



## Clinical trial results:

### An Open-Label, Dose-escalation, Phase I/IIa Study to Determine the Maximum Tolerated Dose, Recommended Dose, Pharmacokinetics, and Pharmacodynamics of the dual VEGFR-FGFR Tyrosine Kinase Inhibitor, E-3810, Given Orally as Single Agent to Patients With Advanced Solid Tumours

#### Summary

EudraCT number	2010-019121-34
Trial protocol	ES
Global end of trial date	04 May 2017

#### Results information

Result version number	v1 (current)
This version publication date	26 April 2018
First version publication date	26 April 2018

#### Trial information

##### Trial identification

Sponsor protocol code	CL1-80881-007 (E-3810)
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01283945
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier
Sponsor organisation address	50 rue Carnot, Suresnes, France, 92284
Public contact	Clinical studies Department, Institut de Recherches Internationales Servier, +33 155723666, clinicaltrials@servier.com
Scientific contact	Clinical studies Department, Institut de Recherches Internationales Servier, +33 155723666, clinicaltrials@servier.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	04 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 May 2017
Global end of trial reached?	Yes
Global end of trial date	04 May 2017
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Phase I: To determine the Maximum Tolerated Dose (MTD) of S80881 when administered orally, once daily for 28 consecutive days.

Phase IIa: To evaluate the objective response rate and the rate of non-progressive disease at 24 weeks in patients with tumours bearing FGFR1 amplification.

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice standards, ethical principles stated in the Declaration of Helsinki and applicable regulatory requirements. After the subject has ended his/her participation in the trial, the investigator provided appropriate medication and/or arranged access to appropriate care for the patient.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 July 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 37
Country: Number of subjects enrolled	France: 85
Country: Number of subjects enrolled	Italy: 12
Worldwide total number of subjects	134
EEA total number of subjects	134

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)	108

From 65 to 84 years	26
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Patients were to have histologically or cytologically confirmed locally advanced or metastatic solid tumour, relapsed or refractory to standard therapy.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	S 80881 5mg
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	S 80881
Investigational medicinal product code	
Other name	E-3810, Lucitanib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One oral capsule of S 80881 5mg, once a day, on a continuous schedule or intermittent dosing schedules (e.g., 5 days on/2days off [5/2], or 21 days on/7 days off [21/7]), for up to 6 cycles of 4 weeks. In exceptional cases, in the best interest of patients who showed continued clinical benefit according to their doctor, treatment beyond cycle 6 could be allowed.

<b>Arm title</b>	S 80881 10mg
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	S 80881
Investigational medicinal product code	
Other name	E-3810, Lucitanib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One oral capsule of S 80881 10mg, once a day, on a continuous schedule or intermittent dosing schedules (e.g., 5 days on/2days off [5/2], or 21 days on/7 days off [21/7]), for up to 6 cycles of 4 weeks. In exceptional cases, in the best interest of patients who showed continued clinical benefit according to their doctor, treatment beyond cycle 6 could be allowed.

<b>Arm title</b>	S 80881 12.5mg
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	S 80881
Investigational medicinal product code	
Other name	E-3810, Lucitanib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One oral capsule of S 80881 12.5mg, once a day, on a continuous schedule or intermittent dosing schedules (e.g., 5 days on/2days off [5/2], or 21 days on/7 days off [21/7]), for up to 6 cycles of 4 weeks. In exceptional cases, in the best interest of patients who showed continued clinical benefit according to their doctor, treatment beyond cycle 6 could be allowed.

<b>Arm title</b>	S 80881 15mg
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	S 80881
Investigational medicinal product code	
Other name	E-3810, Lucitanib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One oral capsule of S 80881 15mg, once a day, on a continuous schedule or intermittent dosing schedules (e.g., 5 days on/2days off [5/2], or 21 days on/7 days off [21/7]), for up to 6 cycles of 4 weeks. In exceptional cases, in the best interest of patients who showed continued clinical benefit according to their doctor, treatment beyond cycle 6 could be allowed.

<b>Arm title</b>	S 80881 20mg
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	S 80881
Investigational medicinal product code	
Other name	E-3810, Lucitanib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One oral capsule of S 80881 20mg, once a day, on a continuous schedule or intermittent dosing schedules (e.g., 5 days on/2days off [5/2], or 21 days on/7 days off [21/7]), for up to 6 cycles of 4 weeks. In exceptional cases, in the best interest of patients who showed continued clinical benefit according to their doctor, treatment beyond cycle 6 could be allowed.

<b>Arm title</b>	S 80881 30mg
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	S 80881
Investigational medicinal product code	
Other name	E-3810, Lucitanib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One oral capsule of S 80881 30mg, once a day, on a continuous schedule or intermittent dosing schedules (e.g., 5 days on/2days off [5/2], or 21 days on/7 days off [21/7]), for up to 6 cycles of 4 weeks. In exceptional cases, in the best interest of patients who showed continued clinical benefit according to their doctor, treatment beyond cycle 6 could be allowed.

<b>Number of subjects in period 1</b>	S 80881 5mg	S 80881 10mg	S 80881 12.5mg
Started	3	11	25
Completed	0	0	0
Not completed	3	11	25
Non-drug related adverse events	-	-	2
Death	-	-	-
Other (compassionate use program)	-	-	1
Patient's request due to subjective intolerance	-	1	-
Progressive disease	3	10	14
Drug-related adverse events	-	-	8

<b>Number of subjects in period 1</b>	S 80881 15mg	S 80881 20mg	S 80881 30mg
Started	71	17	7
Completed	0	0	0
Not completed	71	17	7
Non-drug related adverse events	4	2	-
Death	1	-	-
Other (compassionate use program)	2	-	-
Patient's request due to subjective intolerance	1	2	-
Progressive disease	54	12	3
Drug-related adverse events	9	1	4

## Baseline characteristics

### Reporting groups

Reporting group title	S 80881 5mg
Reporting group description: -	
Reporting group title	S 80881 10mg
Reporting group description: -	
Reporting group title	S 80881 12.5mg
Reporting group description: -	
Reporting group title	S 80881 15mg
Reporting group description: -	
Reporting group title	S 80881 20mg
Reporting group description: -	
Reporting group title	S 80881 30mg
Reporting group description: -	

Reporting group values	S 80881 5mg	S 80881 10mg	S 80881 12.5mg
Number of subjects	3	11	25
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)	2	7	20
From 65-84 years	1	4	5
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	60.3	53.1	56.1
standard deviation	± 7.6	± 14.8	± 11.4
Gender categorical Units: Subjects			
Female	1	7	15
Male	2	4	10

Reporting group values	S 80881 15mg	S 80881 20mg	S 80881 30mg
Number of subjects	71	17	7
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)	60	14	5
From 65-84 years	11	3	2
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	53.9	58.8	57.4
standard deviation	± 9.9	± 9.7	± 7.9
Gender categorical			
Units: Subjects			
Female	41	7	3
Male	30	10	4

<b>Reporting group values</b>	Total		
Number of subjects	134		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	108		
From 65-84 years	26		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	74		
Male	60		



## End points

### End points reporting groups

Reporting group title	S 80881 5mg
Reporting group description: -	
Reporting group title	S 80881 10mg
Reporting group description: -	
Reporting group title	S 80881 12.5mg
Reporting group description: -	
Reporting group title	S 80881 15mg
Reporting group description: -	
Reporting group title	S 80881 20mg
Reporting group description: -	
Reporting group title	S 80881 30mg
Reporting group description: -	
Subject analysis set title	DLT Evaluable Set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients included in the dose-escalation phase. A patient wasn't considered evaluable if:

- He/she discontinued during first cycle without DLT, or
- He/she did not receive at least 21 of 28 doses during first cycle unless patients presented a DLT.

Subject analysis set title	Response Evaluable Set in FGF+ patients
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This set corresponds to all patients in the FAS with solid tumour bearing FGFR1 amplification who had at least one baseline and one post-baseline tumour evaluation.

### Primary: Objective Response Rate

End point title	Objective Response Rate <sup>[1]</sup>
End point description:	Objective Response Rate, evaluated in the Response Evaluable Set in patients with tumour bearing bearing FGFR1 amplification (FGF+), was defined as the proportion of patients with a Complete Response (CR) or a Partial Response (PR) as best overall response (with confirmation of response, i.e. at least 4 weeks after the first assessment) according to RECIST criteria.
End point type	Primary

End point timeframe:

Objective Response Rate was evaluated across all time points from the start of the study treatment until PD or end of treatment period whichever was earlier.

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 analyses was required for this endpoint.

End point values	S 80881 5mg	S 80881 10mg	S 80881 12.5mg	S 80881 15mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 <sup>[2]</sup>	4	1	25
Units: Patients		1	0	3

Notes:

[2] - No patient in the 5mg group had solid tumour bearing FGFR1 amplification.

End point values	S 80881 20mg	S 80881 30mg	Response Evaluable Set in FGF+ patients	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	0 <sup>[3]</sup>	33	
Units: Patients	2		6	

Notes:

[3] - No patient in the 30mg group had solid tumour bearing FGFR1 amplification.

## Statistical analyses

No statistical analyses for this end point

### Primary: Clinical Benefit Rate

End point title	Clinical Benefit Rate <sup>[4]</sup>
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End point description:

The Clinical Benefit Rate, evaluated in the Response Evaluable Set in patients FGF+, was defined as the proportion of patients with a CR or a PR as best overall response (with confirmation of response, i.e. at least 4 weeks after the first assessment) or a prolonged stabilization (Stable Disease or Non CR /Non PD) > 24 weeks after start of treatment (or at cycle 6), according to RECIST criteria.

End point type	Primary
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End point timeframe:

Clinical Benefit Rate was evaluated across all time points from the start of the study treatment until PD or end of treatment period whichever was earlier.

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 analyses was required for this endpoint.

End point values	S 80881 5mg	S 80881 10mg	S 80881 12.5mg	S 80881 15mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 <sup>[5]</sup>	4	1	25
Units: Patients		1	1	7

Notes:

[5] - No patient in the 5mg group had solid tumour bearing FGFR1 amplification.

End point values	S 80881 20mg	S 80881 30mg	Response Evaluable Set in FGF+ patients	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	0 <sup>[6]</sup>	33	
Units: Patients	3		12	

Notes:

[6] - No patient in the 30mg group had solid tumour bearing FGFR1 amplification.

## Statistical analyses

No statistical analyses for this end point

### Primary: Maximum Tolerated Dose (MTD)

End point title	Maximum Tolerated Dose (MTD) <sup>[7]</sup>
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End point description:

During the dose escalation, 17 patients received at least one dose of S 80881 and 16 were evaluable (i.e. received at least 21 doses) for DLT. Four dose levels (i.e. 5, 10, 20, and 30 mg) were tested. No DLTs were observed at the first three levels; at 30 mg once daily, 3 DLTs were observed in the 6 patients assessable for DLT. The MTD assessed in the DLT evaluable Set (N=16) was therefore defined at 30 mg S 80881 once daily.

End point type	Primary
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End point timeframe:

MTD was determined at the end of Cycle 1.

Notes:

[7] - 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 analyses was required for this endpoint.

<b>End point values</b>	DLT Evaluable Set			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: mg once daily	30			

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Emergent adverse events on treatment were defined as adverse events occurring or worsening (in terms of severity) or becoming serious between the first study drug intake date (included) and the last study drug intake date + 28 days (included).

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	18

### Reporting groups

Reporting group title	All patients
Reporting group description: -	
Reporting group title	5 mg
Reporting group description: -	
Reporting group title	10 mg
Reporting group description: -	
Reporting group title	12,5 mg
Reporting group description: -	
Reporting group title	15 mg
Reporting group description: -	
Reporting group title	20 mg
Reporting group description: -	
Reporting group title	30 mg
Reporting group description: -	

Serious adverse events	All patients	5 mg	10 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	67 / 134 (50.00%)	2 / 3 (66.67%)	7 / 11 (63.64%)
number of deaths (all causes)	24	0	4
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	3 / 134 (2.24%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	2 / 134 (1.49%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	4 / 134 (2.99%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	3 / 134 (2.24%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acquired tracheo-oesophageal fistula			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (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
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Bronchospasm			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Cough			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (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
Dyspnoea			
subjects affected / exposed	10 / 134 (7.46%)	1 / 3 (33.33%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 12	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	4 / 134 (2.99%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (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
Respiratory failure			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (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
Electrocardiogram T wave inversion			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (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
Injury, poisoning and procedural complications			
Gingival injury			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (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
Tracheal haemorrhage			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (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
Atrial thrombosis			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (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
Cardiac failure			

subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (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
Cardiac tamponade			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (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
Left ventricular dysfunction			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocarditis			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (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
Pericarditis			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (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
Tricuspid valve disease			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nervous system disorders			
Cerebellar syndrome			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (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
Depressed level of consciousness			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (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
Peripheral motor neuropathy			



subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (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
Seizure			
subjects affected / exposed	2 / 134 (1.49%)	1 / 3 (33.33%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (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
Syncope			
subjects affected / exposed	1 / 134 (0.75%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Thrombotic microangiopathy			
subjects affected / exposed	15 / 134 (11.19%)	1 / 3 (33.33%)	2 / 11 (18.18%)
occurrences causally related to treatment / all	16 / 16	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (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
Dysphagia			

subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (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
Ileus			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (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
Pancreatitis			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cirrhosis			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic pain			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (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			

Proteinuria			
subjects affected / exposed	3 / 134 (2.24%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	3 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	3 / 134 (2.24%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (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
Infections and infestations			
Anorectal infection			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (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
Bronchopulmonary aspergillosis			

subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (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
Lung infection			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 134 (0.75%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 134 (0.75%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (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
Hyponatraemia			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (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

<b>Serious adverse events</b>	12,5 mg	15 mg	20 mg
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Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 25 (72.00%)	29 / 71 (40.85%)	7 / 17 (41.18%)
number of deaths (all causes)	4	15	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	1 / 25 (4.00%)	2 / 71 (2.82%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (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
Hypertension			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	0 / 17 (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
General physical health deterioration			
subjects affected / exposed	3 / 25 (12.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 25 (4.00%)	2 / 71 (2.82%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acquired tracheo-oesophageal fistula			

subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	0 / 17 (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
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Bronchospasm			
subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cough			
subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	0 / 17 (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
Dyspnoea			
subjects affected / exposed	2 / 25 (8.00%)	5 / 71 (7.04%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 3	0 / 6	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	0 / 17 (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
Pleural effusion			
subjects affected / exposed	1 / 25 (4.00%)	2 / 71 (2.82%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 25 (4.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			

subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	0 / 17 (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
Respiratory failure			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (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
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	0 / 17 (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
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	0 / 17 (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
Electrocardiogram T wave inversion			
subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	0 / 17 (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
Injury, poisoning and procedural complications			
Gingival injury			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (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
Tracheal haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac disorders			
Angina pectoris			

subjects affected / exposed	2 / 25 (8.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial thrombosis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	0 / 17 (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
Cardiac failure			
subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	0 / 17 (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
Cardiac tamponade			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular dysfunction			
subjects affected / exposed	0 / 25 (0.00%)	2 / 71 (2.82%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocarditis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	0 / 17 (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
Pericarditis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	0 / 17 (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
Tricuspid valve disease			



subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nervous system disorders			
Cerebellar syndrome			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	0 / 17 (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
Depressed level of consciousness			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (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
Peripheral motor neuropathy			
subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (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
Spinal cord compression			
subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	0 / 17 (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
Syncope			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (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
Blood and lymphatic system disorders			

Thrombotic microangiopathy subjects affected / exposed	3 / 25 (12.00%)	7 / 71 (9.86%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	4 / 4	7 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	0 / 17 (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
Dysphagia subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	0 / 17 (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
Ileus subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (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
Large intestine perforation subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis subjects affected / exposed	0 / 25 (0.00%)	2 / 71 (2.82%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting subjects affected / exposed	2 / 25 (8.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Cholestasis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (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
Hepatic cirrhosis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	0 / 17 (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
Hepatic pain			
subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	0 / 17 (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			
Proteinuria			
subjects affected / exposed	0 / 25 (0.00%)	2 / 71 (2.82%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 25 (0.00%)	2 / 71 (2.82%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	2 / 25 (8.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			

subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	0 / 17 (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
Infections and infestations			
Anorectal infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	0 / 17 (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
Device related infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	0 / 17 (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
Lung infection			
subjects affected / exposed	1 / 25 (4.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (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
Sepsis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (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			

Decreased appetite			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (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
Hypercalcaemia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

<b>Serious adverse events</b>	30 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 7 (57.14%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acquired tracheo-oesophageal fistula			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchospasm			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cough			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Injury, poisoning and procedural complications			
Gingival injury			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tracheal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Angina unstable			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial thrombosis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac tamponade			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Left ventricular dysfunction			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		



Myocarditis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pericarditis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tricuspid valve disease			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebellar syndrome			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Depressed level of consciousness			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral motor neuropathy			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Presyncope			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Thrombotic microangiopathy			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Large intestine perforation			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic cirrhosis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neck pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Anorectal infection			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	All patients	5 mg	10 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	134 / 134 (100.00%)	3 / 3 (100.00%)	11 / 11 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Malignant neoplasm progression			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Metastases to liver			

subjects affected / exposed occurrences (all)	1 / 134 (0.75%) 1	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Hot flush			
subjects affected / exposed	9 / 134 (6.72%)	0 / 3 (0.00%)	2 / 11 (18.18%)
occurrences (all)	12	0	3
Hypertension			
subjects affected / exposed	118 / 134 (88.06%)	2 / 3 (66.67%)	10 / 11 (90.91%)
occurrences (all)	411	39	13
Hypotension			
subjects affected / exposed	5 / 134 (3.73%)	2 / 3 (66.67%)	0 / 11 (0.00%)
occurrences (all)	5	2	0
Thrombophlebitis superficial			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	103 / 134 (76.87%)	3 / 3 (100.00%)	6 / 11 (54.55%)
occurrences (all)	217	23	15
Chest discomfort			
subjects affected / exposed	3 / 134 (2.24%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	3	0	0
Chest pain			
subjects affected / exposed	12 / 134 (8.96%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	14	2	0
Chills			
subjects affected / exposed	11 / 134 (8.21%)	2 / 3 (66.67%)	0 / 11 (0.00%)
occurrences (all)	13	2	0
Condition aggravated			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Face oedema			

subjects affected / exposed	6 / 134 (4.48%)	0 / 3 (0.00%)	3 / 11 (27.27%)
occurrences (all)	8	0	4
General physical health deterioration			
subjects affected / exposed	4 / 134 (2.99%)	0 / 3 (0.00%)	2 / 11 (18.18%)
occurrences (all)	4	0	2
Generalised oedema			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	2	0	1
Impaired healing			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Inflammation			
subjects affected / exposed	3 / 134 (2.24%)	1 / 3 (33.33%)	1 / 11 (9.09%)
occurrences (all)	4	2	1
Influenza like illness			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Localised oedema			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Malaise			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Mucosal inflammation			
subjects affected / exposed	8 / 134 (5.97%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	10	0	0
Non-cardiac chest pain			
subjects affected / exposed	10 / 134 (7.46%)	1 / 3 (33.33%)	1 / 11 (9.09%)
occurrences (all)	10	1	1
Oedema peripheral			
subjects affected / exposed	37 / 134 (27.61%)	0 / 3 (0.00%)	5 / 11 (45.45%)
occurrences (all)	51	0	5
Pyrexia			
subjects affected / exposed	20 / 134 (14.93%)	2 / 3 (66.67%)	3 / 11 (27.27%)
occurrences (all)	26	4	4
Xerosis			

subjects affected / exposed occurrences (all)	14 / 134 (10.45%) 16	1 / 3 (33.33%) 1	1 / 11 (9.09%) 1
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	1 / 134 (0.75%) 1	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0
Reproductive system and breast disorders Amenorrhoea subjects affected / exposed occurrences (all)	1 / 134 (0.75%) 1	0 / 3 (0.00%) 0	1 / 11 (9.09%) 1
Pruritus genital subjects affected / exposed occurrences (all)	1 / 134 (0.75%) 1	0 / 3 (0.00%) 0	1 / 11 (9.09%) 1
Vaginal inflammation subjects affected / exposed occurrences (all)	1 / 134 (0.75%) 1	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Atelectasis subjects affected / exposed occurrences (all)	2 / 134 (1.49%) 2	1 / 3 (33.33%) 1	0 / 11 (0.00%) 0
Cough subjects affected / exposed occurrences (all)	31 / 134 (23.13%) 58	2 / 3 (66.67%) 17	1 / 11 (9.09%) 1
Dysphonia subjects affected / exposed occurrences (all)	32 / 134 (23.88%) 40	0 / 3 (0.00%) 0	3 / 11 (27.27%) 4
Dyspnoea subjects affected / exposed occurrences (all)	44 / 134 (32.84%) 66	2 / 3 (66.67%) 16	4 / 11 (36.36%) 4
Epistaxis subjects affected / exposed occurrences (all)	16 / 134 (11.94%) 22	1 / 3 (33.33%) 4	2 / 11 (18.18%) 4
Haemoptysis subjects affected / exposed occurrences (all)	3 / 134 (2.24%) 4	1 / 3 (33.33%) 2	0 / 11 (0.00%) 0
Hiccups			



subjects affected / exposed	3 / 134 (2.24%)	0 / 3 (0.00%)	2 / 11 (18.18%)
occurrences (all)	3	0	2
Hypoxia			
subjects affected / exposed	2 / 134 (1.49%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	2	1	0
Oropharyngeal pain			
subjects affected / exposed	4 / 134 (2.99%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	4	0	0
Pleural effusion			
subjects affected / exposed	3 / 134 (2.24%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	3	1	0
Pleuritic pain			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	5	0	0
Pneumonitis			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Productive cough			
subjects affected / exposed	5 / 134 (3.73%)	2 / 3 (66.67%)	0 / 11 (0.00%)
occurrences (all)	5	2	0
Rales			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	3	0	2
Respiratory failure			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Rhinitis allergic			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Rhinorrhoea			
subjects affected / exposed	15 / 134 (11.19%)	2 / 3 (66.67%)	2 / 11 (18.18%)
occurrences (all)	18	3	2
Upper respiratory tract inflammation			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Psychiatric disorders			

Affective disorder			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Anxiety			
subjects affected / exposed	23 / 134 (17.16%)	2 / 3 (66.67%)	1 / 11 (9.09%)
occurrences (all)	25	3	1
Attention deficit/hyperactivity disorder			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Bradyphrenia			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Confusional state			
subjects affected / exposed	3 / 134 (2.24%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	3	0	0
Depressed mood			
subjects affected / exposed	9 / 134 (6.72%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	10	1	0
Depression			
subjects affected / exposed	6 / 134 (4.48%)	1 / 3 (33.33%)	2 / 11 (18.18%)
occurrences (all)	7	2	2
Hallucination			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Insomnia			
subjects affected / exposed	24 / 134 (17.91%)	2 / 3 (66.67%)	0 / 11 (0.00%)
occurrences (all)	27	2	0
Psychomotor retardation			
subjects affected / exposed	1 / 134 (0.75%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	2	2	0
Restlessness			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Sleep disorder			

subjects affected / exposed occurrences (all)	6 / 134 (4.48%) 6	0 / 3 (0.00%) 0	1 / 11 (9.09%) 1
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	29 / 134 (21.64%) 37	1 / 3 (33.33%) 1	6 / 11 (54.55%) 11
Amylase increased subjects affected / exposed occurrences (all)	5 / 134 (3.73%) 7	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	34 / 134 (25.37%) 45	0 / 3 (0.00%) 0	5 / 11 (45.45%) 9
Blood albumin decreased subjects affected / exposed occurrences (all)	1 / 134 (0.75%) 1	0 / 3 (0.00%) 0	1 / 11 (9.09%) 1
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	23 / 134 (17.16%) 23	0 / 3 (0.00%) 0	5 / 11 (45.45%) 5
Blood bicarbonate abnormal subjects affected / exposed occurrences (all)	1 / 134 (0.75%) 1	1 / 3 (33.33%) 1	0 / 11 (0.00%) 0
Blood bilirubin increased subjects affected / exposed occurrences (all)	14 / 134 (10.45%) 19	0 / 3 (0.00%) 0	4 / 11 (36.36%) 4
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	5 / 134 (3.73%) 8	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0
Blood creatinine decreased subjects affected / exposed occurrences (all)	1 / 134 (0.75%) 1	0 / 3 (0.00%) 0	1 / 11 (9.09%) 1
Blood creatinine increased subjects affected / exposed occurrences (all)	9 / 134 (6.72%) 14	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0
Blood glucose increased			

subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Blood magnesium decreased			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Blood phosphorus decreased			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Blood potassium decreased			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Brain natriuretic peptide increased			
subjects affected / exposed	5 / 134 (3.73%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	5	0	0
Breath sounds abnormal			
subjects affected / exposed	6 / 134 (4.48%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	10	5	0
C-reactive protein increased			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Ejection fraction decreased			
subjects affected / exposed	6 / 134 (4.48%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	8	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	31 / 134 (23.13%)	1 / 3 (33.33%)	3 / 11 (27.27%)
occurrences (all)	37	5	3
Haemoglobin increased			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Hypophonesis			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	2	0	1
Lipase increased			
subjects affected / exposed	11 / 134 (8.21%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	14	0	0

Platelet count decreased subjects affected / exposed occurrences (all)	23 / 134 (17.16%) 33	0 / 3 (0.00%) 0	2 / 11 (18.18%) 3
Tumour marker increased subjects affected / exposed occurrences (all)	1 / 134 (0.75%) 1	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0
Urine bilirubin increased subjects affected / exposed occurrences (all)	2 / 134 (1.49%) 2	0 / 3 (0.00%) 0	1 / 11 (9.09%) 1
Waist circumference increased subjects affected / exposed occurrences (all)	1 / 134 (0.75%) 1	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0
Weight decreased subjects affected / exposed occurrences (all)	52 / 134 (38.81%) 66	2 / 3 (66.67%) 2	2 / 11 (18.18%) 5
Weight increased subjects affected / exposed occurrences (all)	6 / 134 (4.48%) 6	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0
Injury, poisoning and procedural complications			
Fracture subjects affected / exposed occurrences (all)	1 / 134 (0.75%) 1	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0
Ligament sprain subjects affected / exposed occurrences (all)	2 / 134 (1.49%) 2	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0
Nail injury subjects affected / exposed occurrences (all)	3 / 134 (2.24%) 4	1 / 3 (33.33%) 1	0 / 11 (0.00%) 0
Cardiac disorders			
Bradycardia subjects affected / exposed occurrences (all)	6 / 134 (4.48%) 8	0 / 3 (0.00%) 0	1 / 11 (9.09%) 2
Cardiac disorder subjects affected / exposed occurrences (all)	1 / 134 (0.75%) 1	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0
Cardiac failure			

subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Pericardial effusion			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Sinus tachycardia			
subjects affected / exposed	8 / 134 (5.97%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	21	0	1
Tachycardia			
subjects affected / exposed	9 / 134 (6.72%)	1 / 3 (33.33%)	1 / 11 (9.09%)
occurrences (all)	9	1	1
Nervous system disorders			
Ataxia			
subjects affected / exposed	3 / 134 (2.24%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	3	0	0
Balance disorder			
subjects affected / exposed	4 / 134 (2.99%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	4	0	0
Carpal tunnel syndrome			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Cerebral venous thrombosis			
subjects affected / exposed	1 / 134 (0.75%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Disturbance in attention			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	4 / 134 (2.99%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	4	0	1
Dysaesthesia			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	4	0	3
Dysgeusia			
subjects affected / exposed	10 / 134 (7.46%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	10	0	0

Headache			
subjects affected / exposed	49 / 134 (36.57%)	2 / 3 (66.67%)	3 / 11 (27.27%)
occurrences (all)	76	12	4
Hypergeusia			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Loss of consciousness			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	14 / 134 (10.45%)	1 / 3 (33.33%)	1 / 11 (9.09%)
occurrences (all)	18	1	1
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Presyncope			
subjects affected / exposed	1 / 134 (0.75%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Radicular pain			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	2	0	1
Sciatica			
subjects affected / exposed	10 / 134 (7.46%)	1 / 3 (33.33%)	2 / 11 (18.18%)
occurrences (all)	11	1	2
Sensorimotor disorder			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Somnolence			
subjects affected / exposed	9 / 134 (6.72%)	2 / 3 (66.67%)	1 / 11 (9.09%)
occurrences (all)	11	3	2
Speech disorder			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Syncope			
subjects affected / exposed	1 / 134 (0.75%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	2	2	0

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	17 / 134 (12.69%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	25	0	1
Leukocytosis			
subjects affected / exposed	2 / 134 (1.49%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	2	1	0
Neutropenia			
subjects affected / exposed	4 / 134 (2.99%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	7	0	0
Spontaneous haematoma			
subjects affected / exposed	3 / 134 (2.24%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	3	0	0
Thrombocytopenia			
subjects affected / exposed	18 / 134 (13.43%)	0 / 3 (0.00%)	2 / 11 (18.18%)
occurrences (all)	30	0	6
Thrombotic microangiopathy			
subjects affected / exposed	6 / 134 (4.48%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	6	0	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	6 / 134 (4.48%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	7	1	0
Vertigo			
subjects affected / exposed	12 / 134 (8.96%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	14	2	0
Eye disorders			
Cataract			
subjects affected / exposed	3 / 134 (2.24%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	4	1	0
Dry eye			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Eczema eyelids			
subjects affected / exposed	1 / 134 (0.75%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Eye irritation			



subjects affected / exposed	2 / 134 (1.49%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	2	1	0
Lacrimation increased			
subjects affected / exposed	2 / 134 (1.49%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	3	2	0
Vision blurred			
subjects affected / exposed	5 / 134 (3.73%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	5	1	0
Visual acuity reduced			
subjects affected / exposed	4 / 134 (2.99%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	4	0	0
Visual impairment			
subjects affected / exposed	3 / 134 (2.24%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	3	0	1
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	15 / 134 (11.19%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	18	0	2
Abdominal pain			
subjects affected / exposed	50 / 134 (37.31%)	2 / 3 (66.67%)	4 / 11 (36.36%)
occurrences (all)	78	3	9
Abdominal pain lower			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Abdominal pain upper			
subjects affected / exposed	26 / 134 (19.40%)	1 / 3 (33.33%)	2 / 11 (18.18%)
occurrences (all)	35	1	2
Abdominal wall haematoma			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Anal fissure			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Anal inflammation			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0

Anorectal discomfort			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Aphthous stomatitis			
subjects affected / exposed	12 / 134 (8.96%)	2 / 3 (66.67%)	1 / 11 (9.09%)
occurrences (all)	14	3	1
Ascites			
subjects affected / exposed	3 / 134 (2.24%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	3	0	1
Constipation			
subjects affected / exposed	42 / 134 (31.34%)	2 / 3 (66.67%)	4 / 11 (36.36%)
occurrences (all)	52	3	5
Diarrhoea			
subjects affected / exposed	78 / 134 (58.21%)	2 / 3 (66.67%)	3 / 11 (27.27%)
occurrences (all)	285	35	6
Dry mouth			
subjects affected / exposed	23 / 134 (17.16%)	0 / 3 (0.00%)	2 / 11 (18.18%)
occurrences (all)	31	0	2
Dyspepsia			
subjects affected / exposed	15 / 134 (11.19%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	19	0	0
Dysphagia			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Faecaloma			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	2	0	1
Gastrointestinal motility disorder			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal pain			
subjects affected / exposed	1 / 134 (0.75%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	6 / 134 (4.48%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	8	0	1

Gingival bleeding			
subjects affected / exposed	3 / 134 (2.24%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	7	0	0
Gingival erythema			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Haemorrhoidal haemorrhage			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Haemorrhoids			
subjects affected / exposed	6 / 134 (4.48%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	8	1	0
Nausea			
subjects affected / exposed	73 / 134 (54.48%)	2 / 3 (66.67%)	7 / 11 (63.64%)
occurrences (all)	132	15	9
Odynophagia			
subjects affected / exposed	4 / 134 (2.99%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	4	0	0
Oesophageal pain			
subjects affected / exposed	3 / 134 (2.24%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	3	1	0
Oral pain			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Perianal erythema			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Rectal haemorrhage			
subjects affected / exposed	2 / 134 (1.49%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	2	1	0
Stomatitis			
subjects affected / exposed	8 / 134 (5.97%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	8	0	0
Tongue oedema			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	2	0	2

Toothache subjects affected / exposed occurrences (all)	4 / 134 (2.99%) 4	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	50 / 134 (37.31%) 109	1 / 3 (33.33%) 3	4 / 11 (36.36%) 7
Hepatobiliary disorders			
Hepatic pain subjects affected / exposed occurrences (all)	9 / 134 (6.72%) 11	1 / 3 (33.33%) 3	1 / 11 (9.09%) 1
Hepatocellular injury subjects affected / exposed occurrences (all)	6 / 134 (4.48%) 9	1 / 3 (33.33%) 3	0 / 11 (0.00%) 0
Hepatomegaly subjects affected / exposed occurrences (all)	12 / 134 (8.96%) 14	0 / 3 (0.00%) 0	1 / 11 (9.09%) 3
Hyperbilirubinaemia subjects affected / exposed occurrences (all)	2 / 134 (1.49%) 3	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0
Jaundice subjects affected / exposed occurrences (all)	3 / 134 (2.24%) 3	0 / 3 (0.00%) 0	1 / 11 (9.09%) 1
Liver disorder subjects affected / exposed occurrences (all)	1 / 134 (0.75%) 1	1 / 3 (33.33%) 1	0 / 11 (0.00%) 0
Skin and subcutaneous tissue disorders			
Acne subjects affected / exposed occurrences (all)	2 / 134 (1.49%) 3	0 / 3 (0.00%) 0	1 / 11 (9.09%) 2
Alopecia subjects affected / exposed occurrences (all)	4 / 134 (2.99%) 5	0 / 3 (0.00%) 0	1 / 11 (9.09%) 1
Dermatitis acneiform subjects affected / exposed occurrences (all)	1 / 134 (0.75%) 1	1 / 3 (33.33%) 1	0 / 11 (0.00%) 0
Dry skin			

subjects affected / exposed	28 / 134 (20.90%)	2 / 3 (66.67%)	3 / 11 (27.27%)
occurrences (all)	41	9	4
Ecchymosis			
subjects affected / exposed	1 / 134 (0.75%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	2	2	0
Eczema			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	3	0	0
Erythema			
subjects affected / exposed	9 / 134 (6.72%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	13	1	0
Hair growth abnormal			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Hyperhidrosis			
subjects affected / exposed	1 / 134 (0.75%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Hyperkeratosis			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	3	0	0
Nail dystrophy			
subjects affected / exposed	1 / 134 (0.75%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Night sweats			
subjects affected / exposed	3 / 134 (2.24%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	4	0	1
Onychoclasia			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Onychomadesis			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	9 / 134 (6.72%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	10	0	0

Petechiae			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	2	0	1
Pruritus			
subjects affected / exposed	5 / 134 (3.73%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	7	0	0
Rash			
subjects affected / exposed	17 / 134 (12.69%)	2 / 3 (66.67%)	0 / 11 (0.00%)
occurrences (all)	21	2	0
Rash macular			
subjects affected / exposed	3 / 134 (2.24%)	2 / 3 (66.67%)	0 / 11 (0.00%)
occurrences (all)	3	2	0
Skin exfoliation			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Umbilical erythema			
subjects affected / exposed	1 / 134 (0.75%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Albuminuria			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Dysuria			
subjects affected / exposed	8 / 134 (5.97%)	1 / 3 (33.33%)	1 / 11 (9.09%)
occurrences (all)	8	1	1
Haematuria			
subjects affected / exposed	24 / 134 (17.91%)	1 / 3 (33.33%)	1 / 11 (9.09%)
occurrences (all)	37	6	1
Haemoglobinuria			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Oliguria			

subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	2	0	1
Proteinuria			
subjects affected / exposed	93 / 134 (69.40%)	2 / 3 (66.67%)	8 / 11 (72.73%)
occurrences (all)	215	12	24
Renal failure			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Urogenital fistula			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Hypothyroidism			
subjects affected / exposed	69 / 134 (51.49%)	2 / 3 (66.67%)	7 / 11 (63.64%)
occurrences (all)	78	2	7
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	36 / 134 (26.87%)	1 / 3 (33.33%)	1 / 11 (9.09%)
occurrences (all)	60	1	2
Back pain			
subjects affected / exposed	34 / 134 (25.37%)	1 / 3 (33.33%)	1 / 11 (9.09%)
occurrences (all)	46	1	1
Bone pain			
subjects affected / exposed	6 / 134 (4.48%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	6	0	0
Fistula			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Flank pain			
subjects affected / exposed	4 / 134 (2.99%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	5	1	0
Intervertebral disc degeneration			

subjects affected / exposed	1 / 134 (0.75%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	2	0	2
Muscle spasms			
subjects affected / exposed	35 / 134 (26.12%)	2 / 3 (66.67%)	4 / 11 (36.36%)
occurrences (all)	59	8	5
Muscular weakness			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Musculoskeletal chest pain			
subjects affected / exposed	6 / 134 (4.48%)	0 / 3 (0.00%)	2 / 11 (18.18%)
occurrences (all)	8	0	3
Musculoskeletal pain			
subjects affected / exposed	23 / 134 (17.16%)	1 / 3 (33.33%)	1 / 11 (9.09%)
occurrences (all)	33	1	3
Musculoskeletal stiffness			
subjects affected / exposed	6 / 134 (4.48%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	6	0	0
Myalgia			
subjects affected / exposed	29 / 134 (21.64%)	0 / 3 (0.00%)	3 / 11 (27.27%)
occurrences (all)	44	0	5
Neck pain			
subjects affected / exposed	11 / 134 (8.21%)	0 / 3 (0.00%)	2 / 11 (18.18%)
occurrences (all)	16	0	2
Osteonecrosis			
subjects affected / exposed	1 / 134 (0.75%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Pain in extremity			
subjects affected / exposed	25 / 134 (18.66%)	2 / 3 (66.67%)	1 / 11 (9.09%)
occurrences (all)	30	2	2
Rotator cuff syndrome			
subjects affected / exposed	4 / 134 (2.99%)	1 / 3 (33.33%)	2 / 11 (18.18%)
occurrences (all)	5	2	2
Tendonitis			



subjects affected / exposed	5 / 134 (3.73%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	7	0	1
Vertebral lesion			
subjects affected / exposed	1 / 134 (0.75%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	6 / 134 (4.48%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	7	2	0
Ear lobe infection			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Folliculitis			
subjects affected / exposed	5 / 134 (3.73%)	1 / 3 (33.33%)	1 / 11 (9.09%)
occurrences (all)	7	1	1
Fungal skin infection			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	4 / 134 (2.99%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	4	1	0
Gastroenteritis viral			
subjects affected / exposed	2 / 134 (1.49%)	1 / 3 (33.33%)	1 / 11 (9.09%)
occurrences (all)	2	1	1
Influenza			
subjects affected / exposed	2 / 134 (1.49%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	2	1	0
Nasopharyngitis			
subjects affected / exposed	8 / 134 (5.97%)	2 / 3 (66.67%)	2 / 11 (18.18%)
occurrences (all)	8	2	2
Oral herpes			
subjects affected / exposed	3 / 134 (2.24%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	3	0	0
Perineal infection			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0

Respiratory tract infection subjects affected / exposed occurrences (all)	2 / 134 (1.49%) 3	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0
Rhinitis subjects affected / exposed occurrences (all)	8 / 134 (5.97%) 8	0 / 3 (0.00%) 0	1 / 11 (9.09%) 1
Sepsis subjects affected / exposed occurrences (all)	2 / 134 (1.49%) 2	1 / 3 (33.33%) 1	1 / 11 (9.09%) 1
Staphylococcal infection subjects affected / exposed occurrences (all)	2 / 134 (1.49%) 2	1 / 3 (33.33%) 1	0 / 11 (0.00%) 0
Tooth abscess subjects affected / exposed occurrences (all)	5 / 134 (3.73%) 5	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0
Tooth infection subjects affected / exposed occurrences (all)	3 / 134 (2.24%) 3	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0
Urinary tract infection subjects affected / exposed occurrences (all)	10 / 134 (7.46%) 11	0 / 3 (0.00%) 0	1 / 11 (9.09%) 1
Vaginal infection subjects affected / exposed occurrences (all)	2 / 134 (1.49%) 2	0 / 3 (0.00%) 0	1 / 11 (9.09%) 1
Wound infection subjects affected / exposed occurrences (all)	1 / 134 (0.75%) 2	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	74 / 134 (55.22%) 140	2 / 3 (66.67%) 9	6 / 11 (54.55%) 7
Dehydration subjects affected / exposed occurrences (all)	3 / 134 (2.24%) 3	0 / 3 (0.00%) 0	1 / 11 (9.09%) 1
Hypercholesterolaemia			

subjects affected / exposed	6 / 134 (4.48%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	6	1	0
Hyperkalaemia			
subjects affected / exposed	3 / 134 (2.24%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	3	0	1
Hyperphosphataemia			
subjects affected / exposed	12 / 134 (8.96%)	2 / 3 (66.67%)	3 / 11 (27.27%)
occurrences (all)	16	2	4
Hypertriglyceridaemia			
subjects affected / exposed	6 / 134 (4.48%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	6	0	0
Hyperuricaemia			
subjects affected / exposed	2 / 134 (1.49%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Hypoalbuminaemia			
subjects affected / exposed	11 / 134 (8.21%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	14	0	1
Hypocalcaemia			
subjects affected / exposed	3 / 134 (2.24%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	3	0	1
Hypoglycaemia			
subjects affected / exposed	1 / 134 (0.75%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			
subjects affected / exposed	9 / 134 (6.72%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	11	0	0
Hypomagnesaemia			
subjects affected / exposed	16 / 134 (11.94%)	1 / 3 (33.33%)	1 / 11 (9.09%)
occurrences (all)	21	2	1
Hyponatraemia			
subjects affected / exposed	13 / 134 (9.70%)	0 / 3 (0.00%)	3 / 11 (27.27%)
occurrences (all)	14	0	3
Hypophosphataemia			
subjects affected / exposed	7 / 134 (5.22%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	7	0	0

<b>Non-serious adverse events</b>	12,5 mg	15 mg	20 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 25 (100.00%)	71 / 71 (100.00%)	17 / 17 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	1 / 17 (5.88%)
occurrences (all)	0	1	1
Malignant neoplasm progression			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Metastases to liver			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Hot flush			
subjects affected / exposed	3 / 25 (12.00%)	4 / 71 (5.63%)	0 / 17 (0.00%)
occurrences (all)	3	6	0
Hypertension			
subjects affected / exposed	22 / 25 (88.00%)	63 / 71 (88.73%)	16 / 17 (94.12%)
occurrences (all)	131	147	72
Hypotension			
subjects affected / exposed	0 / 25 (0.00%)	2 / 71 (2.82%)	1 / 17 (5.88%)
occurrences (all)	0	2	1
Thrombophlebitis superficial			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	22 / 25 (88.00%)	54 / 71 (76.06%)	13 / 17 (76.47%)
occurrences (all)	41	96	36
Chest discomfort			
subjects affected / exposed	2 / 25 (8.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences (all)	2	1	0

Chest pain			
subjects affected / exposed	3 / 25 (12.00%)	5 / 71 (7.04%)	3 / 17 (17.65%)
occurrences (all)	4	5	3
Chills			
subjects affected / exposed	5 / 25 (20.00%)	3 / 71 (4.23%)	1 / 17 (5.88%)
occurrences (all)	6	3	2
Condition aggravated			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Face oedema			
subjects affected / exposed	2 / 25 (8.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences (all)	3	1	0
General physical health deterioration			
subjects affected / exposed	0 / 25 (0.00%)	2 / 71 (2.82%)	0 / 17 (0.00%)
occurrences (all)	0	2	0
Generalised oedema			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Impaired healing			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Inflammation			
subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Influenza like illness			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Localised oedema			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	1 / 17 (5.88%)
occurrences (all)	0	1	1
Mucosal inflammation			
subjects affected / exposed	1 / 25 (4.00%)	7 / 71 (9.86%)	0 / 17 (0.00%)
occurrences (all)	1	9	0

Non-cardiac chest pain subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	5 / 71 (7.04%) 5	2 / 17 (11.76%) 2
Oedema peripheral subjects affected / exposed occurrences (all)	11 / 25 (44.00%) 14	19 / 71 (26.76%) 29	2 / 17 (11.76%) 3
Pyrexia subjects affected / exposed occurrences (all)	4 / 25 (16.00%) 5	6 / 71 (8.45%) 8	3 / 17 (17.65%) 3
Xerosis subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 4	6 / 71 (8.45%) 7	3 / 17 (17.65%) 3
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 71 (0.00%) 0	0 / 17 (0.00%) 0
Reproductive system and breast disorders Amenorrhoea subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 71 (0.00%) 0	0 / 17 (0.00%) 0
Pruritus genital subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 71 (0.00%) 0	0 / 17 (0.00%) 0
Vaginal inflammation subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 71 (0.00%) 0	0 / 17 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Atelectasis subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 71 (0.00%) 0	0 / 17 (0.00%) 0
Cough subjects affected / exposed occurrences (all)	10 / 25 (40.00%) 16	14 / 71 (19.72%) 18	4 / 17 (23.53%) 6
Dysphonia subjects affected / exposed occurrences (all)	7 / 25 (28.00%) 8	12 / 71 (16.90%) 13	6 / 17 (35.29%) 11

Dyspnoea			
subjects affected / exposed	11 / 25 (44.00%)	19 / 71 (26.76%)	7 / 17 (41.18%)
occurrences (all)	12	24	8
Epistaxis			
subjects affected / exposed	3 / 25 (12.00%)	8 / 71 (11.27%)	1 / 17 (5.88%)
occurrences (all)	4	8	1
Haemoptysis			
subjects affected / exposed	1 / 25 (4.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences (all)	1	1	0
Hiccups			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Hypoxia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	2 / 25 (8.00%)	2 / 71 (2.82%)	0 / 17 (0.00%)
occurrences (all)	2	2	0
Pleural effusion			
subjects affected / exposed	1 / 25 (4.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences (all)	1	1	0
Pleuritic pain			
subjects affected / exposed	2 / 25 (8.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	5	0	0
Pneumonitis			
subjects affected / exposed	2 / 25 (8.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	2	0	0
Productive cough			
subjects affected / exposed	0 / 25 (0.00%)	2 / 71 (2.82%)	1 / 17 (5.88%)
occurrences (all)	0	2	1
Rales			
subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Respiratory failure			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0

Rhinitis allergic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	1	0	1
Rhinorrhoea			
subjects affected / exposed	5 / 25 (20.00%)	4 / 71 (5.63%)	2 / 17 (11.76%)
occurrences (all)	6	5	2
Upper respiratory tract inflammation			
subjects affected / exposed	2 / 25 (8.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	2	0	0
Psychiatric disorders			
Affective disorder			
subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	1	0	1
Anxiety			
subjects affected / exposed	3 / 25 (12.00%)	13 / 71 (18.31%)	3 / 17 (17.65%)
occurrences (all)	3	13	4
Attention deficit/hyperactivity disorder			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Bradyphrenia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Confusional state			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	1 / 17 (5.88%)
occurrences (all)	0	1	1
Depressed mood			
subjects affected / exposed	5 / 25 (20.00%)	3 / 71 (4.23%)	0 / 17 (0.00%)
occurrences (all)	6	3	0
Depression			
subjects affected / exposed	1 / 25 (4.00%)	2 / 71 (2.82%)	0 / 17 (0.00%)
occurrences (all)	1	2	0
Hallucination			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	1 / 17 (5.88%)
occurrences (all)	0	1	1
Insomnia			



subjects affected / exposed	8 / 25 (32.00%)	10 / 71 (14.08%)	3 / 17 (17.65%)
occurrences (all)	8	12	4
Psychomotor retardation			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Restlessness			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Sleep disorder			
subjects affected / exposed	4 / 25 (16.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	4	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 25 (24.00%)	13 / 71 (18.31%)	2 / 17 (11.76%)
occurrences (all)	7	15	2
Amylase increased			
subjects affected / exposed	1 / 25 (4.00%)	3 / 71 (4.23%)	0 / 17 (0.00%)
occurrences (all)	1	5	0
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 25 (32.00%)	14 / 71 (19.72%)	5 / 17 (29.41%)
occurrences (all)	13	16	5
Blood albumin decreased			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	5 / 25 (20.00%)	9 / 71 (12.68%)	3 / 17 (17.65%)
occurrences (all)	5	9	3
Blood bicarbonate abnormal			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Blood bilirubin increased			
subjects affected / exposed	1 / 25 (4.00%)	6 / 71 (8.45%)	2 / 17 (11.76%)
occurrences (all)	1	10	3
Blood creatine phosphokinase increased			

subjects affected / exposed	2 / 25 (8.00%)	1 / 71 (1.41%)	1 / 17 (5.88%)
occurrences (all)	3	2	2
Blood creatinine decreased			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	5 / 25 (20.00%)	2 / 71 (2.82%)	1 / 17 (5.88%)
occurrences (all)	7	2	1
Blood glucose increased			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Blood magnesium decreased			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Blood phosphorus decreased			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Blood potassium decreased			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Brain natriuretic peptide increased			
subjects affected / exposed	3 / 25 (12.00%)	2 / 71 (2.82%)	0 / 17 (0.00%)
occurrences (all)	3	2	0
Breath sounds abnormal			
subjects affected / exposed	3 / 25 (12.00%)	2 / 71 (2.82%)	0 / 17 (0.00%)
occurrences (all)	3	2	0
C-reactive protein increased			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Ejection fraction decreased			
subjects affected / exposed	4 / 25 (16.00%)	2 / 71 (2.82%)	0 / 17 (0.00%)
occurrences (all)	5	3	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	7 / 25 (28.00%)	13 / 71 (18.31%)	5 / 17 (29.41%)
occurrences (all)	8	13	6

Haemoglobin increased subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	0 / 71 (0.00%) 0	0 / 17 (0.00%) 0
Hypophonesis subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 71 (0.00%) 0	0 / 17 (0.00%) 0
Lipase increased subjects affected / exposed occurrences (all)	5 / 25 (20.00%) 5	5 / 71 (7.04%) 7	0 / 17 (0.00%) 0
Platelet count decreased subjects affected / exposed occurrences (all)	6 / 25 (24.00%) 10	13 / 71 (18.31%) 18	1 / 17 (5.88%) 1
Tumour marker increased subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 71 (0.00%) 0	1 / 17 (5.88%) 1
Urine bilirubin increased subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 71 (0.00%) 0	0 / 17 (0.00%) 0
Waist circumference increased subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 71 (0.00%) 0	1 / 17 (5.88%) 1
Weight decreased subjects affected / exposed occurrences (all)	9 / 25 (36.00%) 10	29 / 71 (40.85%) 35	8 / 17 (47.06%) 12
Weight increased subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3	2 / 71 (2.82%) 2	0 / 17 (0.00%) 0
Injury, poisoning and procedural complications			
Fracture subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 71 (0.00%) 0	1 / 17 (5.88%) 1
Ligament sprain subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	0 / 71 (0.00%) 0	0 / 17 (0.00%) 0
Nail injury			

subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	2 / 71 (2.82%) 3	0 / 17 (0.00%) 0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 25 (0.00%)	2 / 71 (2.82%)	2 / 17 (11.76%)
occurrences (all)	0	2	3
Cardiac disorder			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Cardiac failure			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Pericardial effusion			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Sinus tachycardia			
subjects affected / exposed	1 / 25 (4.00%)	6 / 71 (8.45%)	0 / 17 (0.00%)
occurrences (all)	1	19	0
Tachycardia			
subjects affected / exposed	1 / 25 (4.00%)	5 / 71 (7.04%)	1 / 17 (5.88%)
occurrences (all)	1	5	1
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 25 (4.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences (all)	1	1	0
Balance disorder			
subjects affected / exposed	1 / 25 (4.00%)	1 / 71 (1.41%)	2 / 17 (11.76%)
occurrences (all)	1	1	2
Carpal tunnel syndrome			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	2
Cerebral venous thrombosis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Disturbance in attention			

subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	0 / 25 (0.00%)	2 / 71 (2.82%)	0 / 17 (0.00%)
occurrences (all)	0	2	0
Dysaesthesia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Dysgeusia			
subjects affected / exposed	4 / 25 (16.00%)	4 / 71 (5.63%)	1 / 17 (5.88%)
occurrences (all)	4	4	1
Headache			
subjects affected / exposed	11 / 25 (44.00%)	25 / 71 (35.21%)	7 / 17 (41.18%)
occurrences (all)	12	32	12
Hypergeusia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Loss of consciousness			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Paraesthesia			
subjects affected / exposed	3 / 25 (12.00%)	6 / 71 (8.45%)	3 / 17 (17.65%)
occurrences (all)	6	7	3
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Presyncope			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Radicular pain			
subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Sciatica			
subjects affected / exposed	2 / 25 (8.00%)	3 / 71 (4.23%)	0 / 17 (0.00%)
occurrences (all)	2	4	0
Sensorimotor disorder			

subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 71 (0.00%) 0	0 / 17 (0.00%) 0
Somnolence subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	4 / 71 (5.63%) 4	0 / 17 (0.00%) 0
Speech disorder subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 71 (0.00%) 0	0 / 17 (0.00%) 0
Syncope subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 71 (0.00%) 0	0 / 17 (0.00%) 0
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	4 / 25 (16.00%) 10	9 / 71 (12.68%) 11	1 / 17 (5.88%) 1
Leukocytosis subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 71 (0.00%) 0	0 / 17 (0.00%) 0
Neutropenia subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	2 / 71 (2.82%) 2	1 / 17 (5.88%) 3
Spontaneous haematoma subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	1 / 71 (1.41%) 1	0 / 17 (0.00%) 0
Thrombocytopenia subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 7	5 / 71 (7.04%) 6	4 / 17 (23.53%) 6
Thrombotic microangiopathy subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	4 / 71 (5.63%) 4	0 / 17 (0.00%) 0
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3	1 / 71 (1.41%) 1	1 / 17 (5.88%) 2
Vertigo			

subjects affected / exposed occurrences (all)	4 / 25 (16.00%) 4	4 / 71 (5.63%) 5	3 / 17 (17.65%) 3
Eye disorders			
Cataract			
subjects affected / exposed	1 / 25 (4.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences (all)	1	2	0
Dry eye			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Eczema eyelids			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Eye irritation			
subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Lacrimation increased			
subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Vision blurred			
subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	3 / 17 (17.65%)
occurrences (all)	1	0	3
Visual acuity reduced			
subjects affected / exposed	3 / 25 (12.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences (all)	3	1	0
Visual impairment			
subjects affected / exposed	1 / 25 (4.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences (all)	1	1	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	6 / 25 (24.00%)	7 / 71 (9.86%)	1 / 17 (5.88%)
occurrences (all)	7	8	1
Abdominal pain			
subjects affected / exposed	8 / 25 (32.00%)	27 / 71 (38.03%)	6 / 17 (35.29%)
occurrences (all)	13	41	9
Abdominal pain lower			

subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	1 / 17 (5.88%)
occurrences (all)	0	1	1
Abdominal pain upper			
subjects affected / exposed	6 / 25 (24.00%)	14 / 71 (19.72%)	2 / 17 (11.76%)
occurrences (all)	10	19	2
Abdominal wall haematoma			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Anal fissure			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Anal inflammation			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Anorectal discomfort			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	1 / 17 (5.88%)
occurrences (all)	0	1	1
Aphthous stomatitis			
subjects affected / exposed	3 / 25 (12.00%)	3 / 71 (4.23%)	2 / 17 (11.76%)
occurrences (all)	3	4	2
Ascites			
subjects affected / exposed	0 / 25 (0.00%)	2 / 71 (2.82%)	0 / 17 (0.00%)
occurrences (all)	0	2	0
Constipation			
subjects affected / exposed	11 / 25 (44.00%)	16 / 71 (22.54%)	7 / 17 (41.18%)
occurrences (all)	12	21	9
Diarrhoea			
subjects affected / exposed	10 / 25 (40.00%)	44 / 71 (61.97%)	13 / 17 (76.47%)
occurrences (all)	18	177	40
Dry mouth			
subjects affected / exposed	6 / 25 (24.00%)	10 / 71 (14.08%)	5 / 17 (29.41%)
occurrences (all)	10	13	6
Dyspepsia			
subjects affected / exposed	2 / 25 (8.00%)	11 / 71 (15.49%)	2 / 17 (11.76%)
occurrences (all)	2	14	3
Dysphagia			



subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	1 / 17 (5.88%)
occurrences (all)	0	1	1
Faecaloma			
subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal motility disorder			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 25 (4.00%)	3 / 71 (4.23%)	1 / 17 (5.88%)
occurrences (all)	2	4	1
Gingival bleeding			
subjects affected / exposed	2 / 25 (8.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences (all)	5	2	0
Gingival erythema			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	1 / 17 (5.88%)
occurrences (all)	0	1	1
Haemorrhoids			
subjects affected / exposed	2 / 25 (8.00%)	2 / 71 (2.82%)	0 / 17 (0.00%)
occurrences (all)	3	2	0
Nausea			
subjects affected / exposed	17 / 25 (68.00%)	33 / 71 (46.48%)	9 / 17 (52.94%)
occurrences (all)	22	58	20
Odynophagia			
subjects affected / exposed	2 / 25 (8.00%)	2 / 71 (2.82%)	0 / 17 (0.00%)
occurrences (all)	2	2	0
Oesophageal pain			
subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	1	0	1
Oral pain			

subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Perianal erythema			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	2
Rectal haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	2 / 25 (8.00%)	2 / 71 (2.82%)	2 / 17 (11.76%)
occurrences (all)	2	2	2
Tongue oedema			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	1 / 25 (4.00%)	2 / 71 (2.82%)	0 / 17 (0.00%)
occurrences (all)	1	2	0
Vomiting			
subjects affected / exposed	10 / 25 (40.00%)	21 / 71 (29.58%)	9 / 17 (52.94%)
occurrences (all)	15	45	23
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	2 / 25 (8.00%)	3 / 71 (4.23%)	2 / 17 (11.76%)
occurrences (all)	2	3	2
Hepatocellular injury			
subjects affected / exposed	2 / 25 (8.00%)	2 / 71 (2.82%)	1 / 17 (5.88%)
occurrences (all)	3	2	1
Hepatomegaly			
subjects affected / exposed	4 / 25 (16.00%)	6 / 71 (8.45%)	1 / 17 (5.88%)
occurrences (all)	4	6	1
Hyperbilirubinaemia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	1 / 17 (5.88%)
occurrences (all)	0	2	1
Jaundice			
subjects affected / exposed	0 / 25 (0.00%)	2 / 71 (2.82%)	0 / 17 (0.00%)
occurrences (all)	0	2	0

Liver disorder			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Alopecia			
subjects affected / exposed	2 / 25 (8.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	3	0	1
Dermatitis acneiform			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	4 / 25 (16.00%)	15 / 71 (21.13%)	3 / 17 (17.65%)
occurrences (all)	5	17	5
Ecchymosis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Eczema			
subjects affected / exposed	2 / 25 (8.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	3	0	0
Erythema			
subjects affected / exposed	1 / 25 (4.00%)	6 / 71 (8.45%)	1 / 17 (5.88%)
occurrences (all)	1	10	1
Hair growth abnormal			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Hyperhidrosis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Hyperkeratosis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	2	0	1
Nail dystrophy			

subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	1 / 25 (4.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences (all)	1	2	0
Onychoclasia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Onychomadesis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	3 / 25 (12.00%)	4 / 71 (5.63%)	1 / 17 (5.88%)
occurrences (all)	3	4	2
Petechiae			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	2 / 25 (8.00%)	2 / 71 (2.82%)	1 / 17 (5.88%)
occurrences (all)	2	4	1
Rash			
subjects affected / exposed	2 / 25 (8.00%)	10 / 71 (14.08%)	2 / 17 (11.76%)
occurrences (all)	3	12	3
Rash macular			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Skin exfoliation			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	1 / 17 (5.88%)
occurrences (all)	0	1	1
Umbilical erythema			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	2 / 25 (8.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	2	0	0
Albuminuria			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Dysuria			
subjects affected / exposed	1 / 25 (4.00%)	2 / 71 (2.82%)	1 / 17 (5.88%)
occurrences (all)	1	2	1
Haematuria			
subjects affected / exposed	8 / 25 (32.00%)	7 / 71 (9.86%)	2 / 17 (11.76%)
occurrences (all)	9	9	6
Haemoglobinuria			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Oliguria			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Proteinuria			
subjects affected / exposed	13 / 25 (52.00%)	53 / 71 (74.65%)	10 / 17 (58.82%)
occurrences (all)	30	117	21
Renal failure			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Urogenital fistula			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	2
Hypothyroidism			
subjects affected / exposed	10 / 25 (40.00%)	35 / 71 (49.30%)	10 / 17 (58.82%)
occurrences (all)	14	37	11
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	8 / 25 (32.00%)	19 / 71 (26.76%)	6 / 17 (35.29%)
occurrences (all)	14	34	8
Back pain			
subjects affected / exposed	6 / 25 (24.00%)	20 / 71 (28.17%)	5 / 17 (29.41%)
occurrences (all)	6	29	7
Bone pain			
subjects affected / exposed	1 / 25 (4.00%)	5 / 71 (7.04%)	0 / 17 (0.00%)
occurrences (all)	1	5	0
Fistula			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Flank pain			
subjects affected / exposed	1 / 25 (4.00%)	2 / 71 (2.82%)	0 / 17 (0.00%)
occurrences (all)	2	2	0
Intervertebral disc degeneration			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	9 / 25 (36.00%)	16 / 71 (22.54%)	4 / 17 (23.53%)
occurrences (all)	16	24	6
Muscular weakness			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 25 (4.00%)	2 / 71 (2.82%)	1 / 17 (5.88%)
occurrences (all)	2	2	1
Musculoskeletal pain			
subjects affected / exposed	6 / 25 (24.00%)	14 / 71 (19.72%)	0 / 17 (0.00%)
occurrences (all)	10	18	0
Musculoskeletal stiffness			
subjects affected / exposed	1 / 25 (4.00%)	4 / 71 (5.63%)	1 / 17 (5.88%)
occurrences (all)	1	4	1

Myalgia			
subjects affected / exposed	5 / 25 (20.00%)	17 / 71 (23.94%)	4 / 17 (23.53%)
occurrences (all)	8	26	5
Neck pain			
subjects affected / exposed	4 / 25 (16.00%)	2 / 71 (2.82%)	2 / 17 (11.76%)
occurrences (all)	7	2	3
Osteonecrosis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	6 / 25 (24.00%)	13 / 71 (18.31%)	2 / 17 (11.76%)
occurrences (all)	9	14	2
Rotator cuff syndrome			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Tendonitis			
subjects affected / exposed	0 / 25 (0.00%)	4 / 71 (5.63%)	0 / 17 (0.00%)
occurrences (all)	0	6	0
Vertebral lesion			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 25 (8.00%)	2 / 71 (2.82%)	1 / 17 (5.88%)
occurrences (all)	2	2	1
Ear lobe infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Folliculitis			
subjects affected / exposed	1 / 25 (4.00%)	2 / 71 (2.82%)	0 / 17 (0.00%)
occurrences (all)	1	4	0
Fungal skin infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			

subjects affected / exposed	1 / 25 (4.00%)	2 / 71 (2.82%)	0 / 17 (0.00%)
occurrences (all)	1	2	0
Gastroenteritis viral			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	1 / 25 (4.00%)	3 / 71 (4.23%)	0 / 17 (0.00%)
occurrences (all)	1	3	0
Oral herpes			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	2 / 17 (11.76%)
occurrences (all)	0	1	2
Perineal infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Respiratory tract infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	1 / 17 (5.88%)
occurrences (all)	0	2	1
Rhinitis			
subjects affected / exposed	0 / 25 (0.00%)	6 / 71 (8.45%)	0 / 17 (0.00%)
occurrences (all)	0	6	0
Sepsis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Staphylococcal infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Tooth abscess			
subjects affected / exposed	2 / 25 (8.00%)	2 / 71 (2.82%)	0 / 17 (0.00%)
occurrences (all)	2	2	0
Tooth infection			
subjects affected / exposed	1 / 25 (4.00%)	1 / 71 (1.41%)	1 / 17 (5.88%)
occurrences (all)	1	1	1
Urinary tract infection			



subjects affected / exposed	2 / 25 (8.00%)	4 / 71 (5.63%)	2 / 17 (11.76%)
occurrences (all)	2	4	3
Vaginal infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Wound infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	14 / 25 (56.00%)	38 / 71 (53.52%)	11 / 17 (64.71%)
occurrences (all)	38	63	20
Dehydration			
subjects affected / exposed	1 / 25 (4.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences (all)	1	1	0
Hypercholesterolaemia			
subjects affected / exposed	1 / 25 (4.00%)	3 / 71 (4.23%)	1 / 17 (5.88%)
occurrences (all)	1	3	1
Hyperkalaemia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	2
Hyperphosphataemia			
subjects affected / exposed	1 / 25 (4.00%)	5 / 71 (7.04%)	1 / 17 (5.88%)
occurrences (all)	1	8	1
Hypertriglyceridaemia			
subjects affected / exposed	3 / 25 (12.00%)	1 / 71 (1.41%)	2 / 17 (11.76%)
occurrences (all)	3	1	2
Hyperuricaemia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 71 (1.41%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Hypoalbuminaemia			
subjects affected / exposed	1 / 25 (4.00%)	8 / 71 (11.27%)	1 / 17 (5.88%)
occurrences (all)	1	11	1
Hypocalcaemia			
subjects affected / exposed	0 / 25 (0.00%)	2 / 71 (2.82%)	0 / 17 (0.00%)
occurrences (all)	0	2	0

Hypoglycaemia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 71 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Hypokalaemia			
subjects affected / exposed	3 / 25 (12.00%)	5 / 71 (7.04%)	0 / 17 (0.00%)
occurrences (all)	3	7	0
Hypomagnesaemia			
subjects affected / exposed	1 / 25 (4.00%)	9 / 71 (12.68%)	4 / 17 (23.53%)
occurrences (all)	1	10	7
Hyponatraemia			
subjects affected / exposed	2 / 25 (8.00%)	3 / 71 (4.23%)	4 / 17 (23.53%)
occurrences (all)	2	4	4
Hypophosphataemia			
subjects affected / exposed	3 / 25 (12.00%)	1 / 71 (1.41%)	1 / 17 (5.88%)
occurrences (all)	3	1	1

<b>Non-serious adverse events</b>	30 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Malignant neoplasm progression			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Metastases to liver			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Hot flush			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypertension			

subjects affected / exposed	5 / 7 (71.43%)		
occurrences (all)	9		
Hypotension			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Thrombophlebitis superficial			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 7 (71.43%)		
occurrences (all)	6		
Chest discomfort			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Chest pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Chills			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Condition aggravated			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Face oedema			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
General physical health deterioration			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Generalised oedema			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Impaired healing			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Inflammation			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Influenza like illness			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Localised oedema			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Malaise			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Mucosal inflammation			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Non-cardiac chest pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Xerosis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Reproductive system and breast disorders			

Amenorrhoea			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Pruritus genital			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Vaginal inflammation			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Dysphonia			
subjects affected / exposed	4 / 7 (57.14%)		
occurrences (all)	4		
Dyspnoea			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
Epistaxis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Haemoptysis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hiccups			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypoxia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Pleural effusion			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Pleuritic pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Pneumonitis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Productive cough			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Rales			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Respiratory failure			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Rhinitis allergic			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Upper respiratory tract inflammation			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Affective disorder			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Anxiety			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		

Attention deficit/hyperactivity disorder			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Bradyphrenia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Confusional state			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Depressed mood			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hallucination			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Psychomotor retardation			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Restlessness			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Sleep disorder			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Amylase increased			

subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Blood albumin decreased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Blood bicarbonate abnormal			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Blood bilirubin increased			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Blood creatinine decreased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Blood creatinine increased			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	4		
Blood glucose increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Blood magnesium decreased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Blood phosphorus decreased			



subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Blood potassium decreased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Brain natriuretic peptide increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Breath sounds abnormal			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
C-reactive protein increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Ejection fraction decreased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Haemoglobin increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypophonesis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Lipase increased			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
Platelet count decreased			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Tumour marker increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		

Urine bilirubin increased subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Waist circumference increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Weight decreased subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 2		
Weight increased subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Injury, poisoning and procedural complications Fracture subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Ligament sprain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Nail injury subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Cardiac disorders Bradycardia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Cardiac disorder subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Cardiac failure subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Pericardial effusion subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Sinus tachycardia			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Tachycardia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Balance disorder			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Carpal tunnel syndrome			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Cerebral venous thrombosis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Disturbance in attention			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Dysaesthesia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Dysgeusia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	4		
Hypergeusia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		

Loss of consciousness			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Paraesthesia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Presyncope			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Radicular pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Sciatica			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Sensorimotor disorder			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Speech disorder			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Leukocytosis			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Neutropenia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
Spontaneous haematoma			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	4 / 7 (57.14%)		
occurrences (all)	5		
Thrombotic microangiopathy			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Vertigo			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Eye disorders			
Cataract			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Dry eye			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Eczema eyelids			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Eye irritation			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Lacrimation increased			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Vision blurred			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Visual acuity reduced			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Visual impairment			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	3 / 7 (42.86%)		
occurrences (all)	3		
Abdominal pain lower			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Abdominal wall haematoma			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Anal fissure			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Anal inflammation			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Anorectal discomfort			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		

Aphthous stomatitis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Ascites			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	6 / 7 (85.71%)		
occurrences (all)	9		
Dry mouth			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Dysphagia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Faecaloma			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Gastrointestinal motility disorder			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Gastrointestinal pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Gingival bleeding			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		

Gingival erythema			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Haemorrhoids			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	5 / 7 (71.43%)		
occurrences (all)	8		
Odynophagia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Oesophageal pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Oral pain			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Perianal erythema			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Rectal haemorrhage			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Tongue oedema			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		



Vomiting subjects affected / exposed occurrences (all)	5 / 7 (71.43%) 16		
Hepatobiliary disorders			
Hepatic pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Hepatocellular injury subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Hepatomegaly subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Hyperbilirubinaemia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Jaundice subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Liver disorder subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Skin and subcutaneous tissue disorders			
Acne subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Alopecia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Dermatitis acneiform subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Dry skin subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Ecchymosis			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Eczema			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Erythema			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hair growth abnormal			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hyperhidrosis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hyperkeratosis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Nail dystrophy			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Night sweats			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Onychoclasia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Onychomadesis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Petechiae			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		

Pruritus			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Rash macular			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Skin exfoliation			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Umbilical erythema			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Albuminuria			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Dysuria			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Haematuria			
subjects affected / exposed	5 / 7 (71.43%)		
occurrences (all)	6		
Haemoglobinuria			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Oliguria			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Proteinuria			

subjects affected / exposed	7 / 7 (100.00%)		
occurrences (all)	11		
Renal failure			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Urogenital fistula			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypothyroidism			
subjects affected / exposed	5 / 7 (71.43%)		
occurrences (all)	7		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
Bone pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Fistula			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Flank pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Intervertebral disc degeneration			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Intervertebral disc protrusion			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Muscular weakness			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Musculoskeletal pain			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Musculoskeletal stiffness			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Neck pain			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
Osteonecrosis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Rotator cuff syndrome			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Tendonitis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Vertebral lesion			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Ear lobe infection			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Folliculitis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Fungal skin infection			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Gastroenteritis viral			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Oral herpes			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Perineal infection			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		

Rhinitis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Sepsis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Staphylococcal infection			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Tooth abscess			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Tooth infection			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Vaginal infection			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Wound infection			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 7 (42.86%)		
occurrences (all)	3		
Dehydration			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypercholesterolaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hyperkalaemia			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hyperphosphataemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypertriglyceridaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hyperuricaemia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Hypoalbuminaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypocalcaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypoglycaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypokalaemia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Hypomagnesaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hyponatraemia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Hypophosphataemia			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 May 2010	The amendment was designed: <ul style="list-style-type: none"><li>- to include an interval between the administration of S 80881 to the first and the following subjects for safety reasons, in compliance with EMEA Guideline EMEA/CHMP/SWP/28367/07. The starting dose of S 80881 (5 mg) was to be first administered to a single subject; if no DLT occurred during one week, the same dose of S 80881 was to be administered to 2 additional patients. This enrolment procedure was to be applied until the first DLT was observed.</li><li>- To add blood chemistry and coagulation profile evaluations in cycle 1, at the same time points as those for haematology.</li></ul>
20 August 2010	The amendment aimed to add blood withdrawals for circulating tumours cells (CTC) counts at day 14 of cycle 1 and at the end of cycle 2 (day 56), only for patients enrolled at the Gustave Roussy centre, in order to allow their inclusion in the national project that aimed to analyse the relationship between the changes in CTC and the tumour response evaluated by RECIST criteria in patients enrolled in phase I clinical trials .
13 January 2011	The amendment aimed to allow treatment beyond cycle 6 for exceptional cases of continued benefit.
05 April 2011	The amendment aimed to: <ul style="list-style-type: none"><li>- Better define the characteristics of patients to be enrolled in the dose-expansion phase.</li><li>- Introduce additional safety measures (urine tests for patients with proteinuria and replacement treatment for hypothyroidism).</li><li>- Notify the addition of a new clinical site.</li><li>- Provide clarification concerning DCE-US evaluation.</li><li>- Introduce 2 blood withdrawals for CTC counts: initially submitted in France only.</li><li>- Extend treatment with S 80881 beyond cycle 6 in patients experiencing continued clinical benefit: initially submitted in France only.</li></ul>
19 July 2011	The amendment concerned the addition of the new strength of 10 mg capsules to be used in the expansion phase in order to limit the number of capsules to be swallowed by patients at a dosage of 20 mg/day or lower (applicable in Spain, France and Italy).
22 December 2011	The amendment was designed to: <ul style="list-style-type: none"><li>- Update the sections of the Clinical Study Protocol relevant to non-clinical and clinical studies based on the results of the completed dose-escalation phase and the non-clinical data gathered since the start of the study.</li><li>- Further define the eligible patient population and the required assessments.</li><li>- Introduce a formal efficacy objective supported by statistical methods in the dose expansion stage to which, therefore, a phase IIa was added.</li><li>- Allow an increase in the maximum number of patients, as a consequence of newly added phase IIa portion.</li><li>- Clarify ADME/PD investigations to be conducted on collected plasma samples.</li></ul>
26 April 2012	The amendment aimed to introduce some additional assessments allowing to gain insights about the PD and PK features of the compound under investigation and its anti tumour activity: <ul style="list-style-type: none"><li>- FGF23 analysis had been added to PD tests.</li><li>- The concentration of S 80881 was assessed in patients with suitable lesions (i.e. easily accessible and where a biopsy could be performed with limited risk) and willing to undergo the tumour collection procedure.</li><li>- Genetic testing (e.g. CGH or FISH) was performed on archived tumour samples or on recent biopsy of an active tumour lesion, in order to explore any potentially genetic alteration in tumours of enrolled patients.</li></ul>

17 December 2012	<p>The amendment aimed to:</p> <ul style="list-style-type: none"> <li>- Add intermittent schedules of 5 days on/2 days off (5/2) and 21 days on/7 days off (21/7) for S 80881 administration, taking into account the time course of toxicities observed during the study and the predicted kinetics of S 80881 when administered intermittently in humans.</li> <li>- Determine PK profile of patients receiving S 80881 on intermittent schedules: assuming that 12-15 patients per schedule were sufficient to determine the PK profile, the overall sample size was therefore increased to a maximum of 110 patients.</li> </ul>
22 July 2013	The amendment was designed to submit changes relevant to production, specification, packaging and storage conditions of S 80881 drug product.
04 November 2013	<p>The amendment was designed to add a new dose of S 80881: 12.5 mg daily on a continuous administration schedule.</p> <p>According to the exploratory PK/PD modeling and simulation based on data collected in the present study, a dose of 12.5mg on continuous schedule showed a good performance compared to the 15mg continuous schedule considered as reference and a better safety profile.</p>
12 August 2014	<p>The amendment concerned the reinforcement and management of hypertension, based on safety data from the Phase II FINESSE study. At the same occasion liver, cardiac and renal toxicity management were updated. The main changes were as follows:</p> <ul style="list-style-type: none"> <li>- Modification and strengthening of the management of hypertension.</li> <li>- Addition of clinical management rules in case of LVEF decrease.</li> <li>- Reinforcement of measures regarding the management of liver toxicities (AST/ALT increases).</li> <li>- Additional concomitant treatment to avoid in case of liver failure.</li> <li>- Specific management for proteinuria was included in the protocol consistently with the Investigator's brochure.</li> </ul>
16 February 2015	The amendment was designed to add a new list of concomitant medication with potential interactions with the cytochrome enzymes CYP3A4 and CYP2C8 that could impact the oxidative metabolism of S 80881.
01 February 2016	The amendment concerned the update of the background information section with information about the case of Posterior Reversible Encephalopathy Syndrome (PRES) with S 80881 observed within the context of FINESSE trial (international development). A paragraph for the management of symptoms suggestive of a PRES and confirmed PRES was also added.
28 November 2016	<p>-The amendment aimed to define the end of trial and propose to ongoing patients to continue lucitanib within a compassionate use following discussion with their treating physician at Vall d'Hebron Institute of Oncology.</p> <p>As lucitanib was not likely to be superior than standard of care therapy in the patients with advanced breast and FGF aberrant squamous non-small cell lung cancer, sponsors decided to discontinue enrolment in the ongoing trials and any future development of lucitanib under the current clinical development plan. As of 28 November 2016, all patients but 4 had discontinued the study. For these 4 patients, the benefit:risk ratio supported the continuation of lucitanib on an individual basis.</p>

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported