



Clinical trial results:

A phase I/II study to evaluate safety, tolerability, pharmacokinetics and efficacy of resminostat (4SC-201) in combination with a second-line treatment in patients with k-ras mutated advanced colorectal carcinoma

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2010-020171-23 |
| Trial protocol | DE |
| Global end of trial date | 28 February 2015 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 13 July 2016 |
| First version publication date | 13 July 2016 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | 4SC-201-3-2010 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01277406 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | 4SC AG |
| Sponsor organisation address | Am Klopferspitz 19a, Planegg-Martinsried, Germany, 82152 |
| Public contact | Corporate Communications, 4SC AG, +49 89 7007630, public@4sc.com |
| Scientific contact | Dr. Susanne Danhauser-Riedl, 4SC AG, Clinical Development, +49 89 7007630, susanne.danhauser-riedl@4sc.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 | 29 June 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 28 February 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 February 2015 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

Phase I: To determine the MTD of resminostat in combination with FOLFIRI by investigating safety, tolerability and pharmacokinetics of resminostat and FOLFIRI

Phase II: Progression-free survival (PFS) - phase II of this study was not conducted!

Protection of trial subjects:

The first patient in each cohort had to have completed the first treatment cycle of resminostat and FOLFIRI (14 days) before inclusion of further patients in the same cohort.

Dose escalation decisions were made when safety and tolerability data from the first cycle were collected for all patients of a given cohort. A Data Safety Monitoring Board was involved in dose escalation decisions.

In addition, patients did not receive placebo medication and all patients received full supportive care including antiemetics, antibiotics, and analgetics, as clinically indicated.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 15 December 2010 |
| 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 | Germany: 17 |
| Worldwide total number of subjects | 17 |
| EEA total number of subjects | 17 |

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) | 11 |
| From 65 to 84 years | 6 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Study participants were enrolled between 07 January 2011 and 11 January 2013 at 2 of 3 centers in Germany.

Pre-assignment

Screening details:

22 patients had been screened during a 7-day screening period prior to start of study drug. 5 patients were screening failures due to homozygous state of UGT1A1 (2 times), withdrawal of consent, worsening of general condition, and deterioration of bone marrow deficiency.

Period 1

| | |
|------------------------------|--------------------------|
| Period 1 title | Phase I (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | 200 mg once daily |

Arm description:

In 14-day treatment cycles, patients were dosed on 5 consecutive days (Days 1-5) with 200 mg resminostat once daily, followed by a 9-day rest period (Days 6-14). On Days 3 and 4 compounds of FOLFIRI regimen (5-fluorouracil, folinic acid, irinotecan) were administered according to the respective summary of product characteristics.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Resminostat |
| Investigational medicinal product code | 4SC-201 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

At each treatment cycle, 200 mg resminostat were administered orally once daily in the morning on 5 consecutive days, followed by a 9-day rest period. Intake of resminostat tablets was at least 1 hour after a light breakfast. Tablets were not to be chewed or crushed and were swallowed with 200 mL of non-carbonated water at room temperature.

| | |
|--|--|
| Investigational medicinal product name | 5-Fluorouracil |
| Investigational medicinal product code | 5-FU |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use, Intravenous bolus use |

Dosage and administration details:

At each treatment cycle, 5-Fluorouracil was given as intravenous bolus injection (400 mg/m²) on Day 3, followed by an intravenous continuous infusion lasting until Day 4 (2,400 mg/m² over 46 hours).

| | |
|--|--------------------------------|
| Investigational medicinal product name | Folinic acid |
| Investigational medicinal product code | |
| Other name | Leucovorin, Calciumfolinat-GRY |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

At each treatment cycle, 400 mg/m² folinic acid were given as 2-hour infusion during irinotecan infusion on Day 3.

| | |
|--|-----------------|
| Investigational medicinal product name | Irinotecan |
| Investigational medicinal product code | CPT-11 |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

At each treatment cycle, 180 mg/m² irinotecan were given as intravenous infusion over 90 minutes on Day 3.

| | |
|------------------|-------------------|
| Arm title | 400 mg once daily |
|------------------|-------------------|

Arm description:

In 14-day treatment cycles, patients were dosed on 5 consecutive days (Days 1-5) with 400 mg resminostat once daily, followed by a 9-day rest period (Days 6-14). On Days 3 and 4 compounds of FOLFIRI regimen (5-fluorouracil, folinic acid, irinotecan) were administered according to the respective summary of product characteristics.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Resminostat |
| Investigational medicinal product code | 4SC-201 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

