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/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.

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: Pharmacokinetik (tmax)

End point title	Pharmacokinetik (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: Pharmacokinetik (Cmax)

End point title	Pharmacokinetik (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: Pharmacokinetik (AUClast)

End point title	Pharmacokinetik (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:
- ≥ Grade 3 non-hematological toxicity (excluding alopecia; ALT/AST < 10x ULN; gamma GGT and AP levels, fatigue only Grade 4);
- ≥ 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 ≥ 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;
- ≥ Grade 2 non-hematological toxicity persisting beyond first cycle, juged 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 Cyle 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	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	3
Acute stress disorder			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Investigations			
Amino acid level increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Amylase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Blood calcium decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Blood creatinine phosphokinase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Blood potassium decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Blood testosterone decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Blood uric acid increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
C-reactive protein increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Electrocardiogram PQ interval			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	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
Lmyphocyte 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	1 / 3 (33.33%)	1 / 3 (33.33%)	2 / 3 (66.67%)
occurrences (all)	1	1	3
Blood bilirubin increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Lumbar vertebral fracture			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	2 / 3 (66.67%)
occurrences (all)	0	1	3
Sinus bradycardia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Sinus tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Dysgeusia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Polyneuropathy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	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
Hyperhydrosis			
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	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	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	0 / 8 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Investigations			
Amino acid level increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Amylase increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	2	
Blood calcium decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Blood creatinine phosphokinase increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Blood potassium decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Blood testosterone decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Blood uric acid increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
C-reactive protein increased			
subjects affected / exposed	1 / 8 (12.50%)	2 / 17 (11.76%)	
occurrences (all)	1	2	
Electrocardiogram PQ interval			
subjects affected / exposed	0 / 8 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 8 (12.50%)	3 / 17 (17.65%)	
occurrences (all)	4	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	
Lmyphocyte 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	1 / 8 (12.50%)	1 / 17 (5.88%)	
occurrences (all)	2	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	0 / 8 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	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	2 / 8 (25.00%)	5 / 17 (29.41%)	
occurrences (all)	2	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	0 / 8 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 8 (12.50%)	1 / 17 (5.88%)	
occurrences (all)	2	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Back pain			
subjects affected / exposed	0 / 8 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Muscle spasms			
subjects affected / exposed	1 / 8 (12.50%)	1 / 17 (5.88%)	
occurrences (all)	3	3	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Musculoskeletal pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Musculoskeletal stiffness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Neck pain			
subjects affected / exposed	1 / 8 (12.50%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Proctalgia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Infections and infestations			

Candida infection			
subjects affected / exposed	0 / 8 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	4	
Device related infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Endometritis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Herpes simplex			
subjects affected / exposed	0 / 8 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Herpes zoster			
subjects affected / exposed	1 / 8 (12.50%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	1 / 8 (12.50%)	2 / 17 (11.76%)	
occurrences (all)	1	2	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 8 (50.00%)	4 / 17 (23.53%)	
occurrences (all)	4	4	
Dehydration			
subjects affected / exposed	1 / 8 (12.50%)	1 / 17 (5.88%)	
occurrences (all)	1	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	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: o Patients in ≥ 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	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. The points amended were: o Addition of advice in case of serum electrolyte deviations o Update information about study duration o Adaption of the definition of dose limiting toxicities o Other formal changes and clarifications
28 January 2013	Implementation of administrative changes, and prolongation of the recruiting phase. The points amended were: o Update information about study team members o Update information about study duration o 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: