



Clinical trial results:

A randomized, open-label Phase II multicenter study evaluating the efficacy of oral everolimus alone or in combination with pasireotide LAR im in advanced progressive pancreatic neuroendocrine tumors (PNET) – The COOPERATE-2 study

Summary

EudraCT number	2010-023183-40
Trial protocol	GB SE BE DK DE HU ES NL IT
Global end of trial date	19 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	CSOM230I2201
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01374451
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4004, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	19 February 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	19 February 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to estimate the treatment effect of everolimus in combination with pasireotide LAR relative to everolimus alone on progression-free survival (PFS) in patients with advanced PNET and to assess the predictive probability of success in a possible subsequent Phase III study once 80 PFS events have been observed.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 June 2011
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	Argentina: 1
Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	Brazil: 9
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	France: 30
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Japan: 5
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	New Zealand: 5
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	Thailand: 5
Country: Number of subjects enrolled	Turkey: 2

Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	160
EEA total number of subjects	112

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)	114
From 65 to 84 years	46
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients were randomized in a 1:1 ratio to receive everolimus or everolimus + pasireotide LAR. Randomization was by stratification. Approximately 150 patients were planned to be randomized globally. For each patient there were 3 separate periods in the study: screening/baseline, treatment and follow-up.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pasireotide LAR + Everolimus

Arm description:

everolimus 10 mg once daily po in combination with pasireotide LAR 60 mg every 28 days (q28d) im

Arm type	Experimental
Investigational medicinal product name	Pasireotide LAR
Investigational medicinal product code	SOM230
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Pasireotide LAR im depot injections were supplied as a powder in vials containing 20 mg and 40 mg with ampoules containing 2 mL of vehicle for reconstitution.

Arm title	Everolimus
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Arm description:

everolimus 10 mg once daily po alone

Arm type	Experimental
Investigational medicinal product name	everolimus
Investigational medicinal product code	RAD001
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Everolimus was supplied as tablets of 5 mg strength, blister-packed under aluminum foil in units of 10 tablets.

Number of subjects in period 1	Paseriotide LAR + Everolimus	Everolimus
Started	79	81
Completed	78	81
Not completed	1	0
Administrative problems	1	-

Baseline characteristics

Reporting groups

Reporting group title	Pasireotide LAR + Everolimus
Reporting group description: everolimus 10 mg once daily po in combination with pasireotide LAR 60 mg every 28 days (q28d) im	
Reporting group title	Everolimus
Reporting group description: everolimus 10 mg once daily po alone	

Reporting group values	Pasireotide LAR + Everolimus	Everolimus	Total
Number of subjects	79	81	160
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	59	55	114
From 65-84 years	20	26	46
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	56.52	58.22	
standard deviation	± 11.978	± 12.65	-
Gender, Male/Female Units: Participants			
Female	40	34	74
Male	39	47	86

End points

End points reporting groups

Reporting group title	Paseriotide LAR + Everolimus
Reporting group description:	everolimus 10 mg once daily po in combination with pasireotide LAR 60 mg every 28 days (q28d) im
Reporting group title	Everolimus
Reporting group description:	everolimus 10 mg once daily po alone

Primary: Progression-free survival (PFS) per local radiological review

End point title	Progression-free survival (PFS) per local radiological review
End point description:	PFS per RECIST 1.0. (Response Evaluation Criteria in Solid Tumors). PFS was defined as the time from the date of randomization to the date of the first radiologically documented disease progression or death due to any cause.
End point type	Primary
End point timeframe:	Once 80 PFS events had occurred approximately after 24 months

End point values	Paseriotide LAR + Everolimus	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	81		
Units: months				
median (confidence interval 95%)	16.82 (12.09 to 19.58)	16.59 (11.07 to 19.48)		

Statistical analyses

Statistical analysis title	PFS based on local radiological review
Comparison groups	Everolimus v Paseriotide LAR + Everolimus
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.488
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.991
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.636
upper limit	1.543

Variability estimate	Standard deviation
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Secondary: Safety and tolerability profile of Everolimus alone or in combination with Pasireotide LAR

End point title	Safety and tolerability profile of Everolimus alone or in combination with Pasireotide LAR
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End point description:

Consisted of monitoring and recording the rate, type, severity, and causal relationship of adverse events (AEs) and serious AEs (SAEs) to treatment. The safety analysis was based mainly on the frequency of AEs or SAEs and on the number of laboratory values that fell outside of pre-determined range.

End point type	Secondary
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End point timeframe:

Once 80 PFS events had occurred

End point values	Pasireotide LAR + Everolimus	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	81		
Units: Participants				
Deaths	7	10		
Serious Adverse Events	41	49		
Adverse Events	78	81		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) as per radiology review

End point title	Objective Response Rate (ORR) as per radiology review
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End point description:

Objective response was determined by the local radiologist according to the RECIST Version 1.0. ORR is the percentage of patients with a best overall response of complete response (CR) or partial response (PR). This is also referred to as Overall response rate. CR: Disappearance of all nontarget lesions. PR: At least a 30% decrease in the sum of the longest diameter of all target lesions, taking as reference the smallest sum of the longest diameter of all target lesions recorded at or after baseline.

End point type	Secondary
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End point timeframe:

Once 80 PFS events had occurred

End point values	Pasireotide LAR + Everolimus	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	81		
Units: Percentage of participants				
number (confidence interval 95%)	20.3 (12 to 30.8)	6.2 (2 to 13.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DoR)

End point title	Duration of response (DoR)
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End point description:

Analyzed in patients with best overall response of complete response (CR) or partial response (PR). The start date was the date of first documented response (CR or PR) and the end date was defined as the first documented progression or death due to underlying cancer. If a patient had not had an event or when receiving any further anti-cancer therapy, DoR was censored at the date of last adequate tumor assessment. Based on the mode of action of everolimus and pasireotide and based on current experience, only a low number of objective responses per RECIST were expected. Therefore, DoR was listed with confirmed responses flagged in the listing.

End point type	Secondary
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End point timeframe:

Once 80 PFS events had occurred

End point values	Pasireotide LAR + Everolimus	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[1]	0 ^[2]		
Units: Months				
number (not applicable)				

Notes:

[1] - A low number of objective responses per RECIST was expected. Duration of response was not analyzed.

[2] - A low number of objective responses per RECIST was expected. Duration of response was not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) using Kaplan Meier method

End point title	Overall Survival (OS) using Kaplan Meier method
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End point description:

Overall survival was defined as the time from date of randomization/start of treatment to date of death due to any cause. If a patient is not known to have died, survival was to be censored at the date of last contact.

End point type	Secondary
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End point timeframe:

Once 80 PFS events had occurred

End point values	Paseriotide LAR + Everolimus	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	81		
Units: Percentage of participants				
arithmetic mean (confidence interval 95%)				
6 months	93.5 (85 to 97.2)	93.7 (85.5 to 97.3)		
12 months	85.5 (75.4 to 91.7)	86.1 (76.2 to 92)		
18 months	81.4 (70.6 to 88.5)	75.5 (64.3 to 83.6)		
24 months	77 (65.6 to 85.1)	71 (59.3 to 79.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS and the predictive probability of success in phase III

End point title	PFS and the predictive probability of success in phase III
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End point description:

Since the study was terminated because the study did not meet its primary objective which was based on PFS as per local radiology assessment, minimal efficacy data was obtained. Only 80 PFS events occurred before study was terminated so 105 PFS events was not reached to analyze this data.

End point type	Secondary
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End point timeframe:

Once 105 PFS events had occurred occurred

End point values	Paseriotide LAR + Everolimus	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[3]	0 ^[4]		
Units: Months				
number (not applicable)				

Notes:

[3] - 80 PFS events occurred before study was terminated. 105 PFS events was not reached to analyze data.

[4] - 80 PFS events occurred before study was terminated. 105 PFS events was not reached to analyze data.

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) as per radiology review

End point title	Disease Control Rate (DCR) as per radiology review
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End point description:

Disease control rate is the percentage of patients with a best overall response of CR or PR or stable disease (SD) determined by the local radiologist according to the Response Evaluation Criteria In Solid Tumors Criteria (RECIST) Version 1.0. CR: Disappearance of all nontarget lesions. PR: At least a 30% decrease in the sum of the longest diameter of all target lesions, taking as reference the smallest sum of the longest diameter of all target lesions recorded at or after baseline. SD: Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for progressive disease (PD). PD: Any progression $\leq$ 18 weeks after randomization (and not qualifying for CR, PR or stable disease SD).

End point type	Secondary
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End point timeframe:

Once 80 PFS events had occurred

End point values	Pasireotide LAR + Everolimus	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	81		
Units: Percentage of participants				
number (confidence interval 95%)	77.2 (66.4 to 85.9)	82.7 (72.7 to 90.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Pharmacokinetics (PK) for everolimus for AUClast

End point title	Summary of Pharmacokinetics (PK) for everolimus for AUClast
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End point description:

PK analysis set consisted of all patients who had at least 1 pasireotide LAR injection or 1 everolimus administration and 1 evaluable concentration data.

End point type	Secondary
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End point timeframe:

Cycle 2 Day 1

End point values	Pasireotide LAR + Everolimus	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	8		
Units: ng*hr/mL				
arithmetic mean (standard deviation)	511 ($\pm$ 91.8)	378 ($\pm$ 123)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Pharmacokinetics (PK) for everolimus for CL/F

End point title	Summary of Pharmacokinetics (PK) for everolimus for CL/F
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End point description:

PK analysis set consisted of all patients who had at least 1 pasireotide LAR injection or 1 everolimus administration and 1 evaluable concentration data.

End point type	Secondary
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End point timeframe:

Cycle 2 Day 1

End point values	Pasireotide LAR + Everolimus	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	8		
Units: L/hr				
arithmetic mean (standard deviation)	20 ($\pm$ 3.21)	29 ($\pm$ 9.51)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Pharmacokinetics (PK) for everolimus for Cmax and Cmin

End point title	Summary of Pharmacokinetics (PK) for everolimus for Cmax and Cmin
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End point description:

PK analysis set consisted of all patients who had at least 1 pasireotide LAR injection or 1 everolimus administration and 1 evaluable concentration data

End point type	Secondary
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End point timeframe:

Cycle 2 Day 1

End point values	Pasireotide LAR + Everolimus	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	9		
Units: ng/mL				
arithmetic mean (standard deviation)				
Cmax	58.7 ($\pm$ 25.9)	60.2 ($\pm$ 30.6)		
Cmin	14.7 ($\pm$ 4.81)	7.67 ($\pm$ 4.41)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Pharmacokinetics (PK) for everolimus for Tmax

End point title	Summary of Pharmacokinetics (PK) for everolimus for Tmax
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End point description:

PK analysis set consisted of all patients who had at least 1 pasireotide LAR injection or 1 everolimus administration and 1 evaluable concentration data.

End point type	Secondary
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End point timeframe:

Cycle 2 Day 1

End point values	Pasireotide LAR + Everolimus	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	9		
Units: hr				
median (inter-quartile range (Q1-Q3))	1 (0.333 to 5)	0.5 (0.5 to 5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of pasireotide concentrations following intramuscular injection of pasireotide LAR 60mg

End point title	Summary of pasireotide concentrations following intramuscular injection of pasireotide LAR 60mg ^[5]
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End point description:

PK analysis set consisted of all patients who had at least 1 pasireotide LAR injection or 1 everolimus administration and 1 evaluable concentration data.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 21, Cycle 2 Day 29

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Summary statistics was not planned for this endpoint.

End point values	Paseriotide LAR + Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	69			
Units: ng/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 21 (n:69)	21.6 (± 13.1)			
Cycle 2 Day 29 (n: 64)	19.9 (± 12.1)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse Events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	Everolimus
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Reporting group description:

Everolimus

Reporting group title	Everolimus +Pasireotide
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Reporting group description:

Everolimus +Pasireotide

Serious adverse events	Everolimus	Everolimus +Pasireotide	
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 81 (60.49%)	41 / 78 (52.56%)	
number of deaths (all causes)	10	7	
number of deaths resulting from adverse events	1	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix carcinoma			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrinoma			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipoma			

subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperaemia			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 81 (2.47%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Face oedema			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fatigue			
subjects affected / exposed	1 / 81 (1.23%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 81 (1.23%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised oedema			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	2 / 81 (2.47%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	6 / 81 (7.41%)	5 / 78 (6.41%)	
occurrences causally related to treatment / all	2 / 9	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 81 (3.70%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lung disorder			
subjects affected / exposed	1 / 81 (1.23%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal oedema			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 81 (1.23%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 81 (1.23%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 81 (1.23%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			

subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood albumin decreased			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	2 / 81 (2.47%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose decreased			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose fluctuation			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose increased			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood urea increased			

subjects affected / exposed	1 / 81 (1.23%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	2 / 81 (2.47%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Foreign body aspiration			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skeletal injury			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			

subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 81 (1.23%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 81 (1.23%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			

subjects affected / exposed	1 / 81 (1.23%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nerve compression			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's disease			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 81 (6.17%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Ocular icterus			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 81 (6.17%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	2 / 9	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 81 (1.23%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 81 (2.47%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal stenosis			

subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal oedema			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids thrombosed			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernial eventration			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			

subjects affected / exposed	2 / 81 (2.47%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 81 (3.70%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	4 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	3 / 81 (3.70%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	3 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	3 / 81 (3.70%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	0 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	2 / 81 (2.47%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	1 / 81 (1.23%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			

subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	3 / 81 (3.70%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal failure acute			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			

subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial cyst			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary sepsis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract infection			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis aeromonas			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex meningoencephalitis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			

subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection bacterial			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 81 (2.47%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	4 / 81 (4.94%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	1 / 4	2 / 2	
deaths causally related to treatment / all	0 / 1	1 / 1	
Sinusitis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 81 (1.23%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 81 (2.47%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 81 (1.23%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	2 / 81 (2.47%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			

subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 81 (1.23%)	5 / 78 (6.41%)	
occurrences causally related to treatment / all	0 / 1	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 81 (1.23%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 81 (1.23%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ketoacidosis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	

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

Non-serious adverse events	Everolimus	Everolimus +Pasireotide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	80 / 81 (98.77%)	77 / 78 (98.72%)	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 81 (2.47%)	6 / 78 (7.69%)	
occurrences (all)	5	8	
Alanine aminotransferase increased			
subjects affected / exposed	4 / 81 (4.94%)	7 / 78 (8.97%)	
occurrences (all)	6	7	
Blood alkaline phosphatase increased			
subjects affected / exposed	4 / 81 (4.94%)	5 / 78 (6.41%)	
occurrences (all)	5	8	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 81 (1.23%)	4 / 78 (5.13%)	
occurrences (all)	1	4	
Gamma-glutamyltransferase increased			
subjects affected / exposed	11 / 81 (13.58%)	10 / 78 (12.82%)	
occurrences (all)	11	12	
Glycosylated haemoglobin increased			
subjects affected / exposed	1 / 81 (1.23%)	4 / 78 (5.13%)	
occurrences (all)	1	4	
Weight decreased			
subjects affected / exposed	25 / 81 (30.86%)	24 / 78 (30.77%)	
occurrences (all)	27	28	
Haemoglobin decreased			
subjects affected / exposed	7 / 81 (8.64%)	2 / 78 (2.56%)	
occurrences (all)	8	2	
Vascular disorders			
Hypertension			
subjects affected / exposed	14 / 81 (17.28%)	15 / 78 (19.23%)	
occurrences (all)	16	17	
Nervous system disorders			
Dizziness			

subjects affected / exposed occurrences (all)	5 / 81 (6.17%) 6	4 / 78 (5.13%) 6	
Dysgeusia subjects affected / exposed occurrences (all)	17 / 81 (20.99%) 20	10 / 78 (12.82%) 11	
Headache subjects affected / exposed occurrences (all)	26 / 81 (32.10%) 34	17 / 78 (21.79%) 39	
Paraesthesia subjects affected / exposed occurrences (all)	5 / 81 (6.17%) 6	3 / 78 (3.85%) 7	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	20 / 81 (24.69%) 29	21 / 78 (26.92%) 37	
Leukopenia subjects affected / exposed occurrences (all)	7 / 81 (8.64%) 10	3 / 78 (3.85%) 9	
Lymphopenia subjects affected / exposed occurrences (all)	4 / 81 (4.94%) 4	4 / 78 (5.13%) 6	
Thrombocytopenia subjects affected / exposed occurrences (all)	9 / 81 (11.11%) 20	8 / 78 (10.26%) 11	
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	16 / 81 (19.75%) 18	17 / 78 (21.79%) 27	
Fatigue subjects affected / exposed occurrences (all)	27 / 81 (33.33%) 40	21 / 78 (26.92%) 27	
Influenza like illness subjects affected / exposed occurrences (all)	7 / 81 (8.64%) 8	1 / 78 (1.28%) 2	
Non-cardiac chest pain			

subjects affected / exposed occurrences (all)	6 / 81 (7.41%) 6	1 / 78 (1.28%) 1	
Oedema peripheral subjects affected / exposed occurrences (all)	31 / 81 (38.27%) 53	26 / 78 (33.33%) 30	
Peripheral swelling subjects affected / exposed occurrences (all)	4 / 81 (4.94%) 5	4 / 78 (5.13%) 4	
Pyrexia subjects affected / exposed occurrences (all)	21 / 81 (25.93%) 29	15 / 78 (19.23%) 24	
Gastrointestinal disorders			
Abdominal distension subjects affected / exposed occurrences (all)	8 / 81 (9.88%) 11	7 / 78 (8.97%) 7	
Aphthous stomatitis subjects affected / exposed occurrences (all)	9 / 81 (11.11%) 22	5 / 78 (6.41%) 5	
Abdominal pain upper subjects affected / exposed occurrences (all)	15 / 81 (18.52%) 22	10 / 78 (12.82%) 11	
Abdominal pain subjects affected / exposed occurrences (all)	29 / 81 (35.80%) 41	22 / 78 (28.21%) 46	
Constipation subjects affected / exposed occurrences (all)	18 / 81 (22.22%) 28	11 / 78 (14.10%) 15	
Diarrhoea subjects affected / exposed occurrences (all)	43 / 81 (53.09%) 79	49 / 78 (62.82%) 94	
Dysphagia subjects affected / exposed occurrences (all)	5 / 81 (6.17%) 5	0 / 78 (0.00%) 0	
Flatulence subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	8 / 78 (10.26%) 8	

Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	5 / 81 (6.17%) 5	3 / 78 (3.85%) 3	
Mouth ulceration subjects affected / exposed occurrences (all)	6 / 81 (7.41%) 8	4 / 78 (5.13%) 7	
Nausea subjects affected / exposed occurrences (all)	24 / 81 (29.63%) 48	27 / 78 (34.62%) 41	
Steatorrhoea subjects affected / exposed occurrences (all)	2 / 81 (2.47%) 3	9 / 78 (11.54%) 9	
Stomatitis subjects affected / exposed occurrences (all)	51 / 81 (62.96%) 95	46 / 78 (58.97%) 75	
Vomiting subjects affected / exposed occurrences (all)	15 / 81 (18.52%) 26	22 / 78 (28.21%) 41	
Toothache subjects affected / exposed occurrences (all)	5 / 81 (6.17%) 5	3 / 78 (3.85%) 9	
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	28 / 81 (34.57%) 40	21 / 78 (26.92%) 30	
Dyspnoea subjects affected / exposed occurrences (all)	12 / 81 (14.81%) 16	5 / 78 (6.41%) 5	
Epistaxis subjects affected / exposed occurrences (all)	20 / 81 (24.69%) 24	5 / 78 (6.41%) 5	
Oropharyngeal pain subjects affected / exposed occurrences (all)	6 / 81 (7.41%) 7	4 / 78 (5.13%) 5	
Pneumonitis			

subjects affected / exposed occurrences (all)	11 / 81 (13.58%) 12	5 / 78 (6.41%) 6	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	3 / 81 (3.70%)	4 / 78 (5.13%)	
occurrences (all)	3	4	
Acne			
subjects affected / exposed	7 / 81 (8.64%)	1 / 78 (1.28%)	
occurrences (all)	9	1	
Dermatitis acneiform			
subjects affected / exposed	7 / 81 (8.64%)	6 / 78 (7.69%)	
occurrences (all)	9	7	
Dry skin			
subjects affected / exposed	19 / 81 (23.46%)	12 / 78 (15.38%)	
occurrences (all)	26	12	
Nail disorder			
subjects affected / exposed	5 / 81 (6.17%)	4 / 78 (5.13%)	
occurrences (all)	5	4	
Onychoclasia			
subjects affected / exposed	8 / 81 (9.88%)	5 / 78 (6.41%)	
occurrences (all)	9	5	
Rash			
subjects affected / exposed	25 / 81 (30.86%)	20 / 78 (25.64%)	
occurrences (all)	37	23	
Pruritus			
subjects affected / exposed	18 / 81 (22.22%)	12 / 78 (15.38%)	
occurrences (all)	29	14	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 81 (4.94%)	4 / 78 (5.13%)	
occurrences (all)	4	4	
Insomnia			
subjects affected / exposed	8 / 81 (9.88%)	7 / 78 (8.97%)	
occurrences (all)	10	8	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	13 / 81 (16.05%)	11 / 78 (14.10%)	
occurrences (all)	16	14	
Back pain			
subjects affected / exposed	14 / 81 (17.28%)	11 / 78 (14.10%)	
occurrences (all)	20	15	
Muscle spasms			
subjects affected / exposed	4 / 81 (4.94%)	6 / 78 (7.69%)	
occurrences (all)	6	12	
Musculoskeletal pain			
subjects affected / exposed	5 / 81 (6.17%)	4 / 78 (5.13%)	
occurrences (all)	7	5	
Myalgia			
subjects affected / exposed	7 / 81 (8.64%)	6 / 78 (7.69%)	
occurrences (all)	9	6	
Pain in extremity			
subjects affected / exposed	8 / 81 (9.88%)	11 / 78 (14.10%)	
occurrences (all)	10	15	
Neck pain			
subjects affected / exposed	5 / 81 (6.17%)	2 / 78 (2.56%)	
occurrences (all)	5	2	
Infections and infestations			
Cystitis			
subjects affected / exposed	3 / 81 (3.70%)	7 / 78 (8.97%)	
occurrences (all)	8	9	
Gastroenteritis			
subjects affected / exposed	3 / 81 (3.70%)	4 / 78 (5.13%)	
occurrences (all)	3	5	
Influenza			
subjects affected / exposed	6 / 81 (7.41%)	5 / 78 (6.41%)	
occurrences (all)	7	5	
Nasopharyngitis			
subjects affected / exposed	10 / 81 (12.35%)	12 / 78 (15.38%)	
occurrences (all)	12	27	
Pneumonia			

subjects affected / exposed	5 / 81 (6.17%)	1 / 78 (1.28%)	
occurrences (all)	7	1	
Pharyngitis			
subjects affected / exposed	2 / 81 (2.47%)	5 / 78 (6.41%)	
occurrences (all)	2	6	
Oral herpes			
subjects affected / exposed	6 / 81 (7.41%)	3 / 78 (3.85%)	
occurrences (all)	6	3	
Rhinitis			
subjects affected / exposed	5 / 81 (6.17%)	1 / 78 (1.28%)	
occurrences (all)	6	1	
Upper respiratory tract infection			
subjects affected / exposed	6 / 81 (7.41%)	5 / 78 (6.41%)	
occurrences (all)	6	5	
Urinary tract infection			
subjects affected / exposed	5 / 81 (6.17%)	4 / 78 (5.13%)	
occurrences (all)	6	4	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	22 / 81 (27.16%)	14 / 78 (17.95%)	
occurrences (all)	30	17	
Diabetes mellitus			
subjects affected / exposed	6 / 81 (7.41%)	20 / 78 (25.64%)	
occurrences (all)	6	20	
Hypercholesterolaemia			
subjects affected / exposed	15 / 81 (18.52%)	16 / 78 (20.51%)	
occurrences (all)	17	27	
Hyperglycaemia			
subjects affected / exposed	23 / 81 (28.40%)	56 / 78 (71.79%)	
occurrences (all)	32	111	
Hypertriglyceridaemia			
subjects affected / exposed	7 / 81 (8.64%)	10 / 78 (12.82%)	
occurrences (all)	12	18	
Hypoglycaemia			
subjects affected / exposed	3 / 81 (3.70%)	16 / 78 (20.51%)	
occurrences (all)	4	23	

Hypokalaemia			
subjects affected / exposed	11 / 81 (13.58%)	5 / 78 (6.41%)	
occurrences (all)	16	6	
Hyponatraemia			
subjects affected / exposed	2 / 81 (2.47%)	4 / 78 (5.13%)	
occurrences (all)	2	4	
Hypophosphataemia			
subjects affected / exposed	3 / 81 (3.70%)	9 / 78 (11.54%)	
occurrences (all)	5	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 December 2011	The reason for this protocol amendment was to reflect an urgent safety measure. Monitoring of hepatic function was increased, inclusion and exclusion criteria were updated to increase hepatic safety and clear stopping rules for liver-related AEs were specified. This was based on findings in the pasireotide clinical development program, where three cases meeting Hy's law criteria in healthy volunteers and one patient treated with pasireotide solution for s.c. injection was identified. This was communicated in an Investigator Notification on October 31, 2011.
17 July 2012	Primary reason for this amendment was to clarify the importance of routine patient glucose self-monitoring, to detect and treat hyperglycemia as early as possible, and to give specific guidance on dose adjustment in the different treatment arms. In addition, sections of the protocol were updated and aligned, and corrections and clarifications were made. These modifications were not believed to have influenced the study outcome and did not impact the patient population studied. As of July 3, 2012, 100 patients had been randomized in the SOM230I2201 study.
15 November 2012	The reason for this amendment was that the Danish Health Authority did not consider total abstinence as a 'highly effective contraception' method. These modifications are not believed to have influenced the study outcome and did not impact the patient population studied. As of October 23, 2012, 139 patients had been randomized in the SOM230I2201 study.

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.

A planned primary analysis was completed with data cut of 02-Apr-2014. The study did not meet its primary objective, which was based on progression-free survival as per local radiology assessment and was prematurely terminated.

Notes: