



Clinical trial results:

An Open-Label, Multicenter Phase Ib/2 Study of E7080 Alone, And in Combination With Everolimus in Subjects With Unresectable Advanced or Metastatic Renal Cell Carcinoma Following One Prior VEGF-Targeted Treatment.

Summary

EudraCT number	2010-019484-10
Trial protocol	GB CZ PL ES
Global end of trial date	08 February 2018

Results information

Result version number	v1 (current)
This version publication date	23 February 2019
First version publication date	23 February 2019

Trial information

Trial identification

Sponsor protocol code	E7080-G000-205
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01136733
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai Ltd
Sponsor organisation address	Mosquito Way, Hatfield, Hertfordshire, United Kingdom, AL10 9SN
Public contact	Medical Information, Eisai Ltd, +1 888-274-2378, esi_medinfo@eisai.com
Scientific contact	Medical Information, Eisai Ltd, +1 888-274-2378, esi_medinfo@eisai.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	08 February 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	08 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase Ib: To determine the dose-limiting toxicities (DLTs) and maximally tolerated dose (MTD) and establish the recommended phase 2 (RP2) dose for E7080 in combination with everolimus in subjects with unresectable advanced or metastatic renal cell carcinoma (RCC).

Phase 2: To compare the progression-free survival (PFS) of 1) E7080 in combination with everolimus at the RP2 dose once daily (Arm A) and 2) single agent E7080 24 milligram (mg) once daily (Arm B) to single agent everolimus 10 mg once daily (Arm C) in subjects with unresectable advanced or metastatic RCC and disease progression following one prior vascular endothelial growth factor (VEGF) targeted treatment.

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following: -

Principles of the World Medical Association Declaration of Helsinki (World Medical Association, 2008)
International Council for Harmonisation (ICH) E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products,
International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and Institutional Review Board (IRB) regulations and applicable sections of US 21 CFR Part 312

European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions (SUSARs) were reported, as required, to the Competent Authorities of all involved EU member states. Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP Subject Information and Informed Consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 August 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 26
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	United Kingdom: 51
Country: Number of subjects enrolled	Czech Republic: 23
Country: Number of subjects enrolled	United States: 55

Worldwide total number of subjects	173
EEA total number of subjects	118

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	114
From 65 to 84 years	59
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 41 sites across geographic regions (12 sites in the United Kingdom, 16 sites in the United States, 5 sites in the Czech Republic, 4 sites in Poland, and 4 sites in Spain) from 05 Aug 2010 to 08 Feb 2018.

Pre-assignment

Screening details:

A total of 173 subjects were enrolled into the study and treated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1b (Cohort 1): 12 mg Lenvatinib Plus 5 mg Everolimus

Arm description:

Oral lenvatinib (12 mg) and everolimus (5 mg) were taken once daily in continuous 28-day cycles. In the Dose Escalation Cohort-Cycle 1: both study drugs were taken at the same time of day in a fasting state with water. In Cycles 2, 3, etc. and the Expansion Cohort: both study drugs were taken at the same time of day with water, either after a meal or in a fasting state. Dose escalation began with 3 subjects in Cohort 1. If no DLT occurred, then enrollment proceeded to Cohort 2. If 1 subject had a DLT, 3 more subjects were enrolled in Cohort 1. If 1 or none of the 6 subjects had a DLT, then enrollment proceeded to Cohort 2.

If 2 or more subjects had a DLT during Cycle 1, the dose escalation committee (DEC) decided whether they were lenvatinib-related and whether enrollment could proceed; lenvatinib was reduced to 6 mg daily (the everolimus dose was not reduced). If it could not be determined that the DLTs were lenvatinib-related, enrollment was stopped.

Arm type	Experimental
Investigational medicinal product name	lenvatinib
Investigational medicinal product code	E7080
Other name	Lenvima, Kisplyx
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Lenvatinib 12 mg (one 10 mg capsule and two 1 mg capsules) was taken along with one 5 mg tablet of everolimus once daily in continuous 28-day (4-week) cycles.

Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	Afinitor
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Everolimus 5 mg (one tablet) was taken once daily along with 12 mg lenvatinib (one 10 mg capsule and two 1 mg capsules) in continuous 28-day (4-week) cycles.

Arm title	Phase 1b (Cohort 2): 18 mg Lenvatinib Plus 5 mg Everolimus
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Arm description:

Oral lenvatinib (18 mg) and everolimus (5 mg) were taken once daily in continuous 28-day cycles. In the Dose Escalation Cohort-Cycle 1: both study drugs were taken at the same time of day in the fasting state with water. In Cycles 2, 3, etc. and the Expansion Cohort: both study drugs were taken at the same time of day with water, either after a meal or in a fasting state. Dose escalation began with 3

subjects in Cohort 1. If no DLT occurred, then enrollment would proceed to Cohort 3. If 1 subject had a DLT, 3 more subjects were enrolled in Cohort 2. If 1 or none of the 6 subjects exhibited a DLT, enrollment proceeded to Cohort 3.

If 2 or more subjects had a DLT during Cycle 1, dose escalation ceased and additional subjects were enrolled to the next lower dose to achieve a total of 6 subjects in that cohort.

Arm type	Experimental
Investigational medicinal product name	lenvatinib
Investigational medicinal product code	E7080
Other name	Lenvima, Kispilyx
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Lenvatinib 18 mg (one 10 mg capsule and two 4 mg capsules) was taken along with one 5 mg tablet of everolimus once daily in continuous 28-day (4-week) cycles.

Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	Afinitor
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Everolimus 5 mg (one tablet) was taken along with 18 mg lenvatinib (one 10 mg capsule and two 4 mg capsules) once daily in continuous 28-day (4-week) cycles.

Arm title	Phase 1b (Cohort 3): 24 mg Lenvatinib Plus 5 mg Everolimus
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Arm description:

Oral lenvatinib (24 mg) and everolimus (5 mg) were taken once daily in continuous 28-day cycles. Dose Escalation Cohort-Cycle 1: both study drugs were taken at the same time of day in the fasting state with water. Cycles 2, 3, etc. and Expansion Cohort: both study drugs were taken at the same time of day with water, either after a meal or in a fasting state. Dose escalation began with 3 subjects in Cohort 1. If no DLT occurred, then enrollment proceeded to Cohort 4. If 1 subject had a DLT, 3 more subjects were enrolled Cohort 3. If 1 or none of the 6 subjects exhibited a DLT, then enrollment proceeded to Cohort 4.

If 2 or more subjects had a DLT during Cycle 1, dose escalation ceased and additional subjects were enrolled to the next lower dose to achieve a total of 6 subjects in that cohort.

Arm type	Experimental
Investigational medicinal product name	lenvatinib
Investigational medicinal product code	E7080
Other name	Lenvima, Kispilyx
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Lenvatinib 24 mg (two 10 mg capsule and one 4 mg capsules) was taken along with one 5 mg tablet of everolimus once daily in continuous 28-day (4-week) cycles.

Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	Afinitor
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Everolimus 5 mg (one tablet) was taken along with 24 mg lenvatinib (two 10 mg capsule and one 4 mg capsules) once daily in continuous 28-day (4-week) cycles.

Arm title	Phase 2 (Arm A): 18 mg Lenvatinib Plus 5 mg Everolimus
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Arm description:

Oral lenvatinib (18 mg) and everolimus (5 mg) was once daily in the morning (consistently with or without food) with water, in continuous 28-day (4-week) cycles. Treatment cycles began with the first dose of study drug in Cycle 1 and continued in 28-day (4-week) consecutive cycles until completion of

the off-treatment assessments (within 30 days after the last study treatment administration). Study drugs were administered at the clinic for the first dose and on the pharmacokinetic sampling days.

Arm type	Experimental
Investigational medicinal product name	Lenvatinib
Investigational medicinal product code	E7080
Other name	Lenvima, Kispix
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Oral lenvatinib 18 mg (one 10 mg capsule and two 4 mg capsule) was taken along with one 5 mg tablet of everolimus once daily in the morning (consistently with or without food) with water, in continuous 28-day (4-week) cycles.

Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	Afinitor
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Everolimus 5 mg was taken along with lenvatinib 18 mg (one 10 mg capsule and two 4 mg capsule) once daily in the morning (consistently with or without food) with water, in continuous 28-day (4-week) cycles.

Arm title	Phase 2 (Arm B): 24 mg Lenvatinib
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Arm description:

Oral lenvatinib (24 mg) was taken once daily in the morning (consistently with or without food) with water, in continuous 28-day (4-week) cycles.

Arm type	Experimental
Investigational medicinal product name	Lenvatinib
Investigational medicinal product code	E7080
Other name	Lenvima, Kispix
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Oral lenvatinib 24 mg was taken once daily in the morning (consistently with or without food) with water, in continuous 28-day (4-week) cycles.

Arm title	Phase 2 (Arm C): 10 mg Everolimus
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Arm description:

Oral everolimus (10 mg) was taken once daily in the morning (consistently either with or without food) with water, in continuous 28-day (4-week) cycles.

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

Dosage and administration details:

Oral everolimus 10 mg (two 5 mg tablets) was taken once daily in the morning (consistently either with or without food) with water, in continuous 28-day (4-week) cycles.

Number of subjects in period 1	Phase 1b (Cohort 1): 12 mg Lenvatinib Plus 5 mg Everolimus	Phase 1b (Cohort 2): 18 mg Lenvatinib Plus 5 mg Everolimus	Phase 1b (Cohort 3): 24 mg Lenvatinib Plus 5 mg Everolimus
Started	7	11	2
Completed	6	6	0
Not completed	1	5	2
adverse event	-	3	1
administrative-withdrew consent	-	1	-
participant choice	-	-	1
disease progression	-	-	-
clinical progression	1	1	-
unspecified	-	-	-
administrative withdrew consent	-	-	-

Number of subjects in period 1	Phase 2 (Arm A): 18 mg Lenvatinib Plus 5 mg Everolimus	Phase 2 (Arm B): 24 mg Lenvatinib	Phase 2 (Arm C): 10 mg Everolimus
Started	51	52	50
Completed	0	0	0
Not completed	51	52	50
adverse event	11	13	5
administrative-withdrew consent	-	-	-
participant choice	3	-	1
disease progression	30	32	38
clinical progression	-	-	-
unspecified	6	7	6
administrative withdrew consent	1	-	-

Baseline characteristics

Reporting groups

Reporting group title	Phase 1b (Cohort 1): 12 mg Lenvatinib Plus 5 mg Everolimus
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Reporting group description:

Oral lenvatinib (12 mg) and everolimus (5 mg) were taken once daily in continuous 28-day cycles. In the Dose Escalation Cohort-Cycle 1: both study drugs were taken at the same time of day in a fasting state with water. In Cycles 2, 3, etc. and the Expansion Cohort: both study drugs were taken at the same time of day with water, either after a meal or in a fasting state. Dose escalation began with 3 subjects in Cohort 1. If no DLT occurred, then enrollment proceeded to Cohort 2. If 1 subject had a DLT, 3 more subjects were enrolled in Cohort 1. If 1 or none of the 6 subjects had a DLT, then enrollment proceeded to Cohort 2.

If 2 or more subjects had a DLT during Cycle 1, the dose escalation committee (DEC) decided whether they were lenvatinib-related and whether enrollment could proceed; lenvatinib was reduced to 6 mg daily (the everolimus dose was not reduced). If it could not be determined that the DLTs were lenvatinib-related, enrollment was stopped.

Reporting group title	Phase 1b (Cohort 2): 18 mg Lenvatinib Plus 5 mg Everolimus
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Reporting group description:

Oral lenvatinib (18 mg) and everolimus (5 mg) were taken once daily in continuous 28-day cycles. In the Dose Escalation Cohort-Cycle 1: both study drugs were taken at the same time of day in the fasting state with water. In Cycles 2, 3, etc. and the Expansion Cohort: both study drugs were taken at the same time of day with water, either after a meal or in a fasting state. Dose escalation began with 3 subjects in Cohort 1. If no DLT occurred, then enrollment would proceed to Cohort 3. If 1 subject had a DLT, 3 more subjects were enrolled in Cohort 2. If 1 or none of the 6 subjects exhibited a DLT, enrollment proceeded to Cohort 3.

If 2 or more subjects had a DLT during Cycle 1, dose escalation ceased and additional subjects were enrolled to the next lower dose to achieve a total of 6 subjects in that cohort.

Reporting group title	Phase 1b (Cohort 3): 24 mg Lenvatinib Plus 5 mg Everolimus
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Reporting group description:

Oral lenvatinib (24 mg) and everolimus (5 mg) were taken once daily in continuous 28-day cycles. Dose Escalation Cohort-Cycle 1: both study drugs were taken at the same time of day in the fasting state with water. Cycles 2, 3, etc. and Expansion Cohort: both study drugs were taken at the same time of day with water, either after a meal or in a fasting state. Dose escalation began with 3 subjects in Cohort 1. If no DLT occurred, then enrollment proceeded to Cohort 4. If 1 subject had a DLT, 3 more subjects were enrolled Cohort 3. If 1 or none of the 6 subjects exhibited a DLT, then enrollment proceeded to Cohort 4.

If 2 or more subjects had a DLT during Cycle 1, dose escalation ceased and additional subjects were enrolled to the next lower dose to achieve a total of 6 subjects in that cohort.

Reporting group title	Phase 2 (Arm A): 18 mg Lenvatinib Plus 5 mg Everolimus
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Reporting group description:

Oral lenvatinib (18 mg) and everolimus (5 mg) was once daily in the morning (consistently with or without food) with water, in continuous 28-day (4-week) cycles. Treatment cycles began with the first dose of study drug in Cycle 1 and continued in 28-day (4-week) consecutive cycles until completion of the off-treatment assessments (within 30 days after the last study treatment administration). Study drugs were administered at the clinic for the first dose and on the pharmacokinetic sampling days.

Reporting group title	Phase 2 (Arm B): 24 mg Lenvatinib
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Reporting group description:

Oral lenvatinib (24 mg) was taken once daily in the morning (consistently with or without food) with water, in continuous 28-day (4-week) cycles.

Reporting group title	Phase 2 (Arm C): 10 mg Everolimus
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Reporting group description:

Oral everolimus (10 mg) was taken once daily in the morning (consistently either with or without food) with water, in continuous 28-day (4-week) cycles.

Reporting group values	Phase 1b (Cohort 1): 12 mg Lenvatinib Plus 5 mg Everolimus	Phase 1b (Cohort 2): 18 mg Lenvatinib Plus 5 mg Everolimus	Phase 1b (Cohort 3): 24 mg Lenvatinib Plus 5 mg Everolimus
Number of subjects	7	11	2
Age categorical Units: Subjects			

Age continuous Units: years geometric mean standard deviation	58.0 ± 3.92	58.1 ± 7.97	61.0 ± 2.83
Gender categorical Units: Subjects			
Female	3	2	1
Male	4	9	1

Reporting group values	Phase 2 (Arm A): 18 mg Lenvatinib Plus 5 mg Everolimus	Phase 2 (Arm B): 24 mg Lenvatinib	Phase 2 (Arm C): 10 mg Everolimus
Number of subjects	51	52	50
Age categorical Units: Subjects			

Age continuous Units: years geometric mean standard deviation	61.7 ± 8.2	63.3 ± 8.6	58.9 ± 9.2
Gender categorical Units: Subjects			
Female	16	13	12
Male	35	39	38

Reporting group values	Total		
Number of subjects	173		
Age categorical Units: Subjects			

Age continuous Units: years geometric mean standard deviation	-		
Gender categorical Units: Subjects			
Female	47		
Male	126		

End points

End points reporting groups

Reporting group title	Phase 1b (Cohort 1): 12 mg Lenvatinib Plus 5 mg Everolimus
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Reporting group description:

Oral lenvatinib (12 mg) and everolimus (5 mg) were taken once daily in continuous 28-day cycles. In the Dose Escalation Cohort-Cycle 1: both study drugs were taken at the same time of day in a fasting state with water. In Cycles 2, 3, etc. and the Expansion Cohort: both study drugs were taken at the same time of day with water, either after a meal or in a fasting state. Dose escalation began with 3 subjects in Cohort 1. If no DLT occurred, then enrollment proceeded to Cohort 2. If 1 subject had a DLT, 3 more subjects were enrolled in Cohort 1. If 1 or none of the 6 subjects had a DLT, then enrollment proceeded to Cohort 2.

If 2 or more subjects had a DLT during Cycle 1, the dose escalation committee (DEC) decided whether they were lenvatinib-related and whether enrollment could proceed; lenvatinib was reduced to 6 mg daily (the everolimus dose was not reduced). If it could not be determined that the DLTs were lenvatinib-related, enrollment was stopped.

Reporting group title	Phase 1b (Cohort 2): 18 mg Lenvatinib Plus 5 mg Everolimus
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Reporting group description:

Oral lenvatinib (18 mg) and everolimus (5 mg) were taken once daily in continuous 28-day cycles. In the Dose Escalation Cohort-Cycle 1: both study drugs were taken at the same time of day in the fasting state with water. In Cycles 2, 3, etc. and the Expansion Cohort: both study drugs were taken at the same time of day with water, either after a meal or in a fasting state. Dose escalation began with 3 subjects in Cohort 1. If no DLT occurred, then enrollment would proceed to Cohort 3. If 1 subject had a DLT, 3 more subjects were enrolled in Cohort 2. If 1 or none of the 6 subjects exhibited a DLT, enrollment proceeded to Cohort 3.

If 2 or more subjects had a DLT during Cycle 1, dose escalation ceased and additional subjects were enrolled to the next lower dose to achieve a total of 6 subjects in that cohort.

Reporting group title	Phase 1b (Cohort 3): 24 mg Lenvatinib Plus 5 mg Everolimus
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Reporting group description:

Oral lenvatinib (24 mg) and everolimus (5 mg) were taken once daily in continuous 28-day cycles. Dose Escalation Cohort-Cycle 1: both study drugs were taken at the same time of day in the fasting state with water. Cycles 2, 3, etc. and Expansion Cohort: both study drugs were taken at the same time of day with water, either after a meal or in a fasting state. Dose escalation began with 3 subjects in Cohort 1. If no DLT occurred, then enrollment proceeded to Cohort 4. If 1 subject had a DLT, 3 more subjects were enrolled Cohort 3. If 1 or none of the 6 subjects exhibited a DLT, then enrollment proceeded to Cohort 4.

If 2 or more subjects had a DLT during Cycle 1, dose escalation ceased and additional subjects were enrolled to the next lower dose to achieve a total of 6 subjects in that cohort.

Reporting group title	Phase 2 (Arm A): 18 mg Lenvatinib Plus 5 mg Everolimus
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Reporting group description:

Oral lenvatinib (18 mg) and everolimus (5 mg) was once daily in the morning (consistently with or without food) with water, in continuous 28-day (4-week) cycles. Treatment cycles began with the first dose of study drug in Cycle 1 and continued in 28-day (4-week) consecutive cycles until completion of the off-treatment assessments (within 30 days after the last study treatment administration). Study drugs were administered at the clinic for the first dose and on the pharmacokinetic sampling days.

Reporting group title	Phase 2 (Arm B): 24 mg Lenvatinib
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Reporting group description:

Oral lenvatinib (24 mg) was taken once daily in the morning (consistently with or without food) with water, in continuous 28-day (4-week) cycles.

Reporting group title	Phase 2 (Arm C): 10 mg Everolimus
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Reporting group description:

Oral everolimus (10 mg) was taken once daily in the morning (consistently either with or without food) with water, in continuous 28-day (4-week) cycles.

Subject analysis set title	Cycle 1, Day 1 (0 Hours)
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Subject analysis set type	Full analysis
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Subject analysis set description:

Lenvatinib (18 mg) and everolimus (5 mg) were administered as described previously. Blood samples

were collected immediately prior to study drug administration

Subject analysis set title	Phase 1b: Dose Escalation and MTD Expansion Cohorts
Subject analysis set type	Full analysis

Subject analysis set description:

Oral everolimus (18 mg) and lenvatinib (5 mg) were taken once daily in the morning (consistently with or without food) with water. Any dietary habits around the time of study medication intake had to be kept as consistent as possible throughout the study.

Subject analysis set title	Cycle 1, Day 1 (2-8 Hours)
Subject analysis set type	Full analysis

Subject analysis set description:

Lenvatinib (18 mg) and everolimus (5 mg) were administered as described previously. Blood samples were collected 2 to 8 hours after study drug administration.

Subject analysis set title	Cycle 2, Day 1 (0 Hours)
Subject analysis set type	Full analysis

Subject analysis set description:

Lenvatinib (18 mg) and everolimus (5 mg) were administered as described previously. Blood samples were collected immediately prior to study drug administration.

Subject analysis set title	Cycle 2, Day 1 (2-8 Hours)
Subject analysis set type	Full analysis

Subject analysis set description:

Lenvatinib (18 mg) and everolimus (5 mg) were administered as described previously. Blood samples were collected 2 to 8 hours after study drug administration.

Subject analysis set title	Cycle 3, Day 1 (0 Hours)
Subject analysis set type	Full analysis

Subject analysis set description:

Lenvatinib (18 mg) and everolimus (5 mg) were administered as described previously. Blood samples were collected immediately prior to study drug administration.

Subject analysis set title	Cycle 3, Day 1 (2-8 Hours)
Subject analysis set type	Full analysis

Subject analysis set description:

Lenvatinib (18 mg) and everolimus (5 mg) were administered as described previously. Blood samples were collected 2 to 8 hours after study drug administration.

Primary: Phase 1b: Number of Subjects With Dose-limiting Toxicity (DLT)

End point title	Phase 1b: Number of Subjects With Dose-limiting Toxicity (DLT) ^{[1][2]}
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End point description:

A DLT was defined as either a treatment-related failure to administer greater than or equal to (\geq) 75% of the planned dosage of lenvatinib/everolimus or a specific National Cancer Institute Common Toxicity Criteria (NCI CTC) \geq Grade 3 (severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care daily living activities) hematologic or nonhematologic toxicities considered to be possibly related to lenvatinib and/or everolimus therapy assessed during the first treatment cycle of each dose level. Higher grade indicates more severe toxicity. Safety analysis set included all subjects who received at least one dose of study treatment.

End point type	Primary
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End point timeframe:

First dose of study drug (Cycle 1 Day 1) to end of first 4 weeks of therapy (Cycle 1)

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: Only descriptive data were planned to be reported for this end point.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for only arms Phase 2 (Arm A): 18 mg Lenvatinib + 5 mg Everolimus, Phase 2 (Arm B): 24 mg Lenvatinib, and Phase 2 (Arm C): 10 mg Everolimus were planned to be reported for this end point.

End point values	Phase 1b (Cohort 1): 12 mg Lenvatinib Plus 5 mg Everolimus	Phase 1b (Cohort 2): 18 mg Lenvatinib Plus 5 mg Everolimus	Phase 1b (Cohort 3): 24 mg Lenvatinib Plus 5 mg Everolimus	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	11	2	
Units: subjects				
Grade 3 abdominal pain	1	0	0	
Grade 2 fatigue with Grade 1 GI reflux & anorexia	0	1	0	
Grade 3 nausea	0	0	1	
Grade 2 stomatitis	0	0	1	

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1b: Maximum Tolerated Dose (MTD) and Recommended Phase 2 (RP2) Dose

End point title	Phase 1b: Maximum Tolerated Dose (MTD) and Recommended Phase 2 (RP2) Dose ^[3]
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End point description:

The highest dose level resulting in 0 or 1 DLT in 6 subjects was to be considered the MTD of Phase 1b. Once the MTD was established, the subjects cohort was expanded to a minimum of 10 subjects. The MTD was confirmed by assessing DLTs during Cycle 1 and intolerable toxicities (i.e., not manageable with dose interruption and/or reduction) during Cycle 2 of therapy. Once the dose of lenvatinib/everolimus combination to be used in the succeeding Phase 2 part of the study was established, enrollment into Phase 2 was started. The RP2 dose was the same as the confirmed MTD and was used for the Phase 2 Treatment Arm A of this study. Safety analysis set included all subjects who received at least one dose of study treatment.

End point type	Primary
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End point timeframe:

First dose of study drug (Cycle 1 Day 1) to end of Cycle 2 (1 cycle = 28 days/4 weeks)

Notes:

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

Justification: Only descriptive data were planned to be reported for this end point.

End point values	Phase 1b: Dose Escalation and MTD Expansion Cohorts			
Subject group type	Subject analysis set			
Number of subjects analysed	11			
Units: mg/day				
number (not applicable)	18.0			

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Progression-Free Survival (PFS)

End point title	Phase 2: Progression-Free Survival (PFS) ^[4]
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End point description:

PFS is the time (in months) from the date of first dose of study drug to the first documentation of disease progression or death, whichever occurred first. Kaplan-Meier (K-M) estimates median PFS, presented with 2-sided 95% confidence intervals (CIs). Tumor assessments were performed every 8 weeks (or sooner if there was evidence of progressive disease using computed tomography (CT) or magnetic resonance imaging (MRI) and scan acquisition techniques (including use or nonuse of intravenous (IV) contrast). Tumor response determined at the site by the investigator and radiologist using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 in the evaluation of the tumor assessment scans. The date of objective disease progression is the earliest date of radiological disease progression. Participants removed from therapy due to clinical progression with no radiologic confirmation censored at their last radiologic assessment date. Full analysis set included all randomized subjects.

End point type	Primary
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End point timeframe:

Date of randomization into Phase 2 (Cycle 1 Day 1) to the date of first documentation of disease progression or death (whichever occurred first), assessed up to the data cutoff date (13 Jun 2014), up to approximately 2 years and 3 months.

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data for only arms Phase 2 (Arm A): 18 mg Lenvatinib + 5 mg Everolimus, Phase 2 (Arm B): 24 mg Lenvatinib, and Phase 2 (Arm C): 10 mg Everolimus were planned to be reported for this end point.

End point values	Phase 2 (Arm A): 18 mg Lenvatinib Plus 5 mg Everolimus	Phase 2 (Arm B): 24 mg Lenvatinib	Phase 2 (Arm C): 10 mg Everolimus	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51	52	50	
Units: months				
median (confidence interval 95%)				
Progression free survival	14.6 (5.9 to 20.1)	7.4 (5.6 to 10.2)	5.5 (3.5 to 7.1)	

Statistical analyses

Statistical analysis title	Phase 2 (Arm A) versus (vs) Phase 2 (Arm C)
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Statistical analysis description:

Null hypothesis of no difference in PFS was analyzed using the stratified log-rank test with hemoglobin (less than or equal to 13 g/dL vs greater than 13 g/dL for males; and less than or equal to 11.5 g/dL vs greater than 11.5 g/dL for females) and corrected serum calcium (greater than or equal to 10 mg/dL vs less than 10 mg/dL) as stratification factors. Each null hypothesis was tested at a nominal alpha=0.05.

Comparison groups	Phase 2 (Arm A): 18 mg Lenvatinib Plus 5 mg Everolimus v Phase 2 (Arm C): 10 mg Everolimus
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	0.68

Statistical analysis title	Phase 2 (Arm B) vs Phase 2 (Arm C)
Comparison groups	Phase 2 (Arm B): 24 mg Lenvatinib v Phase 2 (Arm C): 10 mg Everolimus
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0479
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	0.98

Statistical analysis title	Phase 2 (Arm A) vs Phase 2 (Arm B)
Comparison groups	Phase 2 (Arm A): 18 mg Lenvatinib Plus 5 mg Everolimus v Phase 2 (Arm B): 24 mg Lenvatinib
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1209
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	1.1

Secondary: Phase 2: Overall Survival (OS)

End point title	Phase 2: Overall Survival (OS) ^[5]
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End point description:

OS was defined as the time (in months) from the date of randomization until date of death from any cause. Median survival time was calculated using K-M estimate for each treatment arm and presented with 2-sided 95% CIs. Subjects who were lost to follow-up or alive at the data cutoff date (10 Dec 2014) were censored at the date the subjects were last known to be alive. Full analysis set included all

randomized subjects.

End point type	Secondary
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End point timeframe:

Randomization (Cycle 1 Day 1) until date of death from any cause, assessed up to the data cutoff date (10 Dec 2014), up to approximately 2 years and 9 months.

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data for only arms Phase 2 (Arm A): 18 mg Lenvatinib + 5 mg Everolimus, Phase 2 (Arm B): 24 mg Lenvatinib, and Phase 2 (Arm C): 10 mg Everolimus were planned to be reported for this end point.

End point values	Phase 2 (Arm A): 18 mg Lenvatinib Plus 5 mg Everolimus	Phase 2 (Arm B): 24 mg Lenvatinib	Phase 2 (Arm C): 10 mg Everolimus	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51	52	50	
Units: months				
median (confidence interval 95%)				
overall survival	25.5 (16.4 to 99999)	19.1 (13.6 to 26.2)	15.4 (11.8 to 19.6)	

Statistical analyses

Statistical analysis title	Phase 2 (Arm A) vs Phase 2 (Arm C)
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Statistical analysis description:

Planned analyses were performed to test null hypothesis of treatment difference in OS at a nominal significance level of 0.05 (2-sided) using the stratified log-rank test using stratification factors.

Comparison groups	Phase 2 (Arm A): 18 mg Lenvatinib Plus 5 mg Everolimus v Phase 2 (Arm C): 10 mg Everolimus
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0242
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.514
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.299
upper limit	0.884

Statistical analysis title	Phase 2 (Arm B) vs Phase 2 (Arm C)
Comparison groups	Phase 2 (Arm B): 24 mg Lenvatinib v Phase 2 (Arm C): 10 mg Everolimus

Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1181
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.411
upper limit	1.138

Statistical analysis title	Phase 2 (Arm A) vs Phase 2 (Arm B)
Comparison groups	Phase 2 (Arm A): 18 mg Lenvatinib Plus 5 mg Everolimus v Phase 2 (Arm B): 24 mg Lenvatinib
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3157
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.751
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.433
upper limit	1.301

Secondary: Phase 2: Objective Response Rate (ORR)

End point title	Phase 2: Objective Response Rate (ORR) ^[6]
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End point description:

The ORR was defined as the percentage of subjects who had the best overall response (BOR) of complete response (CR) or partial response (PR) as determined by the investigator, using RECIST 1.1 in the evaluation of MRI or CT scans of targeted lesions. Tumor assessments were performed every 8 weeks (or sooner if there was evidence of progressive disease). The BOR was defined as the best response recorded from the start of the study treatment until discontinuation from the study. CR was defined as disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) had to have reduction in short axis to less than 10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. ORR = CR + PR was calculated with exact 95% CIs using the method of Clopper and Pearson. Full analysis set included all randomized subjects.

End point type	Secondary
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End point timeframe:

Randomization (Cycle 1 Day 1) until first evidence of disease progression, assessed up to the data cutoff date (13 Jun 2014), or up to approximately 2 years and 3 months.

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data for only arms Phase 2 (Arm A): 18 mg Lenvatinib + 5 mg Everolimus, Phase 2 (Arm B): 24 mg Lenvatinib, and Phase 2 (Arm C): 10 mg Everolimus were planned to be reported for this end point.

End point values	Phase 2 (Arm A): 18 mg Lenvatinib Plus 5 mg Everolimus	Phase 2 (Arm B): 24 mg Lenvatinib	Phase 2 (Arm C): 10 mg Everolimus	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51	52	50	
Units: percentage of subjects				
number (confidence interval 95%)				
objective response rate	43.1 (29.3 to 57.8)	26.9 (15.6 to 41.0)	6.0 (1.3 to 16.5)	

Statistical analyses

Statistical analysis title	Phase 2 (Arm A) vs Phase 2 (Arm C)
Comparison groups	Phase 2 (Arm A): 18 mg Lenvatinib Plus 5 mg Everolimus v Phase 2 (Arm C): 10 mg Everolimus
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[7]
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	7.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.3
upper limit	22.5

Notes:

[7] - Analysis performed after database lock. P-value was based on the 2-sided Fisher's exact P-value.

Statistical analysis title	Phase 2 (Arm B) vs Phase 2 (Arm C)
Comparison groups	Phase 2 (Arm B): 24 mg Lenvatinib v Phase 2 (Arm C): 10 mg Everolimus
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0067 ^[8]
Method	Fisher exact
Parameter estimate	Rate ratio
Point estimate	4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	14.7

Notes:

[8] - Analysis performed after database lock. P-value was based on the 2-sided Fisher's exact P-value.

Statistical analysis title	Phase 2 (Arm A) vs Phase 2 (Arm B)
Comparison groups	Phase 2 (Arm A): 18 mg Lenvatinib Plus 5 mg Everolimus v Phase 2 (Arm B): 24 mg Lenvatinib
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1007 ^[9]
Method	Fisher exact
Parameter estimate	Rate ratio
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	2.8

Notes:

[9] - Analysis performed after database lock. P-value was based on the 2-sided Fisher's exact P-value.

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR) ^[10]
End point description:	
The DCR was defined as the percentage of subjects who had a BOR of CR or PR or SD (minimum duration from randomization to SD greater than or equal to 7 weeks). Assessments were performed every 8 weeks and were based on investigator review data using RECIST 1.1. The 95% CI was constructed using the method of Clopper and Pearson. DCR = CR + PR + SD greater than or equal to 7 weeks. Full analysis set included all randomized subjects.	
End point type	Secondary

End point timeframe:

Baseline (Randomization) to first evidence of disease progression, assessed up to the data cutoff date (13 Jun 2014), or up to approximately 2 years and 3 months.

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for only arms Phase 2 (Arm A): 18 mg Lenvatinib + 5 mg Everolimus, Phase 2 (Arm B): 24 mg Lenvatinib, and Phase 2 (Arm C): 10 mg Everolimus were planned to be reported for this end point.

End point values	Phase 2 (Arm A): 18 mg Lenvatinib Plus 5 mg Everolimus	Phase 2 (Arm B): 24 mg Lenvatinib	Phase 2 (Arm C): 10 mg Everolimus	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51	52	50	
Units: percentage of subjects				
number (confidence interval 95%)				
Disease control rate	84.3 (71.4 to 93.0)	78.8 (65.3 to 88.9)	68.0 (53.3 to 80.5)	

Statistical analyses

Secondary: Durable Stable Disease (SD) Rate

End point title	Durable Stable Disease (SD) Rate ^[11]
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End point description:

The durable SD rate was defined as the percentage of subjects whose BOR was SD and the duration of SD was greater than or equal to 23 weeks. The durable SD was based on investigator review data using RECIST 1.1. The 95% CI was constructed using the method of Clopper and Pearson. Full analysis set included all randomized subjects.

End point type	Secondary
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End point timeframe:

Baseline (Randomization) to first evidence of disease progression, assessed up to the data cutoff date (13 Jun 2014), or up to approximately 2 years and 3 months

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for only arms Phase 2 (Arm A): 18 mg Lenvatinib + 5 mg Everolimus, Phase 2 (Arm B): 24 mg Lenvatinib, and Phase 2 (Arm C): 10 mg Everolimus were planned to be reported for this end point.

End point values	Phase 2 (Arm A): 18 mg Lenvatinib Plus 5 mg Everolimus	Phase 2 (Arm B): 24 mg Lenvatinib	Phase 2 (Arm C): 10 mg Everolimus	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51	52	50	
Units: percentage of subjects				
number (confidence interval 95%)				
Durable Stable Disease (SD) Rate	25.5 (14.3 to 39.6)	38.5 (25.3 to 53.0)	36.0 (22.9 to 50.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR) ^[12]
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End point description:

The CBR was defined as the percentage of subjects who had BOR of CR, PR, or durable SD (duration of SD was greater than or equal to 23 weeks) and was based on investigator review data using RECIST 1.1. The BOR was defined as the best response recorded from the start of study treatment until discontinuation from the study. There was no requirement for confirmatory measurement of PR or CR to deem either one the BOR. The 95% CI was constructed using the method of Clopper and Pearson. CBR = CR + PR + SD greater than or equal to 23 weeks. Full analysis set included all randomized subjects.

End point type	Secondary
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End point timeframe:

Baseline (Randomization) to first evidence of disease progression, assessed up to the data cutoff date (13 Jun 2014), or up to approximately 2 years and 3 months

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for only arms Phase 2 (Arm A): 18 mg Lenvatinib + 5 mg Everolimus, Phase 2 (Arm

B): 24 mg Lenvatinib, and Phase 2 (Arm C): 10 mg Everolimus were planned to be reported for this end point.

End point values	Phase 2 (Arm A): 18 mg Lenvatinib Plus 5 mg Everolimus	Phase 2 (Arm B): 24 mg Lenvatinib	Phase 2 (Arm C): 10 mg Everolimus	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51	52	50	
Units: percentage of subjects				
number (confidence interval 95%)				
Clinical Benefit Rate (CBR)	68.6 (54.1 to 80.9)	65.4 (50.9 to 78.0)	42.0 (28.2 to 56.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Plasma Concentrations of Lenvatinib for Sparse Pharmacokinetic (PK) Sampling for Phase 1b and Phase 2

End point title	Summary of Plasma Concentrations of Lenvatinib for Sparse Pharmacokinetic (PK) Sampling for Phase 1b and Phase 2
End point description:	
Blood samples were collected during the Randomization Phase. Most subjects had 6 samples taken over 3 cycles of treatment (sparse sampling - 2 samples taken per cycle, one at predose and one at 2 to 8 hours postdose). Plasma concentrations of lenvatinib were measured and concentration data were summarized. The summary statistics at time points with one or more below the limit of quantitation (BLQ) values were calculated by assigning zero for each BLQ value.	
End point type	Secondary
End point timeframe:	
Cycle 1 (Day 1), Cycle 2 (Day 1), Cycle 3 (Day 1)	

End point values	Cycle 1, Day 1 (0 Hours)	Cycle 1, Day 1 (2-8 Hours)	Cycle 2, Day 1 (0 Hours)	Cycle 2, Day 1 (2-8 Hours)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	57	55	45	41
Units: ng/mL				
geometric mean (standard deviation)				
Summary of Plasma Concentrations of Lenvatinib for	5.6 (± 29.8)	197 (± 140)	66.9 (± 52.7)	237 (± 154)

End point values	Cycle 3, Day 1 (0 Hours)	Cycle 3, Day 1 (2-8 Hours)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	40		
Units: ng/mL				

geometric mean (standard deviation)				
Summary of Plasma Concentrations of Lenvatinib for	37.0 (± 35.5)	180 (± 118)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Blood Concentrations of Everolimus for Sparse PK Sampling for Phase 1b and Phase 2

End point title	Summary of Blood Concentrations of Everolimus for Sparse PK Sampling for Phase 1b and Phase 2
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End point description:

Blood samples were collected during the Randomization Phase. Most subjects had 6 samples taken over 3 cycles of treatment (sparse sampling - 2 samples taken per cycle, one at predose and one at 2 to 8 hours postdose). Whole blood concentrations of everolimus were measured and concentration data were summarized. The summary statistics at time points with one or more BLQ values were calculated by assigning zero for each BLQ value. Pharmacokinetic analysis set included all participants who received at least one dose of study drug (lenvatinib or everolimus) and had evaluable concentration data.

End point type	Secondary
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End point timeframe:

Cycle 1 (Day 1), Cycle 2 (Day 1), Cycle 3 (Day 1)

End point values	Cycle 1, Day 1 (0 Hours)	Cycle 1, Day 1 (2-8 Hours)	Cycle 2, Day 1 (0 Hours)	Cycle 2, Day 1 (2-8 Hours)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	35	29	28
Units: ng/mL				
geometric mean (standard deviation)				
Summary of Blood Concentrations of Everolimus for	0.0 (± 0.0)	19.4 (± 9.16)	10.0 (± 7.28)	24.3 (± 14.2)

End point values	Cycle 3, Day 1 (0 Hours)	Cycle 3, Day 1 (2-8 Hours)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	25		
Units: ng/mL				
geometric mean (standard deviation)				
Summary of Blood Concentrations of Everolimus for	6.8 (± 6.06)	26.4 (± 14.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-Time Curve From 0 to 24 Hours (AUC(0-24)) for Lenvatinib When Administered Alone or in Combination With Everolimus

End point title	Area Under the Plasma Concentration-Time Curve From 0 to 24 Hours (AUC(0-24)) for Lenvatinib When Administered Alone or in Combination With Everolimus ^[13]
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End point description:

Between 9 and 12 subjects in each of the 3 treatment arms participated in an optional substudy where instead of the sparse sampling, 9 samples were to be taken over 1 single 24-hour period (i.e., intensive sampling) for full PK profiling. Blood samples were analyzed for study drug using standardized methods. PK parameters for lenvatinib were derived from lenvatinib concentration data using non-compartmental methods. Data were compared via descriptive statistics between single agent and combination therapy. Pharmacokinetic sub analysis set consisted of all subjects who agreed to participate in the intensive PK sampling portion of Phase 2 of the study, had received at least 1 dose of study drug (lenvatinib or everolimus), and had evaluable concentration data.

End point type	Secondary
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End point timeframe:

Phase 2: Cycle 1 Day 15 immediately predose, and 30 minutes, 1, 2, 3, 4, 8, 12 (optional), and 24 hours postdose (predose on Day 16)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for only arms Phase 2 (Arm A): 18 mg Lenvatinib + 5 mg Everolimus, Phase 2 (Arm B): 24 mg Lenvatinib, and Phase 2 (Arm C): 10 mg Everolimus were planned to be reported for this end point.

End point values	Phase 2 (Arm A): 18 mg Lenvatinib Plus 5 mg Everolimus	Phase 2 (Arm B): 24 mg Lenvatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: ng.hr/mL				
arithmetic mean (standard deviation)				
Area Under the Plasma Concentration-Time Curve Fro	3185 (\pm 1030)	5252 (\pm 2717)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax) of Lenvatinib in Plasma When Administered Alone or in Combination With Everolimus

End point title	Maximum Concentration (Cmax) of Lenvatinib in Plasma When Administered Alone or in Combination With Everolimus ^[14]
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End point description:

Cmax for lenvatinib was defined as the maximum observed concentration of lenvatinib in plasma following administration of study treatment on Cycle 1 Day 15 and was obtained directly from the measured plasma concentration-time curves. PK sub analysis set.

End point type	Secondary
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End point timeframe:

Phase 2: Cycle 1 Day 15

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for only arms Phase 2 (Arm A): 18 mg Lenvatinib + 5 mg Everolimus, Phase 2 (Arm B): 24 mg Lenvatinib, and Phase 2 (Arm C): 10 mg Everolimus were planned to be reported for this end point.

End point values	Phase 2 (Arm A): 18 mg Lenvatinib Plus 5 mg Everolimus	Phase 2 (Arm B): 24 mg Lenvatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: ng/mL				
arithmetic mean (standard deviation)				
Maximum Concentration (Cmax) of Lenvatinib in Plas	327 (± 179)	403 (± 165)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Cmax (Tmax) for Lenvatinib When Administered Alone or in Combination With Everolimus

End point title	Time to Cmax (Tmax) for Lenvatinib When Administered Alone or in Combination With Everolimus ^[15]
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End point description:

Tmax for lenvatinib was the amount of time taken after administration of study treatment on Cycle 1 Day 15 to reach maximum concentration (Cmax) of lenvatinib in plasma. PK sub analysis set.

End point type	Secondary
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End point timeframe:

Phase 2: Cycle 1 Day 15

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for only arms Phase 2 (Arm A): 18 mg Lenvatinib + 5 mg Everolimus, Phase 2 (Arm B): 24 mg Lenvatinib, and Phase 2 (Arm C): 10 mg Everolimus were planned to be reported for this end point.

End point values	Phase 2 (Arm A): 18 mg Lenvatinib Plus 5 mg Everolimus	Phase 2 (Arm B): 24 mg Lenvatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: hours				
median (full range (min-max))				
Time to Cmax (Tmax) for Lenvatinib When Administer	2.0 (2.0 to 8.2)	4.0 (0.5 to 8.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Blood Concentration-Time Curve From 0 to 24 Hours for Everolimus When Administered Alone or in Combination With Lenvatinib

End point title	Area Under the Blood Concentration-Time Curve From 0 to 24 Hours for Everolimus When Administered Alone or in Combination With Lenvatinib ^[16]
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End point description:

Between 9 and 12 subjects in each of the 3 treatment arms participated in an optional substudy where instead of the sparse sampling, 9 samples were to be taken over 1 single 24-hour period (i.e., intensive sampling) for full PK profiling. Blood samples were analyzed for study drug using standardized methods. PK parameters for everolimus were derived from everolimus concentration data using non-compartmental methods. Data were compared via descriptive statistics between single agent and combination therapy. PK sub analysis set. n=8 for AUC(0-24).

End point type	Secondary
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End point timeframe:

Phase 2: Cycle 1 Day 15 immediately predose, and 30 minutes, 1, 2, 3, 4, 8, 12 (optional), and 24 hours postdose (predose on Day 16)

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for only arms Phase 2 (Arm A): 18 mg Lenvatinib + 5 mg Everolimus, Phase 2 (Arm B): 24 mg Lenvatinib, and Phase 2 (Arm C): 10 mg Everolimus were planned to be reported for this end point.

End point values	Phase 2 (Arm A): 18 mg Lenvatinib Plus 5 mg Everolimus	Phase 2 (Arm B): 24 mg Lenvatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	8		
Units: ng.hr/mL				
arithmetic mean (standard deviation)				
Area Under the Blood Concentration-Time Curve From	378 (± 88.1)	463 (± 263)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration of Everolimus (C_{max}) in Blood When Administered Alone or in Combination With Lenvatinib

End point title	Maximum Concentration of Everolimus (C _{max}) in Blood When Administered Alone or in Combination With Lenvatinib ^[17]
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End point description:

C_{max} for everolimus was defined as the maximum observed concentration of everolimus in blood following administration of study treatment on Cycle 1 Day 15 and was obtained directly from the measured blood concentration-time curves. PK sub analysis set.

End point type	Secondary
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End point timeframe:

Phase 2: Cycle 1 Day 15

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for only arms Phase 2 (Arm A): 18 mg Lenvatinib + 5 mg Everolimus, Phase 2 (Arm B): 24 mg Lenvatinib, and Phase 2 (Arm C): 10 mg Everolimus were planned to be reported for this end point.

End point values	Phase 2 (Arm A): 18 mg Lenvatinib Plus 5 mg Everolimus	Phase 2 (Arm B): 24 mg Lenvatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	11		
Units: ng/mL				
arithmetic mean (standard deviation)				
Maximum Concentration of Everolimus (C _{max}) in Bloo	38 (± 14.5)	54 (± 24.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to C_{max} (T_{max}) for Everolimus When Administered Alone or in Combination With Lenvatinib

End point title	Time to C _{max} (T _{max}) for Everolimus When Administered Alone or in Combination With Lenvatinib ^[18]
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End point description:

T_{max} for everolimus was the amount of time taken after administration of study treatment on Cycle 1 Day 15 to reach the maximum concentration (C_{max}) of everolimus in blood. PK sub analysis set.

End point type	Secondary
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End point timeframe:

Phase 2: Cycle 1 Day 15

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for only arms Phase 2 (Arm A): 18 mg Lenvatinib + 5 mg Everolimus, Phase 2 (Arm B): 24 mg Lenvatinib, and Phase 2 (Arm C): 10 mg Everolimus were planned to be reported for this end point.

End point values	Phase 2 (Arm A): 18 mg Lenvatinib Plus 5 mg Everolimus	Phase 2 (Arm C): 10 mg Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	11		
Units: Hours				
median (full range (min-max))				
Time to Cmax (Tmax) for Everolimus When Administer	1.0 (0.5 to 8.0)	1.0 (0.5 to 25.9)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (AEs) were collected and defined as those AEs that occurred after the first dose of study medication and up to 30 days after the last dose of study medication. AEs were collected for approximately 4 years.

Adverse event reporting additional description:

Safety analysis set included all subjects who received at least one dose of study drug/s and had at least one postbaseline safety evaluation. AE severity was assessed using Common Terminology for Adverse Events (CTCAE). Serious AEs were followed until the event resolved or the event or sequelae stabilized.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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Reporting groups

Reporting group title	Phase 1b (Cohort 1): 12 mg Lenvatinib Plus 5 mg Everolimus
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Reporting group description:

Oral lenvatinib (12 mg) and everolimus (5 mg) were taken once daily in continuous 28-day cycles. Dose Escalation Cohort-Cycle 1: both study drugs were taken at the same time of day in a fasting state with water. Cycles 2, 3, etc. and Expansion Cohort: both study drugs were taken at the same time of day with water, either after a meal or in a fasting state. Dose escalation began with 3 subjects in Cohort 1. If no dose-limiting toxicity (DLT) occurred, then enrollment proceeded to Cohort 2. If 1 subject had a DLT, 3 more subjects were enrolled in Cohort 1. If 1 or none of the 6 subjects had a DLT, then enrollment proceeded to Cohort 2.

If 2 or more subjects had a DLT during Cycle 1, the dose escalation committee (DEC) decided if they were lenvatinib-related and if enrollment could proceed, lenvatinib was reduced to 6 mg daily (everolimus dose was not reduced). If it could not be determined that the DLTs were lenvatinib-related, enrollment stopped.

Reporting group title	Phase 1b (Cohort 2): 18 mg Lenvatinib Plus 5 mg Everolimus
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Reporting group description:

Oral lenvatinib (18 mg) and everolimus (5 mg) were taken once daily in continuous 28-day cycles. Dose Escalation Cohort-Cycle 1: both study drugs were taken at the same time of day in the fasting state with water. Cycles 2, 3, etc. and Expansion Cohort: both study drugs were taken at the same time of day with water, either after a meal or in a fasting state. Dose escalation began with 3 subjects in Cohort 1. If no DLT occurred, then enrollment would proceed to Cohort 3. If 1 subject had a DLT, 3 more subjects were enrolled in Cohort 2. If 1 or none of the 6 subjects exhibited a DLT, enrollment proceeded to Cohort 3.

If 2 or more subjects had a DLT during Cycle 1, dose escalation ceased and additional subjects were enrolled to the next lower dose to achieve a total of 6 subjects in that cohort.

Reporting group title	Phase 1b (Cohort 3): 24 mg Lenvatinib Plus 5 mg Everolimus
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Reporting group description:

Oral lenvatinib (24 mg) and everolimus (5 mg) were taken once daily in continuous 28-day cycles. Dose Escalation Cohort-Cycle 1: both study drugs were taken at the same time of day in the fasting state with water. Cycles 2, 3, etc. and Expansion Cohort: both study drugs were taken at the same time of day with water, either after a meal or in a fasting state. Dose escalation began with 3 subjects in Cohort 1. If no DLT occurred, then enrollment proceeded to Cohort 4. If 1 subject had a DLT, 3 more subjects were enrolled Cohort 3. If 1 or none of the 6 subjects exhibited a DLT, then enrollment proceeded to Cohort 4.

If 2 or more subjects had a DLT during Cycle 1, dose escalation ceased and additional subjects were enrolled to the next lower dose to achieve a total of 6 subjects in that cohort.

Reporting group title	Phase 2 (Arm A): 18 mg Lenvatinib Plus 5 mg Everolimus
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Reporting group description:

Oral lenvatinib (18 mg) and everolimus (5 mg) were taken once daily in the morning (consistently with or without food) with water, in continuous 28-day (4-week) cycles. Treatment cycles began with the first dose of study drug in Cycle 1 and continued in 28-day (4-week) consecutive cycles until completion of the off-treatment assessments (within 30 days after the last study treatment administration). Study drugs were administered at the clinic for the first dose and on the pharmacokinetic (PK) sampling days.

Reporting group title	Phase 2 (Arm B): 24 mg Lenvatinib
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Reporting group description:

Oral lenvatinib (24 mg) was taken once daily in the morning (consistently with or without food) with water, in continuous 28-day (4-week) cycles.

Reporting group title	Phase 2 (Arm C): 10 mg Everolimus
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Reporting group description:

Oral everolimus (10 mg) was taken once daily in the morning (consistently either with or without food) with water, in continuous 28-day (4 week) cycles.

Serious adverse events	Phase 1b (Cohort 1): 12 mg Lenvatinib Plus 5 mg Everolimus	Phase 1b (Cohort 2): 18 mg Lenvatinib Plus 5 mg Everolimus	Phase 1b (Cohort 3): 24 mg Lenvatinib Plus 5 mg Everolimus
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 7 (85.71%)	8 / 11 (72.73%)	0 / 2 (0.00%)
number of deaths (all causes)	6	9	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant Pleural Effusion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Metastatic Pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	0 / 2 (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
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Hot Flush			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Subclavian Vein Thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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

Venous Thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Chest Discomfort			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Fatigue			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	0 / 2 (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	1 / 7 (14.29%)	0 / 11 (0.00%)	0 / 2 (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
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	0 / 2 (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
Pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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

Immune system disorders			
Drug Hypersensitivity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Reproductive system and breast disorders			
Benign Prostatic Hyperplasia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Dyspnoea			
subjects affected / exposed	1 / 7 (14.29%)	1 / 11 (9.09%)	0 / 2 (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
Haemoptysis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Pleural Effusion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Pulmonary Embolism			

subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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			
Anxiety			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (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
Confusional State			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Investigations			
Blood Bilirubin Increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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 Creatinine Phosphokinase Increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Body Temperature Increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Ejection Fraction Decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram Repolarisation Abnormality			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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

Fibrin D Dimer Increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Lipase Increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Transaminases Increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
White Blood Cell Count Decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Joint Dislocation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Toxicity to Various Agents			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Cardiac Failure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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

Cardiac Failure Congestive			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Cardiomyopathy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (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
Tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Nervous system disorders			
Carotid Artery Occlusion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Cerebral Haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Convulsion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Haemorrhage Intracranial			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Headache			

subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Ischaemic Stroke			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Paresis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Posterior Reversible Encephalopathy Syndrome			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Somnolence			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Trigeminal Neuralgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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			
Anaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Sideroblastic Anaemia			

subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Thrombocytopenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Ear and labyrinth disorders			
Vertigo Positional			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	0 / 2 (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
Diarrhoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Dysphagia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Gastric Haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Gastritis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			

subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Ileus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Vomiting			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (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
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	0 / 2 (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
Cholecystitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Cholecystitis Acute			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Proteinuria			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Failure Acute			

subjects affected / exposed	1 / 7 (14.29%)	2 / 11 (18.18%)	0 / 2 (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
Renal Impairment			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Endocrine disorders			
Inappropriate Antidiuretic Hormone Secretion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Back Pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Flank Pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Haemarthrosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Musculoskeletal Chest Pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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

Pathological Fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Psoriatic Arthropathy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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 Pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Appendicitis Perforated			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Bronchopneumonia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Cellulitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic Foot Infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Escherichia Sepsis			

subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Infectious Pleural Effusion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Lower Respiratory Tract Infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Parotitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Rectal Abscess			

subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Dehydration			
subjects affected / exposed	0 / 7 (0.00%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to Thrive			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Glucose Tolerance Impaired			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Hypercholesterolaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (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
Hyperkalaemia			

subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Hypomagnesaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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
Hyponatraemia			
subjects affected / exposed	2 / 7 (28.57%)	0 / 11 (0.00%)	0 / 2 (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
Malnutrition			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (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

Serious adverse events	Phase 2 (Arm A): 18 mg Lenvatinib Plus 5 mg Everolimus	Phase 2 (Arm B): 24 mg Lenvatinib	Phase 2 (Arm C): 10 mg Everolimus
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 51 (58.82%)	28 / 52 (53.85%)	21 / 50 (42.00%)
number of deaths (all causes)	43	40	45
number of deaths resulting from adverse events	2	3	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant Pleural Effusion			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (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
Metastatic Pain			

subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (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
Hot Flush			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (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
Subclavian Vein Thrombosis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous Thrombosis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (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 disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest Discomfort			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (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
Fatigue			
subjects affected / exposed	1 / 51 (1.96%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General Physical Health Deterioration			
subjects affected / exposed	2 / 51 (3.92%)	0 / 52 (0.00%)	0 / 50 (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
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	2 / 51 (3.92%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug Hypersensitivity			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (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
Reproductive system and breast disorders			
Benign Prostatic Hyperplasia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Dyspnoea			

subjects affected / exposed	2 / 51 (3.92%)	1 / 52 (1.92%)	2 / 50 (4.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural Effusion			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	3 / 50 (6.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Embolism			
subjects affected / exposed	1 / 51 (1.96%)	1 / 52 (1.92%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (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
Confusional State			
subjects affected / exposed	2 / 51 (3.92%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood Bilirubin Increased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (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
Blood Creatinine Phosphokinase			

Increased			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Body Temperature Increased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (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
Ejection Fraction Decreased			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram Repolarisation Abnormality			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibrin D Dimer Increased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (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
Lipase Increased			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases Increased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (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
White Blood Cell Count Decreased			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (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
Injury, poisoning and procedural complications			

Joint Dislocation			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (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
Toxicity to Various Agents			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	0 / 51 (0.00%)	3 / 52 (5.77%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Failure			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (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 Congestive			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiomyopathy			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (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
Myocardial infarction			
subjects affected / exposed	1 / 51 (1.96%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Tachycardia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (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
Nervous system disorders			

Carotid Artery Occlusion			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (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
Cerebral Haemorrhage			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage Intracranial			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Headache			
subjects affected / exposed	0 / 51 (0.00%)	3 / 52 (5.77%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic Stroke			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paresis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Posterior Reversible Encephalopathy Syndrome			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			

subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (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
Spinal Cord Compression			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Trigeminal Neuralgia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 51 (7.84%)	1 / 52 (1.92%)	4 / 50 (8.00%)
occurrences causally related to treatment / all	3 / 4	0 / 1	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sideroblastic Anaemia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (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
Thrombocytopenia			
subjects affected / exposed	3 / 51 (5.88%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	5 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo Positional			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 51 (0.00%)	2 / 52 (3.85%)	0 / 50 (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

Diarrhoea			
subjects affected / exposed	3 / 51 (5.88%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (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
Gastric Haemorrhage			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (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
Gastritis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (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
Haemorrhoids			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (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 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (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
Vomiting			
subjects affected / exposed	2 / 51 (3.92%)	0 / 52 (0.00%)	0 / 50 (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
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (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
Cholecystitis			

subjects affected / exposed	1 / 51 (1.96%)	2 / 52 (3.85%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis Acute			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (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
Proteinuria			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (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
Renal Failure Acute			
subjects affected / exposed	3 / 51 (5.88%)	4 / 52 (7.69%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	2 / 3	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Impairment			
subjects affected / exposed	2 / 51 (3.92%)	0 / 52 (0.00%)	0 / 50 (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
Endocrine disorders			
Inappropriate Antidiuretic Hormone Secretion			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (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
Back Pain			
subjects affected / exposed	1 / 51 (1.96%)	1 / 52 (1.92%)	0 / 50 (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
Flank Pain			
subjects affected / exposed	0 / 51 (0.00%)	2 / 52 (3.85%)	0 / 50 (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
Haemarthrosis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (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 Chest Pain			
subjects affected / exposed	2 / 51 (3.92%)	1 / 52 (1.92%)	0 / 50 (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
Pathological Fracture			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (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
Psoriatic Arthropathy			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Pain			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			

subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (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
Appendicitis Perforated			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (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
Bronchopneumonia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (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
Cellulitis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (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
Diabetic Foot Infection			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia Sepsis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Infection			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (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
Infectious Pleural Effusion			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower Respiratory Tract Infection			

subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	2 / 50 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Infection			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (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
Osteomyelitis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parotitis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 51 (0.00%)	2 / 52 (3.85%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal Abscess			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (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
Sepsis			
subjects affected / exposed	1 / 51 (1.96%)	1 / 52 (1.92%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (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
Metabolism and nutrition disorders			
Decreased Appetite			

subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (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
Dehydration			
subjects affected / exposed	4 / 51 (7.84%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	3 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to Thrive			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glucose Tolerance Impaired			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercholesterolaemia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	2 / 51 (3.92%)	0 / 52 (0.00%)	0 / 50 (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
Hypokalaemia			
subjects affected / exposed	1 / 51 (1.96%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesaemia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (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
Hyponatraemia			

subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (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
Malnutrition			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Phase 1b (Cohort 1): 12 mg Lenvatinib Plus 5 mg Everolimus	Phase 1b (Cohort 2): 18 mg Lenvatinib Plus 5 mg Everolimus	Phase 1b (Cohort 3): 24 mg Lenvatinib Plus 5 mg Everolimus
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	11 / 11 (100.00%)	2 / 2 (100.00%)
Vascular disorders			
Aortic Dilatation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Deep Vein Thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Hot Flush			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	5 / 7 (71.43%)	4 / 11 (36.36%)	0 / 2 (0.00%)
occurrences (all)	7	5	0
Hypotension			
subjects affected / exposed	1 / 7 (14.29%)	3 / 11 (27.27%)	0 / 2 (0.00%)
occurrences (all)	1	4	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Chills			

subjects affected / exposed	0 / 7 (0.00%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Fatigue			
subjects affected / exposed	4 / 7 (57.14%)	11 / 11 (100.00%)	2 / 2 (100.00%)
occurrences (all)	12	26	2
Gait Disturbance			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Influenza Like Illness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Localised Oedema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Malaise			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 7 (0.00%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Oedema Peripheral			
subjects affected / exposed	1 / 7 (14.29%)	6 / 11 (54.55%)	0 / 2 (0.00%)
occurrences (all)	7	16	0
Pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Peripheral Swelling			
subjects affected / exposed	1 / 7 (14.29%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Reproductive system and breast disorders			
Vaginal Haemorrhage			

subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 7 (85.71%)	3 / 11 (27.27%)	0 / 2 (0.00%)
occurrences (all)	6	4	0
Dysphonia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Dyspnoea			
subjects affected / exposed	1 / 7 (14.29%)	7 / 11 (63.64%)	1 / 2 (50.00%)
occurrences (all)	1	10	2
Dyspnoea Exertional			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	2 / 7 (28.57%)	5 / 11 (45.45%)	1 / 2 (50.00%)
occurrences (all)	6	7	1
Haemoptysis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Lung Infiltration			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	1 / 2 (50.00%)
occurrences (all)	0	1	1
Nasal Congestion			
subjects affected / exposed	0 / 7 (0.00%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Oropharyngeal Pain			
subjects affected / exposed	1 / 7 (14.29%)	3 / 11 (27.27%)	0 / 2 (0.00%)
occurrences (all)	1	4	0
Pleural Effusion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Pneumonitis			

subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Productive Cough			
subjects affected / exposed	0 / 7 (0.00%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Rhinorrhoea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Sinus Congestion			
subjects affected / exposed	0 / 7 (0.00%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Sputum Discoloured			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Upper-Airway Cough Syndrome			
subjects affected / exposed	1 / 7 (14.29%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	2	1	0
Wheezing			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Paranasal sinus discomfort			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Confusional State			
subjects affected / exposed	2 / 7 (28.57%)	0 / 11 (0.00%)	1 / 2 (50.00%)
occurrences (all)	2	0	1
Depression			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Insomnia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	1	1	0

Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	4	0
Amylase Increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	4	0
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	5	0
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	2	3	0
Blood Bilirubin Increased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	1	2	0
Blood Cholesterol Increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	0 / 7 (0.00%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences (all)	0	4	0
Blood Creatinine Increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Blood Glucose Increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Blood Phosphorus Increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Blood Potassium Increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Blood Thyroid Stimulating Hormone			

Increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Blood Triglycerides Increased			
subjects affected / exposed	0 / 7 (0.00%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences (all)	0	6	0
Cardiac Murmur			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Computerised Tomogram Thorax Abnormal			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Ejection Fraction Decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT Prolonged			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Haemoglobin Decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Lipase Increased			
subjects affected / exposed	0 / 7 (0.00%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Liver Function Test Abnormal			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Murphy's Sign Positive			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Platelet Count Increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Protein Urine Present			

subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Transaminases Increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Weight Decreased			
subjects affected / exposed	2 / 7 (28.57%)	5 / 11 (45.45%)	0 / 2 (0.00%)
occurrences (all)	3	14	0
White Blood Cell Count Decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
White Blood Cell Count Increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Arthropod Bite			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Contusion			
subjects affected / exposed	1 / 7 (14.29%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Fall			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Periorbital Contusion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Toxicity to Various Agents			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Aortic Valve Incompetence			

subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Coronary Artery Disease			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Coronary Artery Occlusion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Mitral Valve Incompetence			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Palpitations			
subjects affected / exposed	1 / 7 (14.29%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Ventricular Hypokinesia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Left ventricular dysfunction			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Disturbance In Attention			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	1 / 7 (14.29%)	5 / 11 (45.45%)	1 / 2 (50.00%)
occurrences (all)	1	8	1
Dysgeusia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	4 / 7 (57.14%)	3 / 11 (27.27%)	0 / 2 (0.00%)
occurrences (all)	4	3	0

Hyperaesthesia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Hypoaesthesia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences (all)	1	3	0
Lethargy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 11 (9.09%)	1 / 2 (50.00%)
occurrences (all)	1	1	1
Peripheral Sensory Neuropathy			
subjects affected / exposed	2 / 7 (28.57%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences (all)	2	2	0
Sensory Disturbance			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Sinus Headache			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	0 / 7 (0.00%)	2 / 11 (18.18%)	1 / 2 (50.00%)
occurrences (all)	0	2	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 7 (28.57%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences (all)	4	2	0
Haemorrhagic Disorder			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Lymphadenopathy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Neutropenia			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 11 (9.09%) 1	0 / 2 (0.00%) 0
Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	2 / 11 (18.18%) 4	0 / 2 (0.00%) 0
Ear and labyrinth disorders Ear Pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 11 (9.09%) 1	0 / 2 (0.00%) 0
Vertigo subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 11 (0.00%) 0	0 / 2 (0.00%) 0
Eye disorders Diplopia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 11 (9.09%) 1	0 / 2 (0.00%) 0
Eye Swelling subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 11 (9.09%) 1	0 / 2 (0.00%) 0
Ocular Hyperaemia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 11 (0.00%) 0	0 / 2 (0.00%) 0
Vision Blurred subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 11 (9.09%) 1	0 / 2 (0.00%) 0
Gastrointestinal disorders Abdominal Discomfort subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 11 (0.00%) 0	0 / 2 (0.00%) 0
Abdominal Distension subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 11 (9.09%) 1	1 / 2 (50.00%) 1
Abdominal Pain subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 2	3 / 11 (27.27%) 5	0 / 2 (0.00%) 0
Abdominal Pain Lower			

subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Abdominal Pain Upper			
subjects affected / exposed	2 / 7 (28.57%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	4	1	0
Anal Fissure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Anal Pruritus			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Anorectal Discomfort			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Aphthous Stomatitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Cheilitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	3 / 7 (42.86%)	4 / 11 (36.36%)	1 / 2 (50.00%)
occurrences (all)	4	7	1
Diarrhoea			
subjects affected / exposed	3 / 7 (42.86%)	7 / 11 (63.64%)	1 / 2 (50.00%)
occurrences (all)	10	19	1
Dry Mouth			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	1 / 2 (50.00%)
occurrences (all)	1	0	1
Dyspepsia			
subjects affected / exposed	0 / 7 (0.00%)	4 / 11 (36.36%)	0 / 2 (0.00%)
occurrences (all)	0	4	0
Flatulence			
subjects affected / exposed	1 / 7 (14.29%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Gastric Haemorrhage			

subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Gingival Bleeding			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Glossitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	6	0
Glossodynia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Haemorrhoidal Haemorrhage			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Haemorrhoids			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Lip Discolouration			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Mouth Ulceration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	6 / 7 (85.71%)	6 / 11 (54.55%)	1 / 2 (50.00%)
occurrences (all)	10	16	2
Oral Mucosal Blistering			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Oral Pain			

subjects affected / exposed	0 / 7 (0.00%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Paraesthesia Oral			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Stomatitis			
subjects affected / exposed	4 / 7 (57.14%)	7 / 11 (63.64%)	2 / 2 (100.00%)
occurrences (all)	5	18	3
Toothache			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	5 / 7 (71.43%)	5 / 11 (45.45%)	1 / 2 (50.00%)
occurrences (all)	10	8	2
Hepatobiliary disorders			
Dilatation Intrahepatic Duct Acquired			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Dermatitis Acneiform			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Dry Skin			
subjects affected / exposed	3 / 7 (42.86%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences (all)	3	4	0
Ecchymosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Erythema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Erythema Multiforme			

subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Hyperhidrosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Hyperkeratosis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Night Sweats			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Onychoclasia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Palmar-Plantar Erythrodysesthesia Syndrome			
subjects affected / exposed	0 / 7 (0.00%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences (all)	0	4	0
Petechiae			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	2 / 7 (28.57%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	2	1	0
Rash			
subjects affected / exposed	3 / 7 (42.86%)	5 / 11 (45.45%)	1 / 2 (50.00%)
occurrences (all)	3	10	1
Rash Erythematous			
subjects affected / exposed	0 / 7 (0.00%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Rash Macular			
subjects affected / exposed	1 / 7 (14.29%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Skin Mass			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	2	0

Skin Ulcer subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 11 (9.09%) 1	0 / 2 (0.00%) 0
Renal and urinary disorders			
Haematuria subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 11 (9.09%) 1	1 / 2 (50.00%) 1
Nocturia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	3 / 11 (27.27%) 3	0 / 2 (0.00%) 0
Pollakiuria subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 11 (0.00%) 0	0 / 2 (0.00%) 0
Proteinuria subjects affected / exposed occurrences (all)	5 / 7 (71.43%) 7	6 / 11 (54.55%) 28	0 / 2 (0.00%) 0
Renal Failure Acute subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 11 (9.09%) 1	0 / 2 (0.00%) 0
Renal Failure Chronic subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 11 (9.09%) 1	0 / 2 (0.00%) 0
Renal Mass subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 11 (9.09%) 1	0 / 2 (0.00%) 0
Endocrine disorders			
Hypothyroidism subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 2	3 / 11 (27.27%) 3	0 / 2 (0.00%) 0
Inappropriate antidiuretic hormone secretion subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 11 (0.00%) 0	0 / 2 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	4 / 7 (57.14%) 4	2 / 11 (18.18%) 3	0 / 2 (0.00%) 0

Back Pain			
subjects affected / exposed	3 / 7 (42.86%)	4 / 11 (36.36%)	0 / 2 (0.00%)
occurrences (all)	3	4	0
Bone Pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Flank Pain			
subjects affected / exposed	0 / 7 (0.00%)	3 / 11 (27.27%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Groin Pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Muscle Spasms			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Muscular Weakness			
subjects affected / exposed	0 / 7 (0.00%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences (all)	0	4	0
Musculoskeletal Chest Pain			
subjects affected / exposed	1 / 7 (14.29%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences (all)	1	2	0
Musculoskeletal Pain			
subjects affected / exposed	3 / 7 (42.86%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences (all)	5	4	0
Myalgia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Neck Pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Pain In Jaw			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

Pain in Extremity subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 5	4 / 11 (36.36%) 6	0 / 2 (0.00%) 0
Spinal Osteoarthritis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 11 (9.09%) 1	0 / 2 (0.00%) 0
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 11 (9.09%) 1	0 / 2 (0.00%) 0
Cellulitis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	2 / 11 (18.18%) 2	0 / 2 (0.00%) 0
Gingivitis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 11 (9.09%) 1	0 / 2 (0.00%) 0
Infectious Pleural Effusion subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	3 / 11 (27.27%) 3	0 / 2 (0.00%) 0
Influenza subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 2	0 / 11 (0.00%) 0	0 / 2 (0.00%) 0
Lower Respiratory Tract Infection subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 11 (0.00%) 0	0 / 2 (0.00%) 0
Lymph Gland Infection subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 11 (9.09%) 1	0 / 2 (0.00%) 0
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 11 (9.09%) 1	0 / 2 (0.00%) 0
Oral Herpes subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 11 (9.09%) 1	0 / 2 (0.00%) 0
Osteomyelitis			

subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Paronychia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Respiratory Tract Infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Skin Infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 7 (28.57%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	3	0	0
Urinary Tract Infection			
subjects affected / exposed	1 / 7 (14.29%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	3 / 7 (42.86%)	6 / 11 (54.55%)	1 / 2 (50.00%)
occurrences (all)	5	10	2
Dehydration			
subjects affected / exposed	1 / 7 (14.29%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Failure to Thrive			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Hypercalcaemia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	4	1	0

Hypercholesterolaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Hyperglycaemia			
subjects affected / exposed	2 / 7 (28.57%)	3 / 11 (27.27%)	0 / 2 (0.00%)
occurrences (all)	3	3	0
Hyperkalaemia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences (all)	1	2	0
Hyperlipidaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Hypernatraemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Hypertriglyceridaemia			
subjects affected / exposed	1 / 7 (14.29%)	7 / 11 (63.64%)	0 / 2 (0.00%)
occurrences (all)	2	20	0
Hypocalcaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Hypomagnesaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hyponatraemia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 11 (18.18%)	0 / 2 (0.00%)
occurrences (all)	1	5	0
Hypophagia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Hypophosphataemia			
subjects affected / exposed	3 / 7 (42.86%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	4	0	0

Hypovolaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Malnutrition			
subjects affected / exposed	1 / 7 (14.29%)	0 / 11 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Metabolic Acidosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 11 (9.09%)	0 / 2 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Phase 2 (Arm A): 18 mg Lenvatinib Plus 5 mg Everolimus	Phase 2 (Arm B): 24 mg Lenvatinib	Phase 2 (Arm C): 10 mg Everolimus
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 51 (100.00%)	51 / 52 (98.08%)	50 / 50 (100.00%)
Vascular disorders			
Aortic Dilatation			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Deep Vein Thrombosis			
subjects affected / exposed	0 / 51 (0.00%)	3 / 52 (5.77%)	0 / 50 (0.00%)
occurrences (all)	0	3	0
Hot Flush			
subjects affected / exposed	1 / 51 (1.96%)	3 / 52 (5.77%)	0 / 50 (0.00%)
occurrences (all)	2	3	0
Hypertension			
subjects affected / exposed	21 / 51 (41.18%)	26 / 52 (50.00%)	5 / 50 (10.00%)
occurrences (all)	28	44	6
Hypotension			
subjects affected / exposed	3 / 51 (5.88%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences (all)	3	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	13 / 51 (25.49%)	8 / 52 (15.38%)	3 / 50 (6.00%)
occurrences (all)	26	34	5
Chills			
subjects affected / exposed	2 / 51 (3.92%)	3 / 52 (5.77%)	1 / 50 (2.00%)
occurrences (all)	6	5	4

Fatigue			
subjects affected / exposed	26 / 51 (50.98%)	21 / 52 (40.38%)	16 / 50 (32.00%)
occurrences (all)	53	46	18
Gait Disturbance			
subjects affected / exposed	1 / 51 (1.96%)	2 / 52 (3.85%)	1 / 50 (2.00%)
occurrences (all)	1	3	2
Influenza Like Illness			
subjects affected / exposed	4 / 51 (7.84%)	2 / 52 (3.85%)	0 / 50 (0.00%)
occurrences (all)	6	4	0
Localised Oedema			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	1 / 51 (1.96%)	3 / 52 (5.77%)	1 / 50 (2.00%)
occurrences (all)	1	10	1
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 51 (0.00%)	2 / 52 (3.85%)	1 / 50 (2.00%)
occurrences (all)	0	2	1
Oedema Peripheral			
subjects affected / exposed	15 / 51 (29.41%)	9 / 52 (17.31%)	9 / 50 (18.00%)
occurrences (all)	22	15	13
Pain			
subjects affected / exposed	3 / 51 (5.88%)	2 / 52 (3.85%)	1 / 50 (2.00%)
occurrences (all)	4	2	1
Peripheral Swelling			
subjects affected / exposed	5 / 51 (9.80%)	1 / 52 (1.92%)	2 / 50 (4.00%)
occurrences (all)	5	1	3
Pyrexia			
subjects affected / exposed	9 / 51 (17.65%)	5 / 52 (9.62%)	5 / 50 (10.00%)
occurrences (all)	13	8	9
Reproductive system and breast disorders			
Vaginal Haemorrhage			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	20 / 51 (39.22%)	9 / 52 (17.31%)	16 / 50 (32.00%)
occurrences (all)	34	18	24
Dysphonia			
subjects affected / exposed	10 / 51 (19.61%)	19 / 52 (36.54%)	2 / 50 (4.00%)
occurrences (all)	13	26	2
Dyspnoea			
subjects affected / exposed	11 / 51 (21.57%)	11 / 52 (21.15%)	11 / 50 (22.00%)
occurrences (all)	15	12	16
Dyspnoea Exertional			
subjects affected / exposed	4 / 51 (7.84%)	1 / 52 (1.92%)	5 / 50 (10.00%)
occurrences (all)	4	1	6
Epistaxis			
subjects affected / exposed	9 / 51 (17.65%)	4 / 52 (7.69%)	12 / 50 (24.00%)
occurrences (all)	11	5	14
Haemoptysis			
subjects affected / exposed	0 / 51 (0.00%)	3 / 52 (5.77%)	2 / 50 (4.00%)
occurrences (all)	0	4	5
Lung Infiltration			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	3
Nasal Congestion			
subjects affected / exposed	2 / 51 (3.92%)	1 / 52 (1.92%)	1 / 50 (2.00%)
occurrences (all)	2	1	1
Oropharyngeal Pain			
subjects affected / exposed	4 / 51 (7.84%)	2 / 52 (3.85%)	2 / 50 (4.00%)
occurrences (all)	7	2	2
Pleural Effusion			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	3 / 50 (6.00%)
occurrences (all)	0	0	3
Pneumonitis			
subjects affected / exposed	2 / 51 (3.92%)	0 / 52 (0.00%)	4 / 50 (8.00%)
occurrences (all)	2	0	10
Productive Cough			
subjects affected / exposed	1 / 51 (1.96%)	2 / 52 (3.85%)	2 / 50 (4.00%)
occurrences (all)	1	3	4

Rhinorrhoea			
subjects affected / exposed	1 / 51 (1.96%)	2 / 52 (3.85%)	2 / 50 (4.00%)
occurrences (all)	1	4	2
Sinus Congestion			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Sputum Discoloured			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Upper-Airway Cough Syndrome			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Wheezing			
subjects affected / exposed	1 / 51 (1.96%)	2 / 52 (3.85%)	2 / 50 (4.00%)
occurrences (all)	1	3	2
Paranasal sinus discomfort			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 51 (3.92%)	3 / 52 (5.77%)	1 / 50 (2.00%)
occurrences (all)	2	3	2
Confusional State			
subjects affected / exposed	1 / 51 (1.96%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences (all)	2	1	0
Depression			
subjects affected / exposed	3 / 51 (5.88%)	1 / 52 (1.92%)	2 / 50 (4.00%)
occurrences (all)	4	1	3
Insomnia			
subjects affected / exposed	10 / 51 (19.61%)	8 / 52 (15.38%)	1 / 50 (2.00%)
occurrences (all)	20	9	1
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	5 / 51 (9.80%)	3 / 52 (5.77%)	3 / 50 (6.00%)
occurrences (all)	6	4	8
Amylase Increased			

subjects affected / exposed	1 / 51 (1.96%)	2 / 52 (3.85%)	0 / 50 (0.00%)
occurrences (all)	1	3	0
Aspartate Aminotransferase Increased			
subjects affected / exposed	2 / 51 (3.92%)	2 / 52 (3.85%)	3 / 50 (6.00%)
occurrences (all)	4	2	9
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	2 / 51 (3.92%)	1 / 52 (1.92%)	2 / 50 (4.00%)
occurrences (all)	2	1	3
Blood Bilirubin Increased			
subjects affected / exposed	1 / 51 (1.96%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences (all)	1	1	0
Blood Cholesterol Increased			
subjects affected / exposed	4 / 51 (7.84%)	2 / 52 (3.85%)	3 / 50 (6.00%)
occurrences (all)	21	4	11
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	4 / 51 (7.84%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences (all)	18	0	7
Blood Creatinine Increased			
subjects affected / exposed	3 / 51 (5.88%)	2 / 52 (3.85%)	4 / 50 (8.00%)
occurrences (all)	4	3	5
Blood Glucose Increased			
subjects affected / exposed	2 / 51 (3.92%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences (all)	3	0	3
Blood Phosphorus Increased			
subjects affected / exposed	0 / 51 (0.00%)	2 / 52 (3.85%)	0 / 50 (0.00%)
occurrences (all)	0	3	0
Blood Potassium Increased			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Blood Thyroid Stimulating Hormone Increased			
subjects affected / exposed	7 / 51 (13.73%)	2 / 52 (3.85%)	1 / 50 (2.00%)
occurrences (all)	8	2	1
Blood Triglycerides Increased			

subjects affected / exposed	0 / 51 (0.00%)	2 / 52 (3.85%)	1 / 50 (2.00%)
occurrences (all)	0	2	1
Cardiac Murmur			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Computerised Tomogram Thorax Abnormal			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Ejection Fraction Decreased			
subjects affected / exposed	1 / 51 (1.96%)	4 / 52 (7.69%)	0 / 50 (0.00%)
occurrences (all)	1	7	0
Electrocardiogram QT Prolonged			
subjects affected / exposed	1 / 51 (1.96%)	2 / 52 (3.85%)	0 / 50 (0.00%)
occurrences (all)	2	2	0
Haemoglobin Decreased			
subjects affected / exposed	1 / 51 (1.96%)	2 / 52 (3.85%)	5 / 50 (10.00%)
occurrences (all)	1	2	10
Lipase Increased			
subjects affected / exposed	4 / 51 (7.84%)	5 / 52 (9.62%)	3 / 50 (6.00%)
occurrences (all)	10	7	11
Liver Function Test Abnormal			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Murphy's Sign Positive			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Platelet Count Increased			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Protein Urine Present			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Transaminases Increased			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences (all)	0	3	0

Weight Decreased subjects affected / exposed occurrences (all)	16 / 51 (31.37%) 22	26 / 52 (50.00%) 38	4 / 50 (8.00%) 4
White Blood Cell Count Decreased subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	0 / 52 (0.00%) 0	0 / 50 (0.00%) 0
White Blood Cell Count Increased subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	1 / 52 (1.92%) 1	0 / 50 (0.00%) 0
Injury, poisoning and procedural complications			
Arthropod Bite subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	0 / 52 (0.00%) 0	0 / 50 (0.00%) 0
Contusion subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	1 / 52 (1.92%) 2	0 / 50 (0.00%) 0
Fall subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	1 / 52 (1.92%) 1	1 / 50 (2.00%) 1
Periorbital Contusion subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	0 / 52 (0.00%) 0	0 / 50 (0.00%) 0
Toxicity to Various Agents subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	0 / 52 (0.00%) 0	0 / 50 (0.00%) 0
Cardiac disorders			
Angina Pectoris subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	0 / 52 (0.00%) 0	0 / 50 (0.00%) 0
Aortic Valve Incompetence subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	0 / 52 (0.00%) 0	0 / 50 (0.00%) 0
Coronary Artery Disease subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	0 / 52 (0.00%) 0	0 / 50 (0.00%) 0
Coronary Artery Occlusion			

subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	11
Mitral Valve Incompetence			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Palpitations			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	2
Tachycardia			
subjects affected / exposed	0 / 51 (0.00%)	2 / 52 (3.85%)	0 / 50 (0.00%)
occurrences (all)	0	2	0
Ventricular Hypokinesia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Left ventricular dysfunction			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Disturbance In Attention			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	2 / 51 (3.92%)	4 / 52 (7.69%)	2 / 50 (4.00%)
occurrences (all)	2	7	2
Dysgeusia			
subjects affected / exposed	4 / 51 (7.84%)	4 / 52 (7.69%)	1 / 50 (2.00%)
occurrences (all)	4	5	2
Headache			
subjects affected / exposed	10 / 51 (19.61%)	13 / 52 (25.00%)	4 / 50 (8.00%)
occurrences (all)	14	21	6
Hyperaesthesia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Hypoaesthesia			
subjects affected / exposed	1 / 51 (1.96%)	1 / 52 (1.92%)	1 / 50 (2.00%)
occurrences (all)	2	1	1

Lethargy			
subjects affected / exposed	4 / 51 (7.84%)	7 / 52 (13.46%)	2 / 50 (4.00%)
occurrences (all)	7	10	2
Paraesthesia			
subjects affected / exposed	2 / 51 (3.92%)	1 / 52 (1.92%)	1 / 50 (2.00%)
occurrences (all)	3	1	1
Peripheral Sensory Neuropathy			
subjects affected / exposed	0 / 51 (0.00%)	4 / 52 (7.69%)	0 / 50 (0.00%)
occurrences (all)	0	6	0
Sensory Disturbance			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Sinus Headache			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	0 / 51 (0.00%)	2 / 52 (3.85%)	0 / 50 (0.00%)
occurrences (all)	0	2	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 51 (13.73%)	3 / 52 (5.77%)	11 / 50 (22.00%)
occurrences (all)	10	3	13
Haemorrhagic Disorder			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Lymphadenopathy			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Neutropenia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Thrombocytopenia			
subjects affected / exposed	5 / 51 (9.80%)	1 / 52 (1.92%)	4 / 50 (8.00%)
occurrences (all)	18	4	5
Ear and labyrinth disorders			

Ear Pain			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Vertigo			
subjects affected / exposed	0 / 51 (0.00%)	3 / 52 (5.77%)	0 / 50 (0.00%)
occurrences (all)	0	3	0
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Eye Swelling			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Ocular Hyperaemia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Vision Blurred			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
Abdominal Discomfort			
subjects affected / exposed	3 / 51 (5.88%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences (all)	3	1	0
Abdominal Distension			
subjects affected / exposed	4 / 51 (7.84%)	2 / 52 (3.85%)	0 / 50 (0.00%)
occurrences (all)	12	4	0
Abdominal Pain			
subjects affected / exposed	12 / 51 (23.53%)	11 / 52 (21.15%)	1 / 50 (2.00%)
occurrences (all)	16	23	1
Abdominal Pain Lower			
subjects affected / exposed	3 / 51 (5.88%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences (all)	5	1	0
Abdominal Pain Upper			
subjects affected / exposed	8 / 51 (15.69%)	7 / 52 (13.46%)	3 / 50 (6.00%)
occurrences (all)	16	10	4
Anal Fissure			

subjects affected / exposed	3 / 51 (5.88%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences (all)	5	1	0
Anal Pruritus			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Anorectal Discomfort			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Aphthous Stomatitis			
subjects affected / exposed	2 / 51 (3.92%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences (all)	3	1	0
Cheilitis			
subjects affected / exposed	3 / 51 (5.88%)	1 / 52 (1.92%)	1 / 50 (2.00%)
occurrences (all)	3	2	1
Constipation			
subjects affected / exposed	6 / 51 (11.76%)	19 / 52 (36.54%)	9 / 50 (18.00%)
occurrences (all)	6	30	10
Diarrhoea			
subjects affected / exposed	43 / 51 (84.31%)	37 / 52 (71.15%)	17 / 50 (34.00%)
occurrences (all)	199	134	22
Dry Mouth			
subjects affected / exposed	2 / 51 (3.92%)	6 / 52 (11.54%)	3 / 50 (6.00%)
occurrences (all)	2	6	3
Dyspepsia			
subjects affected / exposed	6 / 51 (11.76%)	6 / 52 (11.54%)	6 / 50 (12.00%)
occurrences (all)	9	7	7
Flatulence			
subjects affected / exposed	4 / 51 (7.84%)	3 / 52 (5.77%)	0 / 50 (0.00%)
occurrences (all)	10	3	0
Gastric Haemorrhage			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	3 / 51 (5.88%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	3	0	0
Gastrooesophageal Reflux Disease			

subjects affected / exposed	2 / 51 (3.92%)	2 / 52 (3.85%)	0 / 50 (0.00%)
occurrences (all)	2	3	0
Gingival Bleeding			
subjects affected / exposed	0 / 51 (0.00%)	2 / 52 (3.85%)	0 / 50 (0.00%)
occurrences (all)	0	4	0
Glossitis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Glossodynia			
subjects affected / exposed	0 / 51 (0.00%)	2 / 52 (3.85%)	0 / 50 (0.00%)
occurrences (all)	0	2	0
Haemorrhoidal Haemorrhage			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	2 / 51 (3.92%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences (all)	2	1	0
Lip Discolouration			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Mouth Ulceration			
subjects affected / exposed	5 / 51 (9.80%)	0 / 52 (0.00%)	5 / 50 (10.00%)
occurrences (all)	7	0	9
Nausea			
subjects affected / exposed	22 / 51 (43.14%)	32 / 52 (61.54%)	8 / 50 (16.00%)
occurrences (all)	50	59	12
Oral Mucosal Blistering			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Oral Pain			
subjects affected / exposed	6 / 51 (11.76%)	5 / 52 (9.62%)	1 / 50 (2.00%)
occurrences (all)	6	6	1
Paraesthesia Oral			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Stomatitis			

subjects affected / exposed occurrences (all)	15 / 51 (29.41%) 29	13 / 52 (25.00%) 27	21 / 50 (42.00%) 28
Toothache subjects affected / exposed occurrences (all)	5 / 51 (9.80%) 6	3 / 52 (5.77%) 3	1 / 50 (2.00%) 1
Vomiting subjects affected / exposed occurrences (all)	24 / 51 (47.06%) 50	20 / 52 (38.46%) 50	6 / 50 (12.00%) 6
Hepatobiliary disorders Dilatation Intrahepatic Duct Acquired subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	0 / 52 (0.00%) 0	0 / 50 (0.00%) 0
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3	1 / 52 (1.92%) 1	3 / 50 (6.00%) 3
Dermatitis Acneiform subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	0 / 52 (0.00%) 0	1 / 50 (2.00%) 2
Dry Skin subjects affected / exposed occurrences (all)	5 / 51 (9.80%) 7	3 / 52 (5.77%) 4	3 / 50 (6.00%) 4
Ecchymosis subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	0 / 52 (0.00%) 0	0 / 50 (0.00%) 0
Erythema subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	1 / 52 (1.92%) 1	2 / 50 (4.00%) 2
Erythema Multiforme subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	0 / 52 (0.00%) 0	0 / 50 (0.00%) 0
Hyperhidrosis subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2	0 / 52 (0.00%) 0	1 / 50 (2.00%) 1
Hyperkeratosis			

subjects affected / exposed	2 / 51 (3.92%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences (all)	2	0	1
Night Sweats			
subjects affected / exposed	0 / 51 (0.00%)	2 / 52 (3.85%)	2 / 50 (4.00%)
occurrences (all)	0	2	3
Onychoclasia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	3 / 50 (6.00%)
occurrences (all)	0	0	3
Palmar-Plantar Erythrodysaesthesia Syndrome			
subjects affected / exposed	4 / 51 (7.84%)	8 / 52 (15.38%)	2 / 50 (4.00%)
occurrences (all)	10	19	3
Petechiae			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	7 / 51 (13.73%)	3 / 52 (5.77%)	7 / 50 (14.00%)
occurrences (all)	9	5	7
Rash			
subjects affected / exposed	9 / 51 (17.65%)	8 / 52 (15.38%)	11 / 50 (22.00%)
occurrences (all)	11	17	19
Rash Erythematous			
subjects affected / exposed	2 / 51 (3.92%)	3 / 52 (5.77%)	4 / 50 (8.00%)
occurrences (all)	2	3	5
Rash Macular			
subjects affected / exposed	1 / 51 (1.96%)	2 / 52 (3.85%)	5 / 50 (10.00%)
occurrences (all)	1	3	5
Skin Mass			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Skin Ulcer			
subjects affected / exposed	1 / 51 (1.96%)	2 / 52 (3.85%)	1 / 50 (2.00%)
occurrences (all)	1	4	1
Renal and urinary disorders			
Haematuria			

subjects affected / exposed	2 / 51 (3.92%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences (all)	2	1	0
Nocturia			
subjects affected / exposed	0 / 51 (0.00%)	2 / 52 (3.85%)	3 / 50 (6.00%)
occurrences (all)	0	2	3
Pollakiuria			
subjects affected / exposed	0 / 51 (0.00%)	2 / 52 (3.85%)	4 / 50 (8.00%)
occurrences (all)	0	2	4
Proteinuria			
subjects affected / exposed	13 / 51 (25.49%)	16 / 52 (30.77%)	7 / 50 (14.00%)
occurrences (all)	39	82	8
Renal Failure Acute			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Renal Failure Chronic			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Renal Mass			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	12 / 51 (23.53%)	19 / 52 (36.54%)	1 / 50 (2.00%)
occurrences (all)	16	21	1
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	14 / 51 (27.45%)	13 / 52 (25.00%)	7 / 50 (14.00%)
occurrences (all)	20	27	7
Back Pain			
subjects affected / exposed	11 / 51 (21.57%)	11 / 52 (21.15%)	7 / 50 (14.00%)
occurrences (all)	22	13	11
Bone Pain			

subjects affected / exposed	2 / 51 (3.92%)	4 / 52 (7.69%)	2 / 50 (4.00%)
occurrences (all)	3	5	2
Flank Pain			
subjects affected / exposed	2 / 51 (3.92%)	2 / 52 (3.85%)	2 / 50 (4.00%)
occurrences (all)	2	2	4
Groin Pain			
subjects affected / exposed	4 / 51 (7.84%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences (all)	5	1	0
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Muscle Spasms			
subjects affected / exposed	1 / 51 (1.96%)	1 / 52 (1.92%)	2 / 50 (4.00%)
occurrences (all)	1	2	2
Muscular Weakness			
subjects affected / exposed	2 / 51 (3.92%)	3 / 52 (5.77%)	0 / 50 (0.00%)
occurrences (all)	2	4	0
Musculoskeletal Chest Pain			
subjects affected / exposed	8 / 51 (15.69%)	7 / 52 (13.46%)	2 / 50 (4.00%)
occurrences (all)	14	9	4
Musculoskeletal Pain			
subjects affected / exposed	4 / 51 (7.84%)	8 / 52 (15.38%)	1 / 50 (2.00%)
occurrences (all)	8	16	2
Myalgia			
subjects affected / exposed	4 / 51 (7.84%)	7 / 52 (13.46%)	1 / 50 (2.00%)
occurrences (all)	5	14	1
Neck Pain			
subjects affected / exposed	2 / 51 (3.92%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences (all)	2	0	1
Pain In Jaw			
subjects affected / exposed	3 / 51 (5.88%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences (all)	3	1	0
Pain in Extremity			
subjects affected / exposed	6 / 51 (11.76%)	6 / 52 (11.54%)	3 / 50 (6.00%)
occurrences (all)	7	15	9
Spinal Osteoarthritis			

subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	0 / 52 (0.00%) 0	0 / 50 (0.00%) 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 51 (3.92%)	4 / 52 (7.69%)	1 / 50 (2.00%)
occurrences (all)	3	5	1
Cellulitis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Gingivitis			
subjects affected / exposed	3 / 51 (5.88%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	3	0	0
Infectious Pleural Effusion			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	1 / 51 (1.96%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences (all)	2	1	0
Lower Respiratory Tract Infection			
subjects affected / exposed	2 / 51 (3.92%)	4 / 52 (7.69%)	4 / 50 (8.00%)
occurrences (all)	4	4	4
Lymph Gland Infection			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	7 / 51 (13.73%)	4 / 52 (7.69%)	7 / 50 (14.00%)
occurrences (all)	9	5	8
Oral Herpes			
subjects affected / exposed	1 / 51 (1.96%)	1 / 52 (1.92%)	3 / 50 (6.00%)
occurrences (all)	1	1	3
Osteomyelitis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Paronychia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0

Pneumonia			
subjects affected / exposed	2 / 51 (3.92%)	1 / 52 (1.92%)	1 / 50 (2.00%)
occurrences (all)	2	1	1
Respiratory Tract Infection			
subjects affected / exposed	4 / 51 (7.84%)	4 / 52 (7.69%)	1 / 50 (2.00%)
occurrences (all)	4	4	1
Sinusitis			
subjects affected / exposed	2 / 51 (3.92%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Skin Infection			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Upper Respiratory Tract Infection			
subjects affected / exposed	4 / 51 (7.84%)	7 / 52 (13.46%)	7 / 50 (14.00%)
occurrences (all)	4	9	12
Urinary Tract Infection			
subjects affected / exposed	0 / 51 (0.00%)	4 / 52 (7.69%)	3 / 50 (6.00%)
occurrences (all)	0	4	4
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	27 / 51 (52.94%)	30 / 52 (57.69%)	10 / 50 (20.00%)
occurrences (all)	41	53	12
Dehydration			
subjects affected / exposed	2 / 51 (3.92%)	1 / 52 (1.92%)	1 / 50 (2.00%)
occurrences (all)	2	1	1
Failure to Thrive			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Hypercalcaemia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	2
Hypercholesterolaemia			
subjects affected / exposed	18 / 51 (35.29%)	6 / 52 (11.54%)	8 / 50 (16.00%)
occurrences (all)	42	9	8
Hyperglycaemia			

subjects affected / exposed	8 / 51 (15.69%)	3 / 52 (5.77%)	12 / 50 (24.00%)
occurrences (all)	11	4	44
Hyperkalaemia			
subjects affected / exposed	1 / 51 (1.96%)	3 / 52 (5.77%)	1 / 50 (2.00%)
occurrences (all)	1	3	1
Hyperlipidaemia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	7
Hypernatraemia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Hypertriglyceridaemia			
subjects affected / exposed	18 / 51 (35.29%)	7 / 52 (13.46%)	12 / 50 (24.00%)
occurrences (all)	79	18	14
Hypocalcaemia			
subjects affected / exposed	4 / 51 (7.84%)	3 / 52 (5.77%)	2 / 50 (4.00%)
occurrences (all)	8	4	2
Hypokalaemia			
subjects affected / exposed	7 / 51 (13.73%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences (all)	12	0	2
Hypomagnesaemia			
subjects affected / exposed	1 / 51 (1.96%)	4 / 52 (7.69%)	0 / 50 (0.00%)
occurrences (all)	1	4	0
Hyponatraemia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Hypophagia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Hypovolaemia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Malnutrition			

subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Metabolic Acidosis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 52 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 March 2011	Phase 1b Amendment 01: Change in inclusion criteria with regard to subjects who were treated with Afinitor (everolimus) and change with regard to contraceptive use in subjects. Change in dose reduction and interruption instructions for subjects who experienced lenvatinib-everolimus combination therapy related toxicity and single agent lenvatinib-related toxicity for subjects with tolerable Grade 2 toxicities.
09 July 2012	Phase 1b Amendment 02: Change in dose reduction and interruption instructions for subjects who experienced lenvatinib-everolimus combination therapy-related toxicity and single agent lenvatinib-related toxicity.
28 February 2013	Phase 1b Amendment 03: Window of consent was extended so that informed consent could be signed up to 8 weeks before the first dose of study drug was administered. Phase 2 eligibility criteria were revised to include subjects with evidence of disease progression on or within 9 months of stopping prior therapy instead of 6 months. Phase 2 eligibility criteria were revised from 1 prior VEGF-targeted treatment for unresectable advanced or metastatic RCC to 1 prior disease progression episode on or after VEGF-targeted treatment to allow subjects to have had, for example, 2 prior VEGF-targeted treatments if 1 of these was given in the adjuvant setting. Additional information on dose adjustment for special populations who received everolimus was added to reflect changes in everolimus prescribing information (January 2013). Modification allowed concomitant therapies to allow bisphosphonates to be administered as prescribed by the treating physician. The 12 hour PK sampling time point was made optional, and the intensive PK sampling was to be made mandatory if an insufficient number of subjects entered voluntarily. Vital sign measurements were changed from supine to resting. Definition of end of study was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported