who received at least 1 dose of study drug |                                   |
| Subject analysis set title  | SNF472 600 mg - Safety Population |
| Subject analysis set type   | Safety analysis                   |
| Subject analysis set description:<br>The Safety Population included subjects who received at least 1 dose of study drug |                                   |
| Subject analysis set title  | Placebo - Safety Population       |
| Subject analysis set type   | Safety analysis                   |
| Subject analysis set description:<br>The Safety Population included subjects who received at least 1 dose of study drug |                                   |



|  |                             |
|--|-----------------------------|
| Subject analysis set title   | SNF472 Combined - mITT LOCF |
| Subject analysis set type  | Modified intention-to-treat |
| Subject analysis set description:  |                             |
| The mITT Population included subjects who received at least 1 dose of study drug and had an evaluable baseline and post randomization CT scan with a non missing CAC volume score (Week 52/ET) |                             |
| Subject analysis set title   | SNF472 300 mg - mITT LOCF   |
| Subject analysis set type  | Modified intention-to-treat |
| Subject analysis set description:  |                             |
| The mITT Population included subjects who received at least 1 dose of study drug and had an evaluable baseline and post randomization CT scan with a non missing CAC volume score (Week 52/ET) |                             |
| Subject analysis set title   | SNF472 600 mg - mITT LOCF   |
| Subject analysis set type  | Modified intention-to-treat |
| Subject analysis set description:  |                             |
| The mITT Population included subjects who received at least 1 dose of study drug and had an evaluable baseline and post randomization CT scan with a non missing CAC volume score (Week 52/ET) |                             |
| Subject analysis set title   | Placebo - mITT LOCF         |
| Subject analysis set type  | Modified intention-to-treat |
| Subject analysis set description:  |                             |
| The mITT Population included subjects who received at least 1 dose of study drug and had an evaluable baseline and post randomization CT scan with a non missing CAC volume score (Week 52/ET) |                             |

| Reporting group values  | SNF472 300 mg - Safety Population | SNF472 600 mg - Safety Population | Placebo - Safety Population |
|---|-----------------------------------|-----------------------------------|-----------------------------|
| Number of subjects  | 92                                | 91                                | 90                          |
| Age categorical   |                                   |                                   |                             |
| Units: Subjects   |                                   |                                   |                             |
| In utero  | 0                                 | 0                                 | 0                           |
| Preterm newborn infants (gestational age < 37 wks)                                  | 0                                 | 0                                 | 0                           |
| Newborns (0-27 days)  | 0                                 | 0                                 | 0                           |
| Infants and toddlers (28 days-23 months)  | 0                                 | 0                                 | 0                           |
| Children (2-11 years)   | 0                                 | 0                                 | 0                           |
| Adolescents (12-17 years)   | 0                                 | 0                                 | 0                           |
| Adults (18-64 years)  | 54                                | 51                                | 40                          |
| From 65-84 years  | 38                                | 40                                | 50                          |
| 85 years and over   | 0                                 | 0                                 | 0                           |
| Age continuous  |                                   |                                   |                             |
| Units: years  |                                   |                                   |                             |
| arithmetic mean   | 63.0                              | 63.6                              | 64.1                        |
| standard deviation  | ± 9.48                            | ± 8.94                            | ± 8.18                      |
| Gender categorical  |                                   |                                   |                             |
| Units: Subjects   |                                   |                                   |                             |
| Female  | 38                                | 36                                | 33                          |
| Male  | 54                                | 55                                | 57                          |
| Race  |                                   |                                   |                             |
| Race was self reported by the subjects. Subjects could select more than one option. |                                   |                                   |                             |
| Units: Subjects   |                                   |                                   |                             |
| Asian   | 1                                 |                                   |                             |
| American Indian or Alaska Native  | 2                                 |                                   |                             |
| Black or African American   | 26                                |                                   |                             |
| Native Hawaiian or Other Pacific Islander   | 0                                 |                                   |                             |
| White   | 59                                |                                   |                             |

|              |   |  |  |
|--------------|---|--|--|
| Not Reported | 3 |  |  |
|--------------|---|--|--|

| Reporting group values  | SNF472 Combined -<br>mITT LOCF | SNF472 300 mg -<br>mITT LOCF | SNF472 600 mg -<br>mITT LOCF |
|---|--------------------------------|------------------------------|------------------------------|
| Number of subjects  | 142                            | 77                           | 65                           |
| Age categorical<br>Units: Subjects  |                                |                              |                              |
| In utero<br>Preterm newborn infants<br>(gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23<br>months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                                |                              |                              |
| Age continuous<br>Units: years  |                                |                              |                              |
| arithmetic mean   | 63.8                           | 63.0                         | 64.5                         |
| standard deviation  | ± 9.07                         | ± 9.63                       | ± 9.39                       |
| Gender categorical<br>Units: Subjects   |                                |                              |                              |
| Female  |                                |                              |                              |
| Male  |                                |                              |                              |
| Race  |                                |                              |                              |
| Race was self reported by the subjects. Subjects could select more than one option.   |                                |                              |                              |
| Units: Subjects   |                                |                              |                              |
| Asian<br>American Indian or Alaska Native<br>Black or African American<br>Native Hawaiian or Other Pacific<br>Islander<br>White<br>Not Reported   |                                |                              |                              |

| Reporting group values   | Placebo - mITT<br>LOCF |  |  |
|--|------------------------|--|--|
| Number of subjects   | 77                     |  |  |
| Age categorical<br>Units: Subjects   |                        |  |  |
| In utero<br>Preterm newborn infants<br>(gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23<br>months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years |                        |  |  |

|                   |  |  |  |
|-------------------|--|--|--|
| 85 years and over |  |  |  |
|-------------------|--|--|--|

|  |                |  |  |
|--|----------------|--|--|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation  | 64.1<br>± 8.25 |  |  |
| Gender categorical<br>Units: Subjects  |                |  |  |
| Female<br>Male   |                |  |  |
| Race   |                |  |  |
| Race was self reported by the subjects. Subjects could select more than one option.  |                |  |  |
| Units: Subjects  |                |  |  |
| Asian<br>American Indian or Alaska Native<br>Black or African American<br>Native Hawaiian or Other Pacific Islander<br>White<br>Not Reported |                |  |  |

## End points

### End points reporting groups

|  |                                   |
|--|-----------------------------------|
| Reporting group title  | SNF472 300 mg                     |
| Reporting group description:<br>Subjects were assigned to receive 300 mg SNF472 administered 3 times per week in conjunction with the subject's hemodialysis sessions. All subjects received 2 identical vials of 10 mL each: 1 vial of SNF472 (300 mg/vial) and 1 vial of physiologic saline. |                                   |
| Reporting group title  | SNF472 600 mg                     |
| Reporting group description:<br>Subjects were assigned to receive 600 mg SNF472 administered 3 times per week in conjunction with the subject's hemodialysis sessions. All subjects received 2 identical vials of 10 mL each: 2 vials of SNF472 (300 mg/vial).                                 |                                   |
| Reporting group title  | Placebo                           |
| Reporting group description:<br>Subjects were assigned to receive physiologic saline (0.9% sodium chloride) administered 3 times per week in conjunction with the subject's hemodialysis sessions. All subjects received 2 identical vials of 10 mL each: 2 vial of physiologic saline.        |                                   |
| Subject analysis set title   | SNF472 300 mg - Safety Population |
| Subject analysis set type  | Safety analysis                   |
| Subject analysis set description:<br>The Safety Population included subjects who received at least 1 dose of study drug  |                                   |
| Subject analysis set title   | SNF472 600 mg - Safety Population |
| Subject analysis set type  | Safety analysis                   |
| Subject analysis set description:<br>The Safety Population included subjects who received at least 1 dose of study drug  |                                   |
| Subject analysis set title   | Placebo - Safety Population       |
| Subject analysis set type  | Safety analysis                   |
| Subject analysis set description:<br>The Safety Population included subjects who received at least 1 dose of study drug  |                                   |
| Subject analysis set title   | SNF472 Combined - mITT LOCF       |
| Subject analysis set type  | Modified intention-to-treat       |
| Subject analysis set description:<br>The mITT Population included subjects who received at least 1 dose of study drug and had an evaluable baseline and post randomization CT scan with a non missing CAC volume score (Week 52/ET)  |                                   |
| Subject analysis set title   | SNF472 300 mg - mITT LOCF         |
| Subject analysis set type  | Modified intention-to-treat       |
| Subject analysis set description:<br>The mITT Population included subjects who received at least 1 dose of study drug and had an evaluable baseline and post randomization CT scan with a non missing CAC volume score (Week 52/ET)  |                                   |
| Subject analysis set title   | SNF472 600 mg - mITT LOCF         |
| Subject analysis set type  | Modified intention-to-treat       |
| Subject analysis set description:<br>The mITT Population included subjects who received at least 1 dose of study drug and had an evaluable baseline and post randomization CT scan with a non missing CAC volume score (Week 52/ET)  |                                   |
| Subject analysis set title   | Placebo - mITT LOCF               |
| Subject analysis set type  | Modified intention-to-treat       |
| Subject analysis set description:<br>The mITT Population included subjects who received at least 1 dose of study drug and had an evaluable baseline and post randomization CT scan with a non missing CAC volume score (Week 52/ET)  |                                   |

**Primary: Change in log coronary artery calcification (CAC) volume score from Baseline to Week 52 for the combined dose groups vs placebo**

|   |   |
|---|---|
| End point title   | Change in log coronary artery calcification (CAC) volume score from Baseline to Week 52 for the combined dose groups vs placebo |
| End point description:<br>Change is geometric least squares mean (95% confidence intervals) |   |
| End point type  | Primary   |
| End point timeframe:<br>Baseline to Week 52   |   |

| End point values                         | SNF472<br>Combined -<br>mITT LOCF | Placebo - mITT<br>LOCF |  |  |
|--|-----------------------------------|------------------------|--|--|
| Subject group type                       | Subject analysis set              | Subject analysis set   |  |  |
| Number of subjects analysed              | 142                               | 77                     |  |  |
| Units: volume score                      |                                   |                        |  |  |
| geometric mean (confidence interval 95%) | 1.11 (1.067 to 1.153)             | 1.20 (1.138 to 1.262)  |  |  |

**Statistical analyses**

|  |   |
|--|---|
| Statistical analysis title   | Primary efficacy analysis                         |
| Statistical analysis description:<br>The primary endpoint was the change in log CAC volume scores between baseline and Week 52 for the combined dose groups vs placebo.<br>The primary comparison was that of the combined dose groups vs the placebo group. The primary efficacy analysis in the mITT Population imputed missing Week 52 CAC volume score using the last observation carried forward (LOCF) from the early termination visit. |   |
| Comparison groups  | SNF472 Combined - mITT LOCF v Placebo - mITT LOCF |
| Number of subjects included in analysis  | 219   |
| Analysis specification   | Pre-specified                                     |
| Analysis type  | other   |
| P-value  | = 0.0163 <sup>[1]</sup>                           |
| Method   | ANCOVA  |
| Parameter estimate   | ratio   |
| Point estimate   | 0.93  |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | 0.869   |
| upper limit  | 0.986   |

Notes:

[1] - P-value for treatment effect ratio between the combined dose groups and placebo

**Secondary: Change in log coronary artery calcification (CAC) volume score between baseline and Week 52 for each dose group (300 mg and 600 mg) vs placebo**

|                 |   |
|-----------------|---|
| End point title | Change in log coronary artery calcification (CAC) volume score between baseline and Week 52 for each dose group (300 mg |
|-----------------|---|

and 600 mg) vs placebo

End point description:

Change is geometric least squares mean (95% confidence intervals)

End point type Secondary

End point timeframe:

Baseline to Week 52

| End point values                         | SNF472 300 mg - mITT LOCF | SNF472 600 mg - mITT LOCF | Placebo - mITT LOCF   |  |
|--|---------------------------|---------------------------|-----------------------|--|
| Subject group type                       | Subject analysis set      | Subject analysis set      | Subject analysis set  |  |
| Number of subjects analysed              | 77                        | 65                        | 77                    |  |
| Units: volume score                      |                           |                           |                       |  |
| geometric mean (confidence interval 95%) | 1.12 (1.060 to 1.175)     | 1.10 (1.042 to 1.165)     | 1.20 (1.138 to 1.262) |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in log coronary artery calcification (CAC) Agatston score between baseline and Week 52 for each dose group (300 mg and 600 mg) vs placebo and for the combined dose groups vs the placebo group

|                 |  |
|-----------------|--|
| End point title | Change in log coronary artery calcification (CAC) Agatston score between baseline and Week 52 for each dose group (300 mg and 600 mg) vs placebo and for the combined dose groups vs the placebo group |
|-----------------|--|

End point description:

Change is geometric least squares mean (95% confidence intervals)

End point type Secondary

End point timeframe:

Baseline to Week 52

| End point values                         | SNF472 Combined - mITT LOCF | SNF472 300 mg - mITT LOCF | SNF472 600 mg - mITT LOCF | Placebo - mITT LOCF   |
|--|-----------------------------|---------------------------|---------------------------|-----------------------|
| Subject group type                       | Subject analysis set        | Subject analysis set      | Subject analysis set      | Subject analysis set  |
| Number of subjects analysed              | 142                         | 77                        | 65                        | 77                    |
| Units: Agatston score                    |                             |                           |                           |                       |
| geometric mean (confidence interval 95%) | 1.11 (1.060 to 1.170)       | 1.10 (1.027 to 1.170)     | 1.13 (1.055 to 1.215)     | 1.20 (1.122 to 1.278) |

## Statistical analyses

No statistical analyses for this end point

**Secondary: Number of subjects with <15% progression in coronary artery calcification (CAC) Agatston score at Week 52 for each dose group and the combined dose groups vs placebo**

|                 |   |
|-----------------|---|
| End point title | Number of subjects with <15% progression in coronary artery calcification (CAC) Agatston score at Week 52 for each dose group and the combined dose groups vs placebo |
|-----------------|---|

End point description:

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

End point timeframe:

Baseline to Week 52

| End point values            | SNF472<br>Combined -<br>mITT LOCF | SNF472 300<br>mg - mITT<br>LOCF | SNF472 600<br>mg - mITT<br>LOCF | Placebo - mITT<br>LOCF |
|-----------------------------|-----------------------------------|---------------------------------|---------------------------------|------------------------|
| Subject group type          | Subject analysis set              | Subject analysis set            | Subject analysis set            | Subject analysis set   |
| Number of subjects analysed | 142                               | 77                              | 65                              | 77                     |
| Units: subjects             | 87                                | 46                              | 41                              | 37                     |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Number of subjects with ≥15% progression in coronary artery calcification (CAC) volume score at Week 52 for each dose group and the combined dose groups vs placebo**

|                 |   |
|-----------------|---|
| End point title | Number of subjects with ≥15% progression in coronary artery calcification (CAC) volume score at Week 52 for each dose group and the combined dose groups vs placebo |
|-----------------|---|

End point description:

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

End point timeframe:

Baseline to Week 52

| End point values            | SNF472<br>Combined -<br>mITT LOCF | SNF472 300<br>mg - mITT<br>LOCF | SNF472 600<br>mg - mITT<br>LOCF | Placebo - mITT<br>LOCF |
|-----------------------------|-----------------------------------|---------------------------------|---------------------------------|------------------------|
| Subject group type          | Subject analysis set              | Subject analysis set            | Subject analysis set            | Subject analysis set   |
| Number of subjects analysed | 142                               | 77                              | 65                              | 77                     |
| Units: subjects             | 53                                | 31                              | 22                              | 38                     |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in log thoracic aorta calcification volume score between baseline and Week 52 for each dose group (300 mg and 600 mg) vs placebo and the combined dose groups vs placebo

|                        |   |
|------------------------|---|
| End point title        | Change in log thoracic aorta calcification volume score between baseline and Week 52 for each dose group (300 mg and 600 mg) vs placebo and the combined dose groups vs placebo |
| End point description: | Change is geometric least squares mean (95% confidence intervals)   |
| End point type         | Secondary   |
| End point timeframe:   | Baseline to Week 52   |

| End point values                         | SNF472<br>Combined -<br>mITT LOCF | SNF472 300<br>mg - mITT<br>LOCF | SNF472 600<br>mg - mITT<br>LOCF | Placebo - mITT<br>LOCF |
|--|-----------------------------------|---------------------------------|---------------------------------|------------------------|
| Subject group type                       | Subject analysis set              | Subject analysis set            | Subject analysis set            | Subject analysis set   |
| Number of subjects analysed              | 134                               | 74                              | 60                              | 75                     |
| Units: volume score                      |                                   |                                 |                                 |                        |
| geometric mean (confidence interval 95%) | 1.23 (1.161 to 1.302)             | 1.25 (1.156 to 1.346)           | 1.21 (1.113 to 1.318)           | 1.28 (1.187 to 1.381)  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in log thoracic aorta calcification Agatston score between baseline and Week 52 for each dose group (300 mg and 600 mg) vs placebo and the combined dose groups vs placebo

|                        |   |
|------------------------|---|
| End point title        | Change in log thoracic aorta calcification Agatston score between baseline and Week 52 for each dose group (300 mg and 600 mg) vs placebo and the combined dose groups vs placebo |
| End point description: | Change is geometric least squares mean (95% confidence intervals)   |
| End point type         | Secondary   |
| End point timeframe:   | Baseline to Week 52   |



| <b>End point values</b>                  | SNF472<br>Combined -<br>mITT LOCF | SNF472 300<br>mg - mITT<br>LOCF | SNF472 600<br>mg - mITT<br>LOCF | Placebo - mITT<br>LOCF |
|--|-----------------------------------|---------------------------------|---------------------------------|------------------------|
| Subject group type                       | Subject analysis set              | Subject analysis set            | Subject analysis set            | Subject analysis set   |
| Number of subjects analysed              | 134                               | 74                              | 60                              | 75                     |
| Units: Agatston score                    |                                   |                                 |                                 |                        |
| geometric mean (confidence interval 95%) | 1.29 (1.201 to 1.384)             | 1.30 (1.186 to 1.432)           | 1.28 (1.149 to 1.416)           | 1.32 (1.205 to 1.452)  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in log aortic valve calcification volume score between baseline and Week 52 for each dose group (300 mg and 600 mg) vs placebo and the combined dose groups vs placebo

|                        |   |
|------------------------|---|
| End point title        | Change in log aortic valve calcification volume score between baseline and Week 52 for each dose group (300 mg and 600 mg) vs placebo and the combined dose groups vs placebo |
| End point description: | Change is geometric least squares mean (95% confidence intervals)   |
| End point type         | Secondary   |
| End point timeframe:   | Baseline to Week 52   |

| <b>End point values</b>                  | SNF472<br>Combined -<br>mITT LOCF | SNF472 300<br>mg - mITT<br>LOCF | SNF472 600<br>mg - mITT<br>LOCF | Placebo - mITT<br>LOCF |
|--|-----------------------------------|---------------------------------|---------------------------------|------------------------|
| Subject group type                       | Subject analysis set              | Subject analysis set            | Subject analysis set            | Subject analysis set   |
| Number of subjects analysed              | 138                               | 75                              | 63                              | 69                     |
| Units: volume score                      |                                   |                                 |                                 |                        |
| geometric mean (confidence interval 95%) | 1.14 (1.048 to 1.235)             | 1.28 (1.143 to 1.426)           | 1.01 (0.899 to 1.144)           | 1.98 (1.768 to 2.226)  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in log aortic valve calcification Agatston score between baseline and Week 52 for each dose group (300 mg and 600 mg) vs placebo and the combined dose groups vs placebo

|                 |   |
|-----------------|---|
| End point title | Change in log aortic valve calcification Agatston score between baseline and Week 52 for each dose group (300 mg and 600 mg) vs placebo and the combined dose groups vs placebo |
|-----------------|---|

End point description:

Change is geometric least squares mean (95% confidence intervals)

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

End point timeframe:

Baseline to Week 52

| End point values                            | SNF472<br>Combined -<br>mITT LOCF | SNF472 300<br>mg - mITT<br>LOCF | SNF472 600<br>mg - mITT<br>LOCF | Placebo - mITT<br>LOCF   |
|---|-----------------------------------|---------------------------------|---------------------------------|--------------------------|
| Subject group type                          | Subject analysis set              | Subject analysis set            | Subject analysis set            | Subject analysis set     |
| Number of subjects analysed                 | 138                               | 75                              | 63                              | 69                       |
| Units: Agatston score                       |                                   |                                 |                                 |                          |
| geometric mean (confidence interval<br>95%) | 1.14 (1.022 to<br>1.277)          | 1.33 (1.141 to<br>1.541)        | 0.98 (0.836 to<br>1.160)        | 2.86 (2.449 to<br>3.349) |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Incidence of the composite safety endpoint (death from cardiovascular causes, myocardial infarction, stroke, or heart failure) for each dose group and placebo

|                 |  |
|-----------------|--|
| End point title | Incidence of the composite safety endpoint (death from cardiovascular causes, myocardial infarction, stroke, or heart failure) for each dose group and placebo |
|-----------------|--|

End point description:

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

End point timeframe:

Baseline to Week 52

| End point values            | SNF472 300<br>mg - Safety<br>Population | SNF472 600<br>mg - Safety<br>Population | Placebo -<br>Safety<br>Population |  |
|-----------------------------|---|---|-----------------------------------|--|
| Subject group type          | Subject analysis set                    | Subject analysis set                    | Subject analysis set              |  |
| Number of subjects analysed | 92                                      | 91                                      | 90                                |  |
| Units: subjects             | 7                                       | 6                                       | 10                                |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Mortality rate (all-cause and cardiovascular) for each dose group and placebo

|                        |   |
|------------------------|---|
| End point title        | Mortality rate (all-cause and cardiovascular) for each dose group and placebo |
| End point description: |   |
| End point type         | Secondary   |
| End point timeframe:   |   |
| Baseline to Week 52    |   |

| End point values            | SNF472 300 mg - Safety Population | SNF472 600 mg - Safety Population | Placebo - Safety Population |  |
|-----------------------------|-----------------------------------|-----------------------------------|-----------------------------|--|
| Subject group type          | Subject analysis set              | Subject analysis set              | Subject analysis set        |  |
| Number of subjects analysed | 92                                | 91                                | 90                          |  |
| Units: subjects             | 1                                 | 6                                 | 5                           |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline to Week 52

Adverse event reporting additional description:

Treatment-emergent adverse events (TEAEs), defined as adverse events with an onset date on or after the date of first dose of study drug through the subject's early termination visit or until scheduled completion (Week 52 visit)

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

### Reporting groups

|                       |                                   |
|-----------------------|-----------------------------------|
| Reporting group title | SNF472 300 mg - Safety Population |
|-----------------------|-----------------------------------|

Reporting group description: -

|                       |                                   |
|-----------------------|-----------------------------------|
| Reporting group title | SNF472 600 mg - Safety Population |
|-----------------------|-----------------------------------|

Reporting group description: -

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Placebo - Safety Population |
|-----------------------|-----------------------------|

Reporting group description: -

| Serious adverse events  | SNF472 300 mg - Safety Population | SNF472 600 mg - Safety Population | Placebo - Safety Population |
|---|-----------------------------------|-----------------------------------|-----------------------------|
| Total subjects affected by serious adverse events                   |                                   |                                   |                             |
| subjects affected / exposed   | 38 / 92 (41.30%)                  | 55 / 91 (60.44%)                  | 49 / 90 (54.44%)            |
| number of deaths (all causes)                                       | 1                                 | 6                                 | 5                           |
| number of deaths resulting from adverse events                      |                                   |                                   |                             |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                   |                                   |                             |
| Colon cancer  |                                   |                                   |                             |
| subjects affected / exposed   | 1 / 92 (1.09%)                    | 0 / 91 (0.00%)                    | 0 / 90 (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                       |
| Large intestine benign neoplasm                                     |                                   |                                   |                             |
| subjects affected / exposed   | 0 / 92 (0.00%)                    | 0 / 91 (0.00%)                    | 1 / 90 (1.11%)              |
| occurrences causally related to treatment / all                     | 0 / 0                             | 0 / 0                             | 0 / 1                       |
| deaths causally related to treatment / all                          | 0 / 0                             | 0 / 0                             | 0 / 0                       |
| Vascular disorders  |                                   |                                   |                             |
| Hypotension   |                                   |                                   |                             |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 3 / 92 (3.26%) | 2 / 91 (2.20%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 2          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| Hypertension                                    |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 1 / 91 (1.10%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Haematoma                                       |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hypertensive crisis                             |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Peripheral vascular disorder                    |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 2 / 91 (2.20%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Aortic stenosis                                 |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Deep vein thrombosis                            |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Foreign body embolism                           |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (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 ischaemia                            |                |                |                |

|  |                |                  |                  |
|--|----------------|------------------|------------------|
| subjects affected / exposed                          | 0 / 92 (0.00%) | 0 / 91 (0.00%)   | 1 / 90 (1.11%)   |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0            | 0 / 0            |
| Arteriosclerosis                                     |                |                  |                  |
| subjects affected / exposed                          | 0 / 92 (0.00%) | 1 / 91 (1.10%)   | 0 / 90 (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            |
| Surgical and medical procedures                      |                |                  |                  |
| Renal transplant                                     |                |                  |                  |
| subjects affected / exposed                          | 6 / 92 (6.52%) | 14 / 91 (15.38%) | 11 / 90 (12.22%) |
| occurrences causally related to treatment / all      | 0 / 6          | 0 / 14           | 0 / 11           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0            | 0 / 1            |
| Lymphadenectomy                                      |                |                  |                  |
| subjects affected / exposed                          | 0 / 92 (0.00%) | 0 / 91 (0.00%)   | 1 / 90 (1.11%)   |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0            | 0 / 0            |
| Toe amputation                                       |                |                  |                  |
| subjects affected / exposed                          | 0 / 92 (0.00%) | 0 / 91 (0.00%)   | 1 / 90 (1.11%)   |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0            | 0 / 0            |
| General disorders and administration site conditions |                |                  |                  |
| Chest pain   |                |                  |                  |
| subjects affected / exposed                          | 1 / 92 (1.09%) | 0 / 91 (0.00%)   | 3 / 90 (3.33%)   |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0            | 0 / 4            |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0            | 0 / 0            |
| Pyrexia  |                |                  |                  |
| subjects affected / exposed                          | 0 / 92 (0.00%) | 3 / 91 (3.30%)   | 0 / 90 (0.00%)   |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 3            | 0 / 0            |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0            | 0 / 0            |
| Multiple organ dysfunction syndrome                  |                |                  |                  |
| subjects affected / exposed                          | 0 / 92 (0.00%) | 1 / 91 (1.10%)   | 1 / 90 (1.11%)   |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0            | 0 / 1            |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Asthenia  |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Non-cardiac chest pain                          |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (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          |
| Systemic inflammatory response syndrome         |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (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          |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| Acute pulmonary oedema                          |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Acute respiratory failure                       |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Asthma  |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory distress                            |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory failure                             |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 1 / 91 (1.10%) | 0 / 90 (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          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Chronic obstructive pulmonary disease           |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Dyspnoea  |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Haemoptysis                                     |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (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          |
| Pleural effusion                                |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Pneumonitis                                     |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pulmonary embolism                              |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Pulmonary oedema                                |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Psychiatric disorders                           |                |                |                |
| Mental status changes                           |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |



|   |                |                |                |
|---|----------------|----------------|----------------|
| Investigations                                  |                |                |                |
| Blood lactic acid increased                     |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| 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 stress test abnormal                    |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Influenza A virus test positive                 |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| International normalised ratio increased        |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (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          |
| Myocardial necrosis marker increased            |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Stress echocardiogram abnormal                  |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Troponin increased                              |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (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          |
| Injury, poisoning and procedural complications  |                |                |                |
| Arteriovenous fistula site complication         |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 92 (1.09%) | 3 / 91 (3.30%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 3          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Arteriovenous fistula thrombosis                |                |                |                |
| subjects affected / exposed                     | 2 / 92 (2.17%) | 0 / 91 (0.00%) | 2 / 90 (2.22%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          | 0 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hip fracture                                    |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 2 / 91 (2.20%) | 2 / 90 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Vascular graft complication                     |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 2 / 90 (2.22%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Ankle fracture                                  |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (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          |
| Arterial injury                                 |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (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 site haematoma            |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Arteriovenous fistula site haemorrhage          |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Arteriovenous graft aneurysm                    |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Arteriovenous graft thrombosis                  |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Fall  |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (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          |
| Femoral neck fracture                           |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (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          |
| Fractured sacrum                                |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Limb injury                                     |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Lower limb fracture                             |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Post procedural complication                    |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| Post procedural haemorrhage                     |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Procedural hypotension                          |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Tendon rupture                                  |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Toxicity to various agents                      |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Upper limb fracture                             |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac disorders                               |                |                |                |
| Atrial fibrillation                             |                |                |                |
| subjects affected / exposed                     | 3 / 92 (3.26%) | 3 / 91 (3.30%) | 2 / 90 (2.22%) |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 3          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Acute myocardial infarction                     |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 1 / 91 (1.10%) | 4 / 90 (4.44%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 4          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac arrest                                  |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 3 / 91 (3.30%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 3          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| Atrial flutter                                  |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 92 (0.00%) | 3 / 91 (3.30%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Arteriosclerosis coronary artery                |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Cardiac failure                                 |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 2 / 90 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Coronary artery disease                         |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Angina unstable                                 |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Aortic valve stenosis                           |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Atrioventricular block complete                 |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac failure congestive                      |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| Cardiogenic shock                               |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Coronary artery stenosis                        |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hypertensive heart disease                      |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Left ventricular failure                        |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (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          |
| Mitral valve incompetence                       |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Myocardial infarction                           |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Sinus node dysfunction                          |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Nervous system disorders                        |                |                |                |
| Metabolic encephalopathy                        |                |                |                |
| subjects affected / exposed                     | 2 / 92 (2.17%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Transient ischaemic attack                      |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 2 / 90 (2.22%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Ischaemic stroke                                |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Loss of consciousness                           |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cognitive disorder                              |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (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          |
| Dizziness postural                              |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Epilepsy  |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Myasthenia gravis                               |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Seizure   |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Syncope   |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Uraemic encephalopathy                          |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders            |                |                |                |
| Anaemia   |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 2 / 90 (2.22%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Agranulocytosis                                 |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Anaemia of chronic disease                      |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Coagulopathy                                    |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Haemorrhagic anaemia                            |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Nephrogenic anaemia                             |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (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          |
| Eye disorders                                   |                |                |                |



|   |                |                |                |
|---|----------------|----------------|----------------|
| Retinal detachment                              |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Vitreous haemorrhage                            |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |                |                |                |
| Gastrointestinal haemorrhage                    |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 4 / 91 (4.40%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 5          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pancreatitis acute                              |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 1 / 91 (1.10%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Abdominal pain                                  |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 2 / 90 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Colitis ischaemic                               |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Upper gastrointestinal haemorrhage              |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Abdominal hernia                                |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (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          |
| Abdominal mass                                  |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Ascites   |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Diabetic gastroparesis                          |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Diarrhoea                                       |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Gastrointestinal necrosis                       |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Gastrointestinal ulcer haemorrhage              |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (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          |
| Haemorrhoidal haemorrhage                       |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Impaired gastric emptying                       |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Inguinal hernia                                 |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Lower gastrointestinal haemorrhage              |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Rectal haemorrhage                              |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Ulcerative gastritis                            |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (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          |
| Hepatobiliary disorders                         |                |                |                |
| Acute hepatic failure                           |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Cholecystitis acute                             |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cholecystitis                                   |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Cholelithiasis                                  |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Drug-induced liver injury                       |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (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 ischaemia                               |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hepatitis acute                                 |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                |                |                |
| Renal mass                                      |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Urinary retention                               |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (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          |
| Musculoskeletal and connective tissue disorders |                |                |                |
| Pain in extremity                               |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Arthralgia                                      |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (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          |
| Musculoskeletal pain                            |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (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          |

|  |                                  |                                  |                                  |
|--|----------------------------------|----------------------------------|----------------------------------|
| Infections and infestations<br>Pneumonia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | 4 / 92 (4.35%)<br>0 / 4<br>0 / 0 | 3 / 91 (3.30%)<br>0 / 3<br>0 / 0 | 7 / 90 (7.78%)<br>0 / 7<br>0 / 0 |
| Sepsis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                   | 2 / 92 (2.17%)<br>0 / 2<br>0 / 0 | 2 / 91 (2.20%)<br>0 / 3<br>0 / 0 | 1 / 90 (1.11%)<br>0 / 1<br>0 / 1 |
| Cellulitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                               | 2 / 92 (2.17%)<br>0 / 2<br>0 / 0 | 1 / 91 (1.10%)<br>0 / 1<br>0 / 0 | 1 / 90 (1.11%)<br>0 / 1<br>0 / 0 |
| Septic shock<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                             | 1 / 92 (1.09%)<br>0 / 1<br>0 / 0 | 1 / 91 (1.10%)<br>0 / 1<br>0 / 1 | 1 / 90 (1.11%)<br>0 / 1<br>0 / 0 |
| Staphylococcal bacteraemia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all               | 2 / 92 (2.17%)<br>0 / 2<br>0 / 0 | 1 / 91 (1.10%)<br>0 / 1<br>0 / 0 | 0 / 90 (0.00%)<br>0 / 0<br>0 / 0 |
| Arteriovenous graft site infection<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all       | 1 / 92 (1.09%)<br>0 / 1<br>0 / 0 | 1 / 91 (1.10%)<br>0 / 1<br>0 / 0 | 0 / 90 (0.00%)<br>0 / 0<br>0 / 0 |
| Bronchitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                               | 0 / 92 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 91 (1.10%)<br>0 / 2<br>0 / 0 | 1 / 90 (1.11%)<br>0 / 1<br>0 / 0 |
| Device related infection<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                 | 0 / 92 (0.00%)<br>0 / 0<br>0 / 0 | 2 / 91 (2.20%)<br>0 / 2<br>0 / 0 | 0 / 90 (0.00%)<br>0 / 0<br>0 / 0 |
| Endocarditis   |                                  |                                  |                                  |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 92 (1.09%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Gangrene  |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Respiratory tract infection                     |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 2 / 91 (2.20%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Urinary tract infection                         |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 1 / 91 (1.10%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Arteriovenous graft site abscess                |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (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          |
| Arthritis infective                             |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Bacteraemia                                     |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (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          |
| Clostridium difficile colitis                   |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Clostridium difficile infection                 |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Diabetic foot infection                         |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Diverticulitis                                  |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Emphysematous cystitis                          |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (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          |
| Enterocolitis viral                             |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (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          |
| Gastroenteritis                                 |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (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          |
| Gastroenteritis bacterial                       |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Herpes zoster                                   |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (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          |
| Influenza                                       |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Localised infection                             |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Osteomyelitis bacterial                         |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (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          |
| Pseudomonas infection                           |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Urosepsis                                       |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (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 access site infection                  |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Wound infection                                 |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders              |                |                |                |
| Fluid overload                                  |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 1 / 91 (1.10%) | 3 / 90 (3.33%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 3          | 0 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hyperkalaemia                                   |                |                |                |



|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 2 / 92 (2.17%) | 1 / 91 (1.10%) | 2 / 90 (2.22%) |
| occurrences causally related to treatment / all | 0 / 6          | 0 / 2          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hyperglycaemia                                  |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hypoglycaemia                                   |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 1 / 91 (1.10%) | 0 / 90 (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          |
| Calciophylaxis                                  |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 0 / 91 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Diabetes mellitus inadequate control            |                |                |                |
| subjects affected / exposed                     | 1 / 92 (1.09%) | 0 / 91 (0.00%) | 0 / 90 (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          |
| Malnutrition                                    |                |                |                |
| subjects affected / exposed                     | 0 / 92 (0.00%) | 1 / 91 (1.10%) | 0 / 90 (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          |

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

| Non-serious adverse events                            | SNF472 300 mg - Safety Population | SNF472 600 mg - Safety Population | Placebo - Safety Population |
|---|-----------------------------------|-----------------------------------|-----------------------------|
| Total subjects affected by non-serious adverse events |                                   |                                   |                             |
| subjects affected / exposed                           | 41 / 92 (44.57%)                  | 29 / 91 (31.87%)                  | 29 / 90 (32.22%)            |
| Gastrointestinal disorders                            |                                   |                                   |                             |
| Diarrhoea   |                                   |                                   |                             |
| subjects affected / exposed                           | 7 / 92 (7.61%)                    | 11 / 91 (12.09%)                  | 10 / 90 (11.11%)            |
| occurrences (all)                                     | 7                                 | 11                                | 10                          |
| Abdominal pain upper                                  |                                   |                                   |                             |

|  |                        |                     |                     |
|--|------------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)   | 11 / 92 (11.96%)<br>11 | 2 / 91 (2.20%)<br>2 | 2 / 90 (2.22%)<br>2 |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)   | 1 / 92 (1.09%)<br>1    | 8 / 91 (8.79%)<br>8 | 4 / 90 (4.44%)<br>4 |
| Nausea<br>subjects affected / exposed<br>occurrences (all)   | 2 / 92 (2.17%)<br>2    | 5 / 91 (5.49%)<br>5 | 4 / 90 (4.44%)<br>4 |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)             | 10 / 92 (10.87%)<br>10 | 9 / 91 (9.89%)<br>9 | 8 / 90 (8.89%)<br>8 |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)   | 5 / 92 (5.43%)<br>5    | 7 / 91 (7.69%)<br>7 | 7 / 90 (7.78%)<br>7 |
| Musculoskeletal and connective tissue disorders<br>Pain in extremity<br>subjects affected / exposed<br>occurrences (all) | 7 / 92 (7.61%)<br>7    | 7 / 91 (7.69%)<br>7 | 7 / 90 (7.78%)<br>7 |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)   | 3 / 92 (3.26%)<br>3    | 6 / 91 (6.59%)<br>6 | 5 / 90 (5.56%)<br>5 |
| Back pain<br>subjects affected / exposed<br>occurrences (all)  | 6 / 92 (6.52%)<br>6    | 2 / 91 (2.20%)<br>2 | 4 / 90 (4.44%)<br>4 |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)   | 5 / 92 (5.43%)<br>5    | 2 / 91 (2.20%)<br>2 | 4 / 90 (4.44%)<br>4 |
| Infections and infestations<br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)     | 2 / 92 (2.17%)<br>2    | 4 / 91 (4.40%)<br>4 | 6 / 90 (6.67%)<br>6 |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)  | 3 / 92 (3.26%)<br>3    | 1 / 91 (1.10%)<br>1 | 6 / 90 (6.67%)<br>6 |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 31 July 2017    | Protocol Amendment 1, dated 31 JUL 2017 (Global)<br>The primary purpose of Amendment 1 was to add the sub-study, an opt-in Investigator addition of echocardiographic assessments at 3 time points (sub-study entry, Week 28 and Week 52/Early Termination), to measure reduction in progression of cardiovascular calcification on arterial stiffness for exploratory analyses on subjects participating in the main study and willing to provide additional informed consent. Additionally, this protocol was amended for administrative updates and to clarify procedural details. |
| 29 March 2018   | Protocol Amendment 2, dated 29 MAR 2018 (Global)<br>The main goals of Protocol Amendment 2 were to increase the upper limit of the coronary artery calcification (CAC) Agatston score allowed for enrollment from 2000 to 3500, to clarify the planned sample size re-estimation, to clarify the endpoint descriptions, and to provide additional details on planned statistical analyses, including those in the sub-study.  |
| 27 June 2018    | Protocol Amendment 3, dated 27 JUN 2018 (Global)<br>Protocol Amendment 3 provided a revised sample size calculation that led to a reduction in planned enrollment from approximately 450 to approximately 270 subjects.   |
| 22 October 2018 | Protocol Amendment 4, dated 22 OCT 2018 (Global)<br>Protocol Amendment 4 added a non binding interim futility analysis to be conducted when approximately N=120 subjects (63% of N=190) had provided Week 52 data on the primary endpoint. Pharmacokinetic and pharmacodynamic analyses were also added at the time of the interim analysis. Phosphorus (phosphate) was added to the list of analytes in the safety laboratory assessments. The amendment also clarified that study drug must be added to the dialysis circuit before the dialyzer.                                   |
| 01 March 2019   | Protocol Amendment 5, dated 01 MAR 2019 (Global)<br>Protocol Amendment 5 described additional analyses of the dataset used for the futility analyses that would be conducted in the event of an equivocal result of the futility analysis indicating borderline conditional power of the study. These analyses could include primary and secondary endpoints, demographic and background characteristics, key subgroups, and pharmacokinetic/pharmacodynamic correlations with efficacy.  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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## Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31707860>