At each treatment cycle, 400 mg resminostat were administered orally once daily in the morning on 5 consecutive days, followed by a 9-day rest period. Intake of resminostat tablets was at least 1 hour after a light breakfast. Tablets were not to be chewed or crushed and were swallowed with 200 mL of non-carbonated water at room temperature.

| | |
|--|---|
| Investigational medicinal product name | 5-Fluorouracil |
| Investigational medicinal product code | 5-FU |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous bolus use , Intravenous use |

Dosage and administration details:

At each treatment cycle, 5-Fluorouracil was given as intravenous bolus injection (400 mg/m²) on Day 3, followed by an intravenous continuous infusion lasting until Day 4 (2,400 mg/m² over 46 hours).

| | |
|--|--------------------------------|
| Investigational medicinal product name | Folinic acid |
| Investigational medicinal product code | |
| Other name | Leucovorin, Calciumfolinat-GRY |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

At each treatment cycle, 400 mg/m² folinic acid were given as 2-hour infusion during irinotecan infusion on Day 3.

| | |
|--|-----------------|
| Investigational medicinal product name | Irinotecan |
| Investigational medicinal product code | CPT-11 |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

At each treatment cycle, 180 mg/m² irinotecan were given as intravenous infusion over 90 minutes on Day 3.

| | |
|------------------|-------------------|
| Arm title | 600 mg once daily |
|------------------|-------------------|

Arm description:

In 14-day treatment cycles, patients were dosed on 5 consecutive days (Days 1-5) with 600 mg resminostat once daily, followed by a 9-day rest period (Days 6-14). On Days 3 and 4 compounds of FOLFIRI regimen (5-fluorouracil, folinic acid, irinotecan) were administered according to the respective summary of product characteristics.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Resminostat |
| Investigational medicinal product code | 4SC-201 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

At each treatment cycle, 600 mg resminostat were administered orally once daily in the morning on 5 consecutive days, followed by a 9-day rest period. Intake of resminostat tablets was at least 1 hour after a light breakfast. Tablets were not to be chewed or crushed and were swallowed with 200 mL of non-carbonated water at room temperature.

| | |
|--|---|
| Investigational medicinal product name | 5-Fluorouracil |
| Investigational medicinal product code | 5-FU |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous bolus use , Intravenous use |

Dosage and administration details:

At each treatment cycle, 5-Fluorouracil was given as intravenous bolus injection (400 mg/m²) on Day 3, followed by an intravenous continuous infusion lasting until Day 4 (2,400 mg/m² over 46 hours).

| | |
|--|--------------------------------|
| Investigational medicinal product name | Folinic acid |
| Investigational medicinal product code | |
| Other name | Leucovorin, Calciumfolinat-GRY |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

At each treatment cycle, 400 mg/m² folinic acid were given as 2-hour infusion during irinotecan infusion on Day 3.

| | |
|--|-----------------|
| Investigational medicinal product name | Irinotecan |
| Investigational medicinal product code | CPT-11 |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

At each treatment cycle, 180 mg/m² irinotecan were given as intravenous infusion over 90 minutes on Day 3.

| | |
|------------------|--------------------|
| Arm title | 400 mg twice daily |
|------------------|--------------------|

Arm description:

In 14-day treatment cycles, patients were dosed on 5 consecutive days (Days 1-5) with 400 mg resminostat twice daily, followed by a 9-day rest period (Days 6-14). On Days 3 and 4 compounds of FOLFIRI regimen (5-fluorouracil, folinic acid, irinotecan) were administered according to the respective summary of product characteristics.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Resminostat |
| Investigational medicinal product code | 4SC-201 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

At each treatment cycle, 400 mg resminostat were administered orally twice daily in the morning and about 12 hours later in the evening on 5 consecutive days, followed by a 9-day rest period. Intake of resminostat tablets was at least 1 hour after a light breakfast or meal. Tablets were not to be chewed or crushed and were swallowed with 200 mL of non-carbonated water at room temperature.

| | |
|--|----------------|
| Investigational medicinal product name | 5-Fluorouracil |
| Investigational medicinal product code | 5-FU |
| Other name | |

| | |
|---|---|
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous bolus use , Intravenous use |
| Dosage and administration details: | |
| At each treatment cycle, 5-Fluorouracil was given as intravenous bolus injection (400 mg/m ²) on Day 3, followed by an intravenous continuous infusion lasting until Day 4 (2,400 mg/m ² over 46 hours). | |
| Investigational medicinal product name | Folinic acid |
| Investigational medicinal product code | |
| Other name | Leucovorin, Calciumfolinat-GRY |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

At each treatment cycle, 400 mg/m² folinic acid were given as 2-hour infusion during irinotecan infusion on Day 3.

| | |
|--|-----------------|
| Investigational medicinal product name | Irinotecan |
| Investigational medicinal product code | CPT-11 |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

At each treatment cycle, 180 mg/m² irinotecan were given as intravenous infusion over 90 minutes on Day 3.

| Number of subjects in period 1 | 200 mg once daily | 400 mg once daily | 600 mg once daily |
|---------------------------------------|-------------------|-------------------|-------------------|
| Started | 3 | 3 | 3 |
| Completed | 3 | 3 | 3 |
| Not completed | 0 | 0 | 0 |
| Consent withdrawn by subject | - | - | - |

| Number of subjects in period 1 | 400 mg twice daily |
|---------------------------------------|--------------------|
| Started | 8 |
| Completed | 7 |
| Not completed | 1 |
| Consent withdrawn by subject | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Phase I |
|-----------------------|---------|

Reporting group description: -

| Reporting group values | Phase I | Total | |
|------------------------|---------|-------|--|
| Number of subjects | 17 | 17 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 11 | 11 | |
| From 65-84 years | 6 | 6 | |
| 85 years and over | 0 | 0 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 5 | 5 | |
| Male | 12 | 12 | |

End points

End points reporting groups

| | |
|--|--------------------|
| Reporting group title | 200 mg once daily |
| Reporting group description: In 14-day treatment cycles, patients were dosed on 5 consecutive days (Days 1-5) with 200 mg resminostat once daily, followed by a 9-day rest period (Days 6-14). On Days 3 and 4 compounds of FOLFIRI regimen (5-fluorouracil, folinic acid, irinotecan) were administered according to the respective summary of product characteristics. | |
| Reporting group title | 400 mg once daily |
| Reporting group description: In 14-day treatment cycles, patients were dosed on 5 consecutive days (Days 1-5) with 400 mg resminostat once daily, followed by a 9-day rest period (Days 6-14). On Days 3 and 4 compounds of FOLFIRI regimen (5-fluorouracil, folinic acid, irinotecan) were administered according to the respective summary of product characteristics. | |
| Reporting group title | 600 mg once daily |
| Reporting group description: In 14-day treatment cycles, patients were dosed on 5 consecutive days (Days 1-5) with 600 mg resminostat once daily, followed by a 9-day rest period (Days 6-14). On Days 3 and 4 compounds of FOLFIRI regimen (5-fluorouracil, folinic acid, irinotecan) were administered according to the respective summary of product characteristics. | |
| Reporting group title | 400 mg twice daily |
| Reporting group description: In 14-day treatment cycles, patients were dosed on 5 consecutive days (Days 1-5) with 400 mg resminostat twice daily, followed by a 9-day rest period (Days 6-14). On Days 3 and 4 compounds of FOLFIRI regimen (5-fluorouracil, folinic acid, irinotecan) were administered according to the respective summary of product characteristics. | |

Primary: Pharmacokinetic (tmax)

| | |
|--|---------------------------------------|
| End point title | Pharmacokinetic (tmax) ^[1] |
| End point description: Time to maximum plasma concentration. Pharmacokinetic parameters were estimated by non-compartmental analysis, using the kinetic evaluation software WinNonlin. tmax was determined directly from the plasma concentration-time profiles. | |
| End point type | Primary |
| End point timeframe: Cycle 1 Day 5 | |

Notes:

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

Justification: No statistical analysis was planned for this endpoint.

| End point values | 200 mg once daily | 400 mg once daily | 600 mg once daily | 400 mg twice daily |
|-------------------------------|-------------------|-------------------|-------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 3 | 2 | 4 |
| Units: hour | | | | |
| median (full range (min-max)) | 2 (2 to 3) | 2 (2 to 2) | 1.5 (1 to 2) | 3 (2 to 5) |

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetic (Cmax)

End point title | Pharmacokinetic (Cmax)^[2]

End point description:

Maximum plasma concentration.

Pharmacokinetic parameters were estimated by non-compartmental analysis, using the kinetic evaluation software WinNonlin. Cmax was determined directly from the plasma concentration-time profiles.

End point type | Primary

End point timeframe:

Cycle 1 Day 5

Notes:

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

Justification: No statistical analysis was planned for this endpoint.

| End point values | 200 mg once daily | 400 mg once daily | 600 mg once daily | 400 mg twice daily |
|---------------------------------------|----------------------|--------------------|--------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 3 | 2 | 4 |
| Units: mg/L | | | | |
| geometric mean (full range (min-max)) | 0.716 (0.35 to 1.18) | 1.92 (1.53 to 2.3) | 3.3 (2.32 to 4.68) | 1.52 (0.794 to 2.95) |

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetic (AUClast)

End point title | Pharmacokinetic (AUClast)^[3]

End point description:

Area under the plasma concentration-time curve from time zero to last measurable concentration time point.

Pharmacokinetic parameters were estimated by non-compartmental analysis, using the kinetic evaluation software WinNonlin. AUClast values were calculated by linear/log trapezoidal rule from time zero to the last measurable concentration time point.

End point type | Primary

End point timeframe:

Cycle 1 Day 5

Notes:

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

Justification: No statistical analysis was planned for this endpoint.

| End point values | 200 mg once daily | 400 mg once daily | 600 mg once daily | 400 mg twice daily |
|---------------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 3 | 2 | 4 |
| Units: mg x h/L | | | | |
| geometric mean (full range (min-max)) | 2.04 (1.05 to 3.19) | 6.06 (4.87 to 7.74) | 9.99 (7.62 to 13.1) | 4.73 (2.61 to 7.55) |

Statistical analyses

No statistical analyses for this end point

Primary: Maximum tolerated dose (number of subjects with DLTs)

| | |
|-----------------|--|
| End point title | Maximum tolerated dose (number of subjects with DLTs) ^[4] |
|-----------------|--|

End point description:

Dose-limiting toxicity was defined as any of the following conditions occurring in Cycle 1:

- \geq Grade 3 non-hematological toxicity (excluding alopecia; ALT/AST $<$ 10x ULN; gamma GGT and AP levels, fatigue only Grade 4);
- \geq Grade 3 nausea, uncontrolled vomiting, or diarrhea over more than 48 h;
- Grade 3 elevated troponin levels if other evidence of cardiac damage is present;
- Grade 4 granulocytopenia lasting \geq 7 days, febrile neutropenia, thrombocytopenia, or anemia;
- Inability to receive the scheduled regimen of resminostat and FOLFIRI due to toxicity, and to begin the next dosing within two weeks;
- \geq Grade 2 non-hematological toxicity persisting beyond first cycle, judged by the investigator/sponsor as dose limiting;
- Toxicities which in the judgment of the investigator/sponsor are dose limiting;

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

End point timeframe:

Only DLTs proclaimed in Cycle 1 (14 days) were used for the purpose of MTD decisions.

Notes:

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

Justification: No statistical analysis was planned for this endpoint.

| End point values | 200 mg once daily | 400 mg once daily | 600 mg once daily | 400 mg twice daily |
|-------------------------------------|-------------------|-------------------|-------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 3 | 3 | 8 |
| Units: Number of subjects with DLTs | 0 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The period of observation for collection of adverse events extended from the first dose of resminostat through 30 days following the last dose of resminostat.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------|
| Reporting group title | 200 mg once daily |
|-----------------------|-------------------|

Reporting group description:

In 14-day treatment cycles, patients were dosed on 5 consecutive days (Days 1-5) with 200 mg resminostat once daily, followed by a 9-day rest period (Days 6-14). On Days 3 and 4 compounds of FOLFIRI regimen (5-fluorouracil, folinic acid, irinotecan) were administered according to the respective summary of product characteristics.

| | |
|-----------------------|-------------------|
| Reporting group title | 400 mg once daily |
|-----------------------|-------------------|

Reporting group description:

In 14-day treatment cycles, patients were dosed on 5 consecutive days (Days 1-5) with 400 mg resminostat once daily, followed by a 9-day rest period (Days 6-14). On Days 3 and 4 compounds of FOLFIRI regimen (5-fluorouracil, folinic acid, irinotecan) were administered according to the respective summary of product characteristics.

| | |
|-----------------------|-------------------|
| Reporting group title | 600 mg once daily |
|-----------------------|-------------------|

Reporting group description:

In 14-day treatment cycles, patients were dosed on 5 consecutive days (Days 1-5) with 600 mg resminostat once daily, followed by a 9-day rest period (Days 6-14). On Days 3 and 4 compounds of FOLFIRI regimen (5-fluorouracil, folinic acid, irinotecan) were administered according to the respective summary of product characteristics.

| | |
|-----------------------|--------------------|
| Reporting group title | 400 mg twice daily |
|-----------------------|--------------------|

Reporting group description:

In 14-day treatment cycles, patients were dosed on 5 consecutive days (Days 1-5) with 400 mg resminostat twice daily, followed by a 9-day rest period (Days 6-14). On Days 3 and 4 compounds of FOLFIRI regimen (5-fluorouracil, folinic acid, irinotecan) were administered according to the respective summary of product characteristics.

| | |
|-----------------------|-------|
| Reporting group title | Total |
|-----------------------|-------|

Reporting group description: -

| Serious adverse events | 200 mg once daily | 400 mg once daily | 600 mg once daily |
|---|-------------------|-------------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 3 (33.33%) | 2 / 3 (66.67%) |
| number of deaths (all causes) | 3 | 3 | 3 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Overdose | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| 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 | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (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 disorders | | | |
| Portal venous gas | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Somnolence | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 3 (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 |
| Renal and urinary disorders | | | |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Device related infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung abscess | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| 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 | | | |
| Dehydration | | | |

| | | | |
|---|----------------|---------------|---------------|
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 3 (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 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | 400 mg twice daily | Total | |
|--|--------------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 6 / 17 (35.29%) | |
| number of deaths (all causes) | 6 | 15 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Overdose | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Portal venous gas | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Somnolence | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Device related infection | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 17 (5.88%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung abscess | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 17 (5.88%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 17 (5.88%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | 200 mg once daily | 400 mg once daily | 600 mg once daily |
|---|-------------------|-------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | 3 / 3 (100.00%) | 3 / 3 (100.00%) |
| Vascular disorders | | | |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hot flush | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Jugular vein thrombosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Surgical and medical procedures | | | |
| Nutritional supplementation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Stent placement | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Chills | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Device leakage | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Fatigue | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 3 / 3 (100.00%) | 2 / 3 (66.67%) | 1 / 3 (33.33%) |
| occurrences (all) | 3 | 3 | 2 |
| Feeling hot | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 0 | 2 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Local swelling | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 3 (66.67%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 4 | 1 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 3 (33.33%) | 2 / 3 (66.67%) |
| occurrences (all) | 1 | 2 | 2 |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchial obstruction | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cough | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysaesthesia pharynx | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Dysphonia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Hiccups | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Productive cough | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Wheezing | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Depression | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Sleep disorder | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|---------------------|---------------------|---------------------|
| Sleep disturbance subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 1 / 3 (33.33%) 3 |
| Acute stress disorder subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 3 (33.33%) 1 | 0 / 3 (0.00%) 0 |
| Investigations | | | |
| Amino acid level increased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 1 / 3 (33.33%) 1 |
| Amylase increased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 1 / 3 (33.33%) 2 |
| Blood calcium decreased subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Blood creatinine phosphokinase increased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 3 (33.33%) 1 | 0 / 3 (0.00%) 0 |
| Blood potassium decreased subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Blood testosterone decreased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 3 (33.33%) 1 | 0 / 3 (0.00%) 0 |
| Blood uric acid increased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 1 / 3 (33.33%) 1 |
| C-reactive protein increased subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Electrocardiogram PQ interval subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 1 / 3 (33.33%) 1 |
| Electrocardiogram QT prolonged | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 2 | 5 |
| Electrocardiogram T wave inversion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Electrocardiogram repolarisation abnormality | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| International normalised ratio increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 3 | 1 |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 3 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Prothrombin time prolonged | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Thyroxine free decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Tri-iodothyronine free decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Weight decreased | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 1 / 3 (33.33%) 1 | 2 / 3 (66.67%) 3 |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |
| Limb injury subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 3 (33.33%) 1 | 0 / 3 (0.00%) 0 |
| Lumbar vertebral fracture subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Cardiac disorders | | | |
| Bradycardia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 3 (33.33%) 1 | 2 / 3 (66.67%) 3 |
| Sinus bradycardia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Sinus tachycardia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 1 / 3 (33.33%) 1 |
| Dysgeusia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 3 (33.33%) 1 | 0 / 3 (0.00%) 0 |
| Headache subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Polyneuropathy subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Vocal cord paralysis | | | |

| | | | |
|--------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cholinergic syndrome | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 2 / 3 (66.67%) | 3 / 3 (100.00%) |
| occurrences (all) | 2 | 3 | 4 |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Aphthous stomatitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ascites | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Constipation | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 3 (66.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Diarrhoea | | | |

| | | | |
|-----------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed | 3 / 3 (100.00%) | 2 / 3 (66.67%) | 3 / 3 (100.00%) |
| occurrences (all) | 4 | 5 | 3 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Eructation | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Flatulence | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Melaena | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 2 / 3 (66.67%) | 2 / 3 (66.67%) |
| occurrences (all) | 3 | 3 | 3 |
| Oral mucosal erythema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tongue dry | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Varices oesophageal | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vomiting | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 2 / 3 (66.67%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 7 | 6 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 2 / 3 (66.67%) |
| occurrences (all) | 0 | 1 | 2 |
| Hepatobiliary disorders | | | |
| Hepatic pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dry skin | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Eczema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Erythema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperhidrosis | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Night sweats | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 3 (66.67%) | 2 / 3 (66.67%) |
| occurrences (all) | 0 | 2 | 2 |
| Rash | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rosacea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Scab | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin fissures | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Endocrine disorders | | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Back pain | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Proctalgia | | | |

| | | | |
|--|--------------------|---------------------|--------------------|
| subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 3 (33.33%) 1 | 0 / 3 (0.00%) 0 |
| Infections and infestations | | | |
| Candida infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 3 (66.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Endometritis | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Herpes simplex | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infection | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dehydration | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Hyperuricaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 3 (66.67%) | 2 / 3 (66.67%) |
| occurrences (all) | 1 | 2 | 2 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 2 / 3 (66.67%) |
| occurrences (all) | 1 | 0 | 5 |
| Polydipsia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vitamin K deficiency | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 1 | 1 |

| | | | |
|---|--------------------|-------------------|--|
| Non-serious adverse events | 400 mg twice daily | Total | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 8 / 8 (100.00%) | 17 / 17 (100.00%) | |
| Vascular disorders | | | |
| Circulatory collapse | | | |

| | | | |
|--|----------------|------------------|--|
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Hot flush | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 3 / 17 (17.65%) | |
| occurrences (all) | 1 | 3 | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 17 (11.76%) | |
| occurrences (all) | 1 | 2 | |
| Jugular vein thrombosis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 17 (5.88%) | |
| occurrences (all) | 1 | 1 | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 17 (5.88%) | |
| occurrences (all) | 1 | 1 | |
| Surgical and medical procedures | | | |
| Nutritional supplementation | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Stent placement | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 17 (5.88%) | |
| occurrences (all) | 1 | 1 | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Chills | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 2 | |
| Device leakage | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Fatigue | | | |
| subjects affected / exposed | 4 / 8 (50.00%) | 10 / 17 (58.82%) | |
| occurrences (all) | 5 | 13 | |
| Feeling hot | | | |

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 17 (11.76%) | |
| occurrences (all) | 0 | 3 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 17 (5.88%) | |
| occurrences (all) | 1 | 1 | |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 17 (5.88%) | |
| occurrences (all) | 1 | 1 | |
| Local swelling | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 3 / 17 (17.65%) | |
| occurrences (all) | 2 | 3 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 4 / 17 (23.53%) | |
| occurrences (all) | 0 | 6 | |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 7 / 17 (41.18%) | |
| occurrences (all) | 4 | 9 | |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchial obstruction | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 17 (5.88%) | |
| occurrences (all) | 1 | 1 | |
| Cough | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 2 / 17 (11.76%) | |
| occurrences (all) | 2 | 2 | |
| Dysaesthesia pharynx | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Dysphonia | | | |

| | | | |
|-----------------------------|----------------|-----------------|--|
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 17 (5.88%) | |
| occurrences (all) | 1 | 1 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 3 / 17 (17.65%) | |
| occurrences (all) | 1 | 3 | |
| Hiccups | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 3 / 17 (17.65%) | |
| occurrences (all) | 2 | 3 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 2 / 17 (11.76%) | |
| occurrences (all) | 2 | 2 | |
| Productive cough | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 17 (5.88%) | |
| occurrences (all) | 1 | 1 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 17 (5.88%) | |
| occurrences (all) | 1 | 1 | |
| Wheezing | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 17 (5.88%) | |
| occurrences (all) | 1 | 1 | |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Depression | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 17 (5.88%) | |
| occurrences (all) | 1 | 1 | |
| Insomnia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 3 / 17 (17.65%) | |
| occurrences (all) | 1 | 3 | |
| Sleep disorder | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Sleep disturbance | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 3 | |

| | | | |
|---|---------------------|-----------------------|--|
| Acute stress disorder subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 17 (5.88%) 1 | |
| Investigations | | | |
| Amino acid level increased subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 17 (5.88%) 1 | |
| Amylase increased subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 17 (5.88%) 2 | |
| Blood calcium decreased subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 17 (5.88%) 1 | |
| Blood creatinine phosphokinase increased subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 17 (5.88%) 1 | |
| Blood potassium decreased subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 17 (5.88%) 1 | |
| Blood testosterone decreased subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 17 (5.88%) 1 | |
| Blood uric acid increased subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 17 (5.88%) 1 | |
| C-reactive protein increased subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 2 / 17 (11.76%) 2 | |
| Electrocardiogram PQ interval subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 17 (5.88%) 1 | |
| Electrocardiogram QT prolonged subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 4 | 3 / 17 (17.65%) 11 | |
| Electrocardiogram T wave inversion | | | |

| | | |
|--|----------------|-----------------|
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 17 (5.88%) |
| occurrences (all) | 1 | 1 |
| Electrocardiogram repolarisation abnormality | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 1 |
| Gamma-glutamyltransferase increased | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 1 |
| International normalised ratio increased | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 3 / 17 (17.65%) |
| occurrences (all) | 1 | 5 |
| Lipase increased | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 3 |
| Lymphocyte count decreased | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 17 (5.88%) |
| occurrences (all) | 1 | 1 |
| Neutrophil count decreased | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 17 (5.88%) |
| occurrences (all) | 3 | 3 |
| Prothrombin time prolonged | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 1 |
| Thyroxine free decreased | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 1 |
| Tri-iodothyronine free decreased | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 17 (11.76%) |
| occurrences (all) | 1 | 2 |
| Weight decreased | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 5 / 17 (29.41%) |
| occurrences (all) | 1 | 6 |
| Blood bilirubin increased | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 2 | 1 / 17 (5.88%) 2 | |
| Injury, poisoning and procedural complications | | | |
| Limb injury | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Cardiac disorders | | | |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 4 / 17 (23.53%) | |
| occurrences (all) | 1 | 5 | |
| Sinus bradycardia | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 2 / 17 (11.76%) | |
| occurrences (all) | 2 | 2 | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 17 (5.88%) | |
| occurrences (all) | 1 | 1 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 17 (11.76%) | |
| occurrences (all) | 2 | 3 | |
| Dysgeusia | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 3 / 17 (17.65%) | |
| occurrences (all) | 2 | 3 | |
| Headache | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Polyneuropathy | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 17 (5.88%) | |
| occurrences (all) | 1 | 1 | |
| Vocal cord paralysis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 17 (5.88%) | |
| occurrences (all) | 1 | 1 | |
| Cholinergic syndrome | | | |

| | | | |
|--|--------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 17 (5.88%) 2 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 8 / 17 (47.06%) | |
| occurrences (all) | 1 | 10 | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 17 (11.76%) | |
| occurrences (all) | 0 | 2 | |
| Lymphopenia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 17 (5.88%) | |
| occurrences (all) | 2 | 2 | |
| Neutropenia | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 3 / 17 (17.65%) | |
| occurrences (all) | 5 | 6 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 17 (11.76%) | |
| occurrences (all) | 2 | 3 | |
| Aphthous stomatitis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 17 (11.76%) | |
| occurrences (all) | 1 | 2 | |
| Ascites | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 17 (11.76%) | |
| occurrences (all) | 0 | 4 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 4 / 17 (23.53%) | |
| occurrences (all) | 1 | 4 | |
| Diarrhoea | | | |
| subjects affected / exposed | 4 / 8 (50.00%) | 12 / 17 (70.59%) | |
| occurrences (all) | 8 | 20 | |
| Dyspepsia | | | |

| | | |
|-----------------------------|----------------|------------------|
| subjects affected / exposed | 2 / 8 (25.00%) | 3 / 17 (17.65%) |
| occurrences (all) | 2 | 3 |
| Dysphagia | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 17 (11.76%) |
| occurrences (all) | 1 | 2 |
| Eructation | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 1 |
| Flatulence | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 17 (11.76%) |
| occurrences (all) | 2 | 3 |
| Haematemesis | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 1 |
| Melaena | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 1 |
| Nausea | | |
| subjects affected / exposed | 5 / 8 (62.50%) | 11 / 17 (64.71%) |
| occurrences (all) | 7 | 16 |
| Oral mucosal erythema | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 17 (5.88%) |
| occurrences (all) | 1 | 1 |
| Stomatitis | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 1 |
| Tongue dry | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 17 (5.88%) |
| occurrences (all) | 1 | 1 |
| Varices oesophageal | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 1 |
| Vomiting | | |
| subjects affected / exposed | 5 / 8 (62.50%) | 8 / 17 (47.06%) |
| occurrences (all) | 8 | 21 |
| Abdominal pain | | |

| | | | |
|--|---------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 2 / 8 (25.00%) 2 | 5 / 17 (29.41%) 5 | |
| Hepatobiliary disorders | | | |
| Hepatic pain | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 17 (5.88%) | |
| occurrences (all) | 1 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Dry skin | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 17 (11.76%) | |
| occurrences (all) | 1 | 2 | |
| Eczema | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 17 (5.88%) | |
| occurrences (all) | 1 | 1 | |
| Erythema | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 17 (5.88%) | |
| occurrences (all) | 1 | 1 | |
| Hyperhydrosis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 3 / 17 (17.65%) | |
| occurrences (all) | 1 | 4 | |
| Night sweats | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 4 / 17 (23.53%) | |
| occurrences (all) | 0 | 4 | |
| Rash | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 2 / 17 (11.76%) | |
| occurrences (all) | 2 | 2 | |
| Rosacea | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Scab | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Skin fissures | | | |

| | | | |
|---|---------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 2 / 17 (11.76%) 2 | |
| Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 2 | 1 / 17 (5.88%) 2 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 2 / 17 (11.76%) 2 | |
| Back pain subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 2 / 17 (11.76%) 2 | |
| Muscle spasms subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 3 | 1 / 17 (5.88%) 3 | |
| Musculoskeletal chest pain subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 17 (5.88%) 1 | |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 17 (5.88%) 1 | |
| Musculoskeletal stiffness subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 17 (5.88%) 1 | |
| Myalgia subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 17 (5.88%) 1 | |
| Neck pain subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 17 (5.88%) 1 | |
| Proctalgia subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 17 (5.88%) 1 | |
| Infections and infestations | | | |

| | | | |
|---|---------------------|----------------------|--|
| Candida infection subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 2 / 17 (11.76%) 4 | |
| Device related infection subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 17 (5.88%) 1 | |
| Endometritis subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 17 (5.88%) 1 | |
| Herpes simplex subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 17 (5.88%) 1 | |
| Herpes zoster subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 17 (5.88%) 1 | |
| Infection subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 17 (5.88%) 1 | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 17 (5.88%) 1 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 17 (5.88%) 1 | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 2 / 17 (11.76%) 2 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 4 / 8 (50.00%) 4 | 4 / 17 (23.53%) 4 | |
| Dehydration subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 17 (5.88%) 1 | |
| Hypercalcaemia | | | |

| | | |
|-----------------------------|----------------|-----------------|
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 1 |
| Hyperglycaemia | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 17 (11.76%) |
| occurrences (all) | 1 | 3 |
| Hyperuricaemia | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 1 |
| Hypoalbuminaemia | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 17 (11.76%) |
| occurrences (all) | 0 | 2 |
| Hypocalcaemia | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 17 (11.76%) |
| occurrences (all) | 0 | 2 |
| Hypokalaemia | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 7 / 17 (41.18%) |
| occurrences (all) | 4 | 9 |
| Hypomagnesaemia | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 3 / 17 (17.65%) |
| occurrences (all) | 0 | 6 |
| Polydipsia | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 17 (5.88%) |
| occurrences (all) | 1 | 1 |
| Vitamin K deficiency | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 17 (11.76%) |
| occurrences (all) | 0 | 2 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 15 March 2011 | Documentation of change of LKP and Principal Investigator at one site. |
| 21 July 2011 | <p>To improve patient recruitment in phase I of the study, an additional participating site was submitted. Furthermore the protocol and patient informed consent were adapted regarding the in- and exclusion criteria of phase I of the clinical trial:</p> <ul style="list-style-type: none">o Patients in \geq 2nd line treatment were allowed to participate in phase I of the clinical trial.o Patients without k-ras mutation were included in phase I of the study.o The inclusion and exclusion criteria of phase II of the study were not changed. |
| 15 December 2011 | <p>During study conduct it was observed that a special focus on the serum electrolyte levels of the patients was needed. In order to increase the safety of the study participants, the recommendation of prophylactic and interventional substitution of electrolytes was added to the study protocol. Furthermore, the definition of dose-limiting toxicities was adjusted according to current knowledge of the safety profile of the resminostat/FOLFIRI combination.</p> <p>The points amended were:</p> <ul style="list-style-type: none">o Addition of advice in case of serum electrolyte deviationso Update information about study durationo Adaption of the definition of dose limiting toxicitieso Other formal changes and clarifications |
| 28 January 2013 | <p>Implementation of administrative changes, and prolongation of the recruiting phase.</p> <p>The points amended were:</p> <ul style="list-style-type: none">o Update information about study team memberso Update information about study durationo Other formal changes, e.g. punctuation |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

After completion of phase I, and even though the phase I part raised no safety concerns, 4SC AG decided to primarily focus on the development of resminostat in other indications. Therefore, the SHORE study was terminated without conducting phase II.

Notes: