Clinical trial results:
An Open-Label, Multicenter, Randomized, Phase 1b/2 Study of Golvatinib (E7050) in Combination with Sorafenib versus Sorafenib Alone as First Line Therapy in Patients with Hepatocellular Carcinoma

Summary

EudraCT number	2011-000752-41
Trial protocol	ES BE GB IT
Global end of trial date	23 June 2015

Results information

Result version number	v1 (current)
This version publication date	10 June 2021
First version publication date	10 June 2021

Trial information

Trial identification

Sponsor protocol code	E7050-701

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01271504
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai Inc.
Sponsor organisation address	155 Tice Boulevard, Woodcliff Lake, United States, 07677
Public contact	Eisai Medical Information, Eisai Inc., +1 888-274-2378, esi_oncmedinfo@eisai.com
Scientific contact	Eisai Medical Information, Eisai Inc., +1 888-274-2378, esi_oncmedinfo@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	23 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 June 2015
Global end of trial reached?	Yes
Global end of trial date	23 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose for Phase Ib was to determine the maximum-tolerated dose (MTD)/recommended Phase 2 dose (RP2D) and characterize the pharmacokinetics (PK) of golvatinib (E7050) when administered in combination with sorafenib in subjects with locally advanced or metastatic hepatocellular carcinoma (HCC) and for Phase 2 was to evaluate the safety and tolerability of golvatinib (E7050) when administered in combination with sorafenib as compared with sorafenib alone in subjects with locally advanced or metastatic HCC.

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 on 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 Registration of 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 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	19 July 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Ukraine: 14
Country: Number of subjects enrolled	United States: 32
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	Italy: 10
Worldwide total number of subjects	102
EEA total number of subjects	37

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)	50
From 65 to 84 years	51
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 23 investigative sites in Belgium, Italy, Spain, the Ukraine, the United Kingdom and the United States from 19 July 2011 to 23 June 2015.

Pre-assignment

Screening details:

A total of 102 subjects were enrolled and randomized in this study, out of which, 15 subjects were enrolled in Phase 1b of study, of which 14 received study drug, and 87 subjects were enrolled in Phase 2 of study, of which 84 subjects received the study drug.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1b: Golvatinib 200 mg + Sorafenib 400 mg

Arm description:

Subjects received golvatinib 200 mg, tablet, orally, once daily in combination with sorafenib 400milligram (mg), tablet, orally, twice daily in 28-days treatment cycles until the occurrence of progressive disease (PD), unacceptable toxicity, withdrawal of consent, withdrawal by the Investigator, lost to follow-up, or death, whichever occurred first (Up to 513 Days).

Arm type	Experimental
Investigational medicinal product name	Golvatinib
Investigational medicinal product code	E7050
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Golvatinib 200 mg, tablet, orally, once daily in 28-days treatment cycles until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the Investigator, lost to follow-up, or death, whichever occurred first (Up to 513 Days).

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

Dosage and administration details:

Sorafenib 400 mg, tablet, orally, twice daily in 28-days treatment cycles until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the Investigator, lost to follow-up, or death, whichever occurred first (Up to 513 Days).

Arm title	Phase 1b: Golvatinib 300 mg + Sorafenib 400 mg

Arm description:

Subjects received golvatinib 300 mg, tablet, orally, once daily in combination with sorafenib 400 mg, tablet, orally, twice daily in 28-days treatment cycles until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the Investigator, lost to follow-up, or death, whichever occurred first (Up to 513 Days).

Arm type	Experimental

Investigational medicinal product name	Golvatinib
Investigational medicinal product code	E7050
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Golvatinib 300 mg, tablet, orally, once daily in 28-days treatment cycles until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the Investigator, lost to follow-up, or death, whichever occurred first (Up to 513 Days).

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

Dosage and administration details:

Sorafenib 400 mg, tablet, orally, twice daily in 28-days treatment cycles until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the Investigator, lost to follow-up, or death, whichever occurred first (Up to 513 Days).

Arm title	Phase 2: Golvatinib 200 mg + Sorafenib 400 mg

Arm description:

Subjects received golvatinib 200 mg, tablet, orally, once daily in combination with sorafenib 400 mg, tablet, orally, twice daily in 28-days treatment cycles until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the Investigator, lost to follow-up, or death, whichever occurred first (Up to 705 Days).

Arm type	Experimental
Investigational medicinal product name	Golvatinib
Investigational medicinal product code	E7050
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Golvatinib 200 mg, tablet, orally, once daily in 28-days treatment cycles until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the Investigator, lost to follow-up, or death, whichever occurred first (Up to 705 Days).

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

Dosage and administration details:

Sorafenib 400 mg, tablet, orally, twice daily in 28-days treatment cycles until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the Investigator, lost to follow-up, or death, whichever occurred first (Up to 705 Days).

Arm title	Phase 2: Sorafenib 400 mg

Arm description:

Subjects received sorafenib 400 mg, tablet, orally, twice daily in 28-days treatment cycles until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the Investigator, lost to follow-up, or death, whichever occurred first (Up to 705 Days).

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

Dosage and administration details:

Sorafenib 400 mg, tablet, orally, twice daily in 28-days treatment cycles until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the Investigator, lost to follow-up, or death, whichever occurred first (Up to 513 Days).

Number of subjects in period 1[1]	Phase 1b: Golvatinib 200 mg + Sorafenib 400 mg	Phase 1b: Golvatinib 300 mg + Sorafenib 400 mg	Phase 2: Golvatinib 200 mg + Sorafenib 400 mg
Started	7	7	42
Completed	0	0	0
Not completed	7	7	42
Consent withdrawn by subject	-	-	1
Death	7	6	32
Administrative reasons	-	-	6
Lost to follow-up	-	1	3
Consent withdrawn by subject	-	-	-
Protocol deviation	-	-	-

Number of subjects in period 1[1]	Phase 2: Sorafenib 400 mg
Started	42
Completed	0
Not completed	42
Consent withdrawn by subject	-
Death	32
Administrative reasons	5
Lost to follow-up	1
Consent withdrawn by subject	2
Protocol deviation	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects in the Baseline period are those who received study treatment.

Baseline characteristics

Reporting groups	
Reporting group title	Phase 1b: Golvatinib 200 mg + Sorafenib 400 mg
Reporting group description:	
Subjects received golvatinib 200 mg, tablet, orally, once daily in combination with sorafenib 400milligram (mg), tablet, orally, twice daily in 28-days treatment cycles until the occurrence of progressive disease (PD), unacceptable toxicity, withdrawal of consent, withdrawal by the Investigator, lost to follow-up, or death, whichever occurred first (Up to 513 Days).	
Reporting group title	Phase 1b: Golvatinib 300 mg + Sorafenib 400 mg
Reporting group description:	
Subjects received golvatinib 300 mg, tablet, orally, once daily in combination with sorafenib 400 mg, tablet, orally, twice daily in 28-days treatment cycles until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the Investigator, lost to follow-up, or death, whichever occurred first (Up to 513 Days).	
Reporting group title	Phase 2: Golvatinib 200 mg + Sorafenib 400 mg
Reporting group description:	
Subjects received golvatinib 200 mg, tablet, orally, once daily in combination with sorafenib 400 mg, tablet, orally, twice daily in 28-days treatment cycles until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the Investigator, lost to follow-up, or death, whichever occurred first (Up to 705 Days).	
Reporting group title	Phase 2: Sorafenib 400 mg
Reporting group description:	
Subjects received sorafenib 400 mg, tablet, orally, twice daily in 28-days treatment cycles until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the Investigator, lost to follow-up, or death, whichever occurred first (Up to 705 Days).	

Reporting group values	Phase 1b: Golvatinib 200 mg + Sorafenib 400 mg	Phase 1b: Golvatinib 300 mg + Sorafenib 400 mg	Phase 2: Golvatinib 200 mg + Sorafenib 400 mg
Number of subjects	7	7	42
Age categorical Units: subjects			
Age continuous Units: years			
arithmetic mean	52.9	68.1	63.2
standard deviation	± 15.68	± 9.56	± 9.31
Gender categorical Units: Subjects			
Female	1	2	10
Male	6	5	32
Ethnicity Units: Subjects			
Hispanic or Latino	0	2	1
Not Hispanic or Latino	7	5	36
Unknown or Not Reported	0	0	5
Race Units: Subjects			
American Indian or Alaska Native	0	2	0
Black or African American	0	0	4
White	7	5	37
Unknown or Not Reported	0	0	1

Asian	0	0	0

Reporting group values	Phase 2: Sorafenib 400 mg	Total	
Number of subjects	42	98	
Age categorical Units: subjects			
Age continuous Units: years			
arithmetic mean	65.8		
standard deviation	± 8.02	-	
Gender categorical Units: Subjects			
Female	12	25	
Male	30	73	
Ethnicity Units: Subjects			
Hispanic or Latino	5	8	
Not Hispanic or Latino	36	84	
Unknown or Not Reported	1	6	
Race Units: Subjects			
American Indian or Alaska Native	0	2	
Black or African American	1	5	
White	37	86	
Unknown or Not Reported	3	4	
Asian	1	1	

End points

End points reporting groups

Reporting group title	Phase 1b: Golvatinib 200 mg + Sorafenib 400 mg

Reporting group description:

Subjects received golvatinib 200 mg, tablet, orally, once daily in combination with sorafenib 400milligram (mg), tablet, orally, twice daily in 28-days treatment cycles until the occurrence of progressive disease (PD), unacceptable toxicity, withdrawal of consent, withdrawal by the Investigator, lost to follow-up, or death, whichever occurred first (Up to 513 Days).

Reporting group title	Phase 1b: Golvatinib 300 mg + Sorafenib 400 mg

Reporting group description:

Subjects received golvatinib 300 mg, tablet, orally, once daily in combination with sorafenib 400 mg, tablet, orally, twice daily in 28-days treatment cycles until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the Investigator, lost to follow-up, or death, whichever occurred first (Up to 513 Days).

Reporting group title	Phase 2: Golvatinib 200 mg + Sorafenib 400 mg

Reporting group description:

Subjects received golvatinib 200 mg, tablet, orally, once daily in combination with sorafenib 400 mg, tablet, orally, twice daily in 28-days treatment cycles until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the Investigator, lost to follow-up, or death, whichever occurred first (Up to 705 Days).

Reporting group title	Phase 2: Sorafenib 400 mg

Reporting group description:

Subjects received sorafenib 400 mg, tablet, orally, twice daily in 28-days treatment cycles until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the Investigator, lost to follow-up, or death, whichever occurred first (Up to 705 Days).

Primary: Phase 1b: Number of Subjects Who Experienced Any Dose Limiting Toxicity (DLT)

End point title	Phase 1b: Number of Subjects Who Experienced Any Dose Limiting Toxicity (DLT)[1][2]

End point description:

DLTs were defined as clinically significant adverse events (AEs) (non-hematological, hematological and other events) occurring less than or equal to (<=) 28 days after commencing study treatment and considered to be at least possibly or probably related to study drug by the Investigator. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v.4.0). Safety analysis set included all subjects enrolled and randomized into the Phase 1b of this study, except those who dropped out of the study prior to receiving any study drug, or were without any safety assessment after first dose of study drug.

End point type	Primary

End point timeframe:

Cycle 1 (Cycle length is 28 days)

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 was planned to be analyzed 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: This outcome measure was planned to be assessed only for subjects treated in Phase 1b arm.

End point values	Phase 1b: Golvatinib 200 mg + Sorafenib 400 mg	Phase 1b: Golvatinib 300 mg + Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	7		
Units: subject	1	2		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1b: Cmax: Maximum Observed Plasma Concentration for Golvatinib When Administered in Combination With Sorafenib at Day -7

End point title	Phase 1b: Cmax: Maximum Observed Plasma Concentration for Golvatinib When Administered in Combination With Sorafenib at Day -7[3][4]

End point description:

Pharmacokinetic (PK) analysis set was defined as all subjects in the safety population who had sufficient concentration data to derive one or more of the PK parameters.

End point type	Primary

End point timeframe:

Day -7: 0-72 hours post-dose

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 was planned to be analyzed for this end point.

[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: This outcome measure was planned to be assessed only for subjects treated in Phase 1b arm.

End point values	Phase 1b: Golvatinib 200 mg + Sorafenib 400 mg	Phase 1b: Golvatinib 300 mg + Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)	1330 (± 858)	2320 (± 2720)		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1b: Cmax: Maximum Observed Plasma Concentration for Golvatinib When Administered in Combination With Sorafenib at Day 1 Cycle 1

End point title	Phase 1b: Cmax: Maximum Observed Plasma Concentration for Golvatinib When Administered in Combination With Sorafenib at Day 1 Cycle 1[5][6]

End point description:

PK analysis set was defined as all subjects in the safety population who had sufficient concentration data to derive one or more of the PK parameters.

End point type	Primary

End point timeframe:

Cycle 1 Day 1: 0-24 hours post-dose (Cycle length is 28 days)

Notes:

[5] - 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 was planned to be analyzed for this end point.

[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: This outcome measure was planned to be assessed only for subjects treated in Phase 1b arm.

End point values	Phase 1b: Golvatinib 200 mg + Sorafenib 400 mg	Phase 1b: Golvatinib 300 mg + Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: ng/mL				
arithmetic mean (standard deviation)	1820 (± 750)	2820 (± 3170)		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1b: Cmax: Maximum Observed Plasma Concentration for Golvatinib When Administered in Combination With Sorafenib at Day 28 Cycle 1

End point title	Phase 1b: Cmax: Maximum Observed Plasma Concentration for Golvatinib When Administered in Combination With Sorafenib at Day 28 Cycle 1[7][8]

End point description:

PK analysis set was defined as all subjects in the safety population who had sufficient concentration data to derive one or more of the PK parameters. Here, overall number analyzed "N" were the subjects who were evaluable for the outcome measure.

End point type	Primary

End point timeframe:

Cycle 1 Day 28: 0-24 hours post-dose

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this end point.

[8] - 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: This outcome measure was planned to be assessed only for subjects treated in Phase 1b arm.

End point values	Phase 1b: Golvatinib 200 mg + Sorafenib 400 mg	Phase 1b: Golvatinib 300 mg + Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	4		
Units: ng/mL				
arithmetic mean (standard deviation)	2140 (± 757)	4570 (± 3610)		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1b: Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Golvatinib When Administered in Combination With Sorafenib at Day -7

End point title	Phase 1b: Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Golvatinib When Administered in Combination With Sorafenib at Day -7[9][10]

End point description:

PK analysis set was defined as all subjects in the safety population who had sufficient concentration data to derive one or more of the PK parameters.

End point type	Primary

End point timeframe:

Day -7: 0-72 hours post-dose

Notes:

[9] - 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 was planned to be analyzed for this end point.

[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: This outcome measure was planned to be assessed only for subjects treated in Phase 1b arm.

End point values	Phase 1b: Golvatinib 200 mg + Sorafenib 400 mg	Phase 1b: Golvatinib 300 mg + Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: hour				
arithmetic mean (full range (min-max))	2 (1.03 to 24.3)	2.38 (1 to 4)		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1b: Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Golvatinib When Administered in Combination With Sorafenib at Day 1

Cycle 1

End point title	Phase 1b: Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Golvatinib When Administered in Combination With Sorafenib at Day 1 Cycle 1[11][12]

End point description:

PK analysis set was defined as all subjects in the safety population who had sufficient concentration data to derive one or more of the PK parameters.

End point type	Primary

End point timeframe:

Cycle 1 Day 1: 0-24 hours post-dose (Cycle length is 28 days)

Notes:

[11] - 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 was planned to be analyzed for this end point.

[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: This outcome measure was planned to be assessed only for subjects treated in Phase 1b arm.

End point values	Phase 1b: Golvatinib 200 mg + Sorafenib 400 mg	Phase 1b: Golvatinib 300 mg + Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	4		
Units: hour				
median (full range (min-max))	3 (2 to 23.8)	3.53 (2 to 24)		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1b: Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Golvatinib When Administered in Combination With Sorafenib at Day 28 Cycle 1

End point title	Phase 1b: Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Golvatinib When Administered in Combination With Sorafenib at Day 28 Cycle 1[13][14]

End point description:

PK analysis set was defined as all subjects in the safety population who had sufficient concentration data to derive one or more of the PK parameters. Here, overall number analyzed "N" were the subjects who were evaluable for the outcome measure.

End point type	Primary

End point timeframe:

Cycle 1 Day 28: 0-24 hours post-dose

Notes:

[13] - 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 was planned to be analyzed for this end point.

[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: This outcome measure was planned to be assessed only for subjects treated in Phase 1b arm.

End point values	Phase 1b: Golvatinib 200 mg + Sorafenib 400 mg	Phase 1b: Golvatinib 300 mg + Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	4		
Units: hour				
median (full range (min-max))	2.98 (1.08 to 4.03)	5.01 (0.833 to 23.5)		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1b: AUCt: Area Under the Plasma Concentration-time Curve From Time 0 to Time t Over the Dosing Interval for Golvatinib When Administered in Combination With Sorafenib at Day -7

End point title	Phase 1b: AUCt: Area Under the Plasma Concentration-time Curve From Time 0 to Time t Over the Dosing Interval for Golvatinib When Administered in Combination With Sorafenib at Day -7[15][16]

End point description:

PK analysis set was defined as all subjects in the safety population who had sufficient concentration data to derive one or more of the PK parameters.

End point type	Primary

End point timeframe:

Day -7: 0-72 hours post-dose

Notes:

[15] - 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 was planned to be analyzed for this end point.

[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: This outcome measure was planned to be assessed only for subjects treated in Phase 1b arm.

End point values	Phase 1b: Golvatinib 200 mg + Sorafenib 400 mg	Phase 1b: Golvatinib 300 mg + Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: nanogram*hour per milliliter(ng*h/mL)				
arithmetic mean (standard deviation)	30400 (± 18900)	47200 (± 37500)		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1b: AUCt: Area Under the Plasma Concentration-time Curve From Time 0 to Time t Over the Dosing Interval for Golvatinib When Administered in Combination With Sorafenib at Day 1 Cycle 1

End point title	Phase 1b: AUCt: Area Under the Plasma Concentration-time Curve From Time 0 to Time t Over the Dosing Interval for Golvatinib When Administered in Combination With Sorafenib at Day 1 Cycle 1[17][18]

End point description:

PK analysis set was defined as all subjects in the safety population who had sufficient concentration data to derive one or more of the PK parameters.

End point type	Primary

End point timeframe:

Cycle 1 Day 1: 0-24 hours post-dose (Cycle length is 28 days)

Notes:

[17] - 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 was planned to be analyzed for this end point.

[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: This outcome measure was planned to be assessed only for subjects treated in Phase 1b arm.

End point values	Phase 1b: Golvatinib 200 mg + Sorafenib 400 mg	Phase 1b: Golvatinib 300 mg + Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: ng*h/mL				
arithmetic mean (standard deviation)	24000 (± 14300)	36800 (± 38000)		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1b: AUCt: Area Under the Plasma Concentration-time Curve From Time 0 to Time t Over the Dosing Interval for Golvatinib When Administered in Combination With Sorafenib at Day 28 Cycle 1

End point title	Phase 1b: AUCt: Area Under the Plasma Concentration-time Curve From Time 0 to Time t Over the Dosing Interval for Golvatinib When Administered in Combination With Sorafenib at Day 28 Cycle 1[19][20]

End point description:

PK analysis set was defined as all subjects in the safety population who had sufficient concentration data to derive one or more of the PK parameters. Here, overall number analyzed "N" were the subjects who were evaluable for the outcome measure.

End point type	Primary

End point timeframe:

Cycle 1 Day 28: 0-24 hours post-dose (Cycle length is 28 days)

Notes:

[19] - 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 was planned to be analyzed for this end point.

[20] - 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: This outcome measure was planned to be assessed only for subjects treated in Phase 2 arm.

End point values	Phase 1b: Golvatinib 200 mg + Sorafenib 400 mg	Phase 1b: Golvatinib 300 mg + Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	4		
Units: ng*h/mL				
arithmetic mean (standard deviation)	35300 (± 16700)	68700 (± 72500)		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1b: t1/2: Terminal Elimination Half-life for Golvatinib When Administered in Combination With Sorafenib at Day -7

End point title	Phase 1b: t1/2: Terminal Elimination Half-life for Golvatinib When Administered in Combination With Sorafenib at Day -7[21][22]

End point description:

PK analysis set was defined as all subjects in the safety population who had sufficient concentration data to derive one or more of the PK parameters.

End point type	Primary

End point timeframe:

Day -7: 0-72 hours post-dose

Notes:

[21] - 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 was planned to be analyzed for this end point.

[22] - 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: This outcome measure was planned to be assessed only for subjects treated in Phase 2 arm.

End point values	Phase 1b: Golvatinib 200 mg + Sorafenib 400 mg	Phase 1b: Golvatinib 300 mg + Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: hour				
arithmetic mean (standard deviation)	38.1 (± 6.82)	35.9 (± 11.7)		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Phase 2: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)[23][24]

End point description:

Safety analysis set included all subjects enrolled and randomized to treatment in the Phase 2 of this study, except for those who dropped out prior to receiving any study drug, or were without any safety assessment following the first dose of study drug.

End point type	Primary

End point timeframe:

From first dose of study drug up to 30 days after last dose of study drug (up to approximately 3 years 11 months)

Notes:

[23] - 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 was planned to be analyzed for this end point.

[24] - 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: This outcome measure was planned to be assessed only for subjects treated in Phase 2 arm.

End point values	Phase 2: Golvatinib 200 mg + Sorafenib 400 mg	Phase 2: Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: subjects				
TEAEs	42	40		
SAEs	20	17		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Number of Subjects With AEs by Severity Grades

End point title	Phase 2: Number of Subjects With AEs by Severity

End point description:

AE severity was graded using CTCAE version 4.0, where Grade 1 = mild, Grade 2 = moderate, Grade 3 = Severe, Grade 4 = Life-threatening, and Grade 5 = Death related to the AE. All AEs graded as 4 or 5

were considered to be serious. Higher grade indicates more severe condition. Safety analysis set included all subjects enrolled and randomized to treatment in the Phase 2 of this study, except for those who dropped out prior to receiving any study drug, or were without any safety assessment following the first dose of study drug. Here, overall number analyzed are those subjects who were evaluable for this outcome measure.

End point type	Primary

End point timeframe:

From first dose of study drug up to 30 days after last dose of study drug (up to approximately 3 years 11 months)

Notes:

[25] - 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 was planned to be analyzed for this end point.

[26] - 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: This outcome measure was planned to be assessed only for subjects treated in Phase 2 arm.

End point values	Phase 2: Golvatinib 200 mg + Sorafenib 400 mg	Phase 2: Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	40		
Units: subjects				
Any AE: Grade 1	0	2		
Any AE: Grade 2	4	6		
Any AE: Grade 3	24	25		
Any AE: Grade 4	6	5		
Any AE: Grade 5	8	2		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Number of Subjects With Adverse Events Related to Vital Signs

End point title	Phase 2: Number of Subjects With Adverse Events Related to Vital Signs[27][28]

End point description:

Number of subjects are reported with AEs related to Vital signs including body temperature, respiratory rate, heart rate, height, and weight. Safety analysis set included all subjects enrolled and randomized to treatment in the Phase 2 of this study, except for those who dropped out prior to receiving any study drug, or were without any safety assessment following the first dose of study drug.

End point type	Primary

End point timeframe:

From first dose of study drug up to 30 days after last dose of study drug (up to approximately 3 years 11 months)

Notes:

[27] - 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 was planned to be analyzed for this end point.

[28] - 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: This outcome measure was planned to be assessed only for subjects treated in Phase 2 arm.

End point values	Phase 2: Golvatinib 200 mg + Sorafenib 400 mg	Phase 2: Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: subjects	2	0		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Number of Subjects With Clinically Significant Change From Baseline in Blood Pressure Including Systolic and Diastolic Blood Pressures

End point title	Phase 2: Number of Subjects With Clinically Significant Change From Baseline in Blood Pressure Including Systolic and Diastolic Blood Pressures[29][30]

End point description:

Safety analysis set included all subjects enrolled and randomized to treatment in the Phase 2 of this study, except for those who dropped out prior to receiving any study drug, or were without any safety assessment following the first dose of study drug.

End point type	Primary

End point timeframe:

From first dose of study drug up to 30 days after last dose of study drug (up to approximately 3 years 11 months)

Notes:

[29] - 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 was planned to be analyzed for this end point.

[30] - 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: This outcome measure was planned to be assessed only for subjects treated in Phase 2 arm.

End point values	Phase 2: Golvatinib 200 mg + Sorafenib 400 mg	Phase 2: Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Number of Subjects With Worst Shifts Post Baseline in Eastern Cooperative Oncology Group Performance Status (ECOG-PS)

End point title	Phase 2: Number of Subjects With Worst Shifts Post Baseline in Eastern Cooperative Oncology Group Performance Status (ECOG-PS)[31][32]

End point description:

Number of subjects with worst shifts post baseline in ECOG-PS levels were reported. ECOG had 6 levels (0-5). Level 0 is best status (fully active, able to carry on all pre-disease performance without restriction);Level 1: mildly restricted (Restricted in physically strenuous activity but ambulatory ad able to carry out work of a light/sedentary nature, e.g. light house work, office work);Level 2: more restricted (Ambulatory and capable of selfcare but unable to carry out any work activities;up and about more than 50% of waking hours); Level 3: restricted (Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours);Level 4: highly restricted (completely disabled; cannot carry on any selfcare; totally confined to bed/chair) and Level 5:death. Safety analysis set:all subjects enrolled and randomized to treatment in Phase 2 of study, except who dropped out prior to receiving study drug/were without any safety assessment following first dose of study drug.

End point type	Primary

End point timeframe:

From first dose of study drug up to 30 days after last dose of study drug (up to approximately 3 years 11 months)

Notes:

[31] - 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 was planned to be analyzed for this end point.

[32] - 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: This outcome measure was planned to be assessed only for subjects treated in Phase 2 arm.

End point values	Phase 2: Golvatinib 200 mg + Sorafenib 400 mg	Phase 2: Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: Subjects				
ECOG PS Level change from 0 to 1	7	4		
ECOG PS Level change from 0 to 2	3	7		
ECOG PS Level change from 0 to 3	3	0		
ECOG PS Level change from 1 to 2	4	6		
ECOG PS Level change from 0 to 4	0	1		
ECOG PS Level change from 1 to 3	0	5		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Number of Subjects With Clinically Significant Change From Baseline in Laboratory Values

End point title	Phase 2: Number of Subjects With Clinically Significant Change From Baseline in Laboratory Values[33][34]

End point description:

Safety analysis set included all subjects enrolled and randomized to treatment in the Phase 2 of this study, except for those who dropped out prior to receiving any study drug, or were without any safety

assessment following the first dose of study drug.

End point type	Primary

End point timeframe:

From first dose of study drug up to 30 days after last dose of study drug (up to approximately 3 years 11 months)

Notes:

[33] - 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 was planned to be analyzed for this end point.

[34] - 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: This outcome measure was planned to be assessed only for subjects treated in Phase 2 arm.

End point values	Phase 2: Golvatinib 200 mg + Sorafenib 400 mg	Phase 2: Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Number of Subjects With Markedly Abnormal Change From Baseline in Electrocardiograms (ECGs) Parameters

End point title	Phase 2: Number of Subjects With Markedly Abnormal Change From Baseline in Electrocardiograms (ECGs) Parameters[35][36]

End point description:

Safety analysis set included all subjects enrolled and randomized to treatment in the Phase 2 of this study, except for those who dropped out prior to receiving any study drug, or were without any safety assessment following the first dose of study drug.

End point type	Primary

End point timeframe:

From first dose of study drug up to 30 days after last dose of study drug (up to approximately 3 years 11 months)

Notes:

[35] - 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 was planned to be analyzed for this end point.

[36] - 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: This outcome measure was planned to be assessed only for subjects treated in Phase 2 arm.

End point values	Phase 2: Golvatinib 200 mg + Sorafenib 400 mg	Phase 2: Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Time to Progression (TTP)

End point title	Phase 2: Time to Progression (TTP)[37]

End point description:

TTP was defined as the time from the date of randomization until the date of PD of such subject's disease based on independent assessments according to Response Evaluation Criteria in Solid Tumors (RECIST) version (v) 1.1. PD was defined as at least a 20% increase or 5 millimeter (mm) increase in the sum of diameters of target lesions (taking as reference the smallest sum on study) recorded since the treatment started or the appearance of 1 or more new lesions. TTP was estimated and analyzed using Kaplan-Meier (K-M) method. Modified Intent-to-Treat (MITT) set included all subjects randomized in the applicable study arm, except a subject who dropped out of such arm prior to receiving any comparator or investigative drug. Here 'N' (Overall number of subjects analyzed) signifies subjects with events (PD).

End point type	Secondary

End point timeframe:

From the date of randomization until the date of PD (up to approximately 3 years 11 months)

Notes:

[37] - 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: This outcome measure was planned to be assessed only for subjects treated in Phase 2 arm.

End point values	Phase 2: Golvatinib 200 mg + Sorafenib 400 mg	Phase 2: Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	36		
Units: weeks				
median (confidence interval 95%)	10.29 (8.57 to 17.14)	16.00 (8.57 to 23.29)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Phase 2: Golvatinib 200 mg + Sorafenib 400 mg v Phase 2: Sorafenib 400 mg

Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.5

Secondary: Phase 2: Progression Free Survival (PFS)

End point title	Phase 2: Progression Free Survival (PFS)[38]

End point description:

PFS was defined as the time from the date of randomization of a subject until (1) the date of first documented progression (2) the date of such subject's death due to any cause based on independent assessments according to RECIST v. 1.1. PD was defined as at least a 20% increase or 5 mm increase in the sum of diameters of target lesions (taking as reference the smallest sum on study) recorded since the treatment started or the appearance of 1 or more new lesions. PFS was estimated and analyzed using KM method. MITT analysis set included all subjects randomized in the applicable study arm, except a subject who dropped out of such arm prior to receiving any comparator or investigative drug. Here 'N' (Overall number of subjects analyzed) signifies subjects with events (PD or/and death).

End point type	Secondary

End point timeframe:

From the date of randomization until the earlier of the following two events: the date of PD or the date of death (Up to approximately 3 years 11 months)

Notes:

[38] - 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: This outcome measure was planned to be assessed only for subjects treated in Phase 2 arm.

End point values	Phase 2: Golvatinib 200 mg + Sorafenib 400 mg	Phase 2: Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	37		
Units: weeks				
median (confidence interval 95%)	10.29 (8.14 to 17.14)	15.57 (8.57 to 23.14)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Phase 2: Golvatinib 200 mg + Sorafenib 400 mg v Phase 2: Sorafenib 400 mg

Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.5

Secondary: Phase 2: Percentage of Subjects With PFS at Week 12

End point title	Phase 2: Percentage of Subjects With PFS at Week 12[39]

End point description:

The PFS rate at week 12 was defined as the percentage of subjects who were still alive without disease progression at 12 weeks from the date of randomization. PFS was defined as the time from the date of randomization of a subject until (1) the date of first documented progression (2) the date of such subject's death due to any cause based on independent assessments according to RECIST v. 1.1. PD was defined as at least a 20% increase or 5 mm increase in the sum of diameters of target lesions (taking as reference the smallest sum on study) recorded since the treatment started or the appearance of 1 or more new lesions. MITT analysis set included all subjects randomized in the applicable study arm, except a subject who dropped out of such arm prior to receiving any comparator or investigative drug. Here 'N' (overall number of subjects analyzed) signifies subjects with events (PD or/and death).

End point type	Secondary

End point timeframe:

At 12 weeks

Notes:

[39] - 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: This outcome measure was planned to be assessed only for subjects treated in Phase 2 arm.

End point values	Phase 2: Golvatinib 200 mg + Sorafenib 400 mg	Phase 2: Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	37		
Units: percentage of subject				
number (not applicable)	47.4	57.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Overall Survival (OS)

End point title	Phase 2: Overall Survival (OS)[40]

End point description:

OS was defined as the time from the date of randomization until the date of death. Subjects were

censored at the date of last known alive. OS was analyzed using K-M method. MITT analysis set included all subjects randomized in the applicable study arm, except a subject who dropped out of such arm prior to receiving any comparator or investigative drug.

End point type	Secondary

End point timeframe:

From the date of randomization until the date of death (Up to approximately 3 years 11 months)

Notes:

[40] - 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: This outcome measure was planned to be assessed only for subjects treated in Phase 2 arm.

End point values	Phase 2: Golvatinib 200 mg + Sorafenib 400 mg	Phase 2: Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: weeks				
median (confidence interval 95%)	27.86 (20.86 to 67.71)	37.71 (23.29 to 57.00)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Phase 2: Sorafenib 400 mg v Phase 2: Golvatinib 200 mg + Sorafenib 400 mg
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.62

Secondary: Phase 2: Percentage of Subjects With Overall Response

End point title	Phase 2: Percentage of Subjects With Overall Response[41]

End point description:

Overall response rate was defined as percentage of subjects with best confirmed response (CR) or partial response (PR) assessed by investigator per RECIST v1.1. A confirmatory scan was required after no less than 4 weeks and no later than 8 weeks, starting on the date that the response was first recorded. CR was defined as the disappearance of all target and non-target lesions (non-lymph nodes). All pathological lymph nodes (whether target or non-target) must have a reduction in their short axis to less than (<)10 mm. PR was defined as at least a 30 percent (%) decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. MITT analysis set included all subjects randomized in the applicable study arm, except a subject who dropped out of such arm prior to receiving any comparator or investigative drug.

End point type	Secondary

End point timeframe:

From the date of randomization until disease progression or death (Up to approximately 3 years 11 months)

Notes:

[41] - 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: This outcome measure was planned to be assessed only for subjects treated in Phase 2 arm.

End point values	Phase 2: Golvatinib 200 mg + Sorafenib 400 mg	Phase 2: Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: percentage of subject				
number (confidence interval 95%)	4.8 (0.0 to 11.2)	4.8 (-1.7 to 11.2)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 30 days after last dose of study drug (up to approximately 3 years 11 months)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	Phase 1b: Golvatinib 200 mg + Sorafenib 400 mg

Reporting group description:

Subjects received golvatinib 200 mg, tablet, orally, once daily in combination with sorafenib 400 mg, tablet, orally, twice daily in 28-days treatment cycles until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the Investigator, lost to follow-up, or death, whichever occurred first (Up to 513 days).

Reporting group title	Phase 1b: Golvatinib 300 mg + Sorafenib 400 mg

Reporting group description:

Subjects received golvatinib 300 mg, tablet, orally, once daily in combination with sorafenib 400 mg, tablet, orally, twice daily in 28-days treatment cycles until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the Investigator, lost to follow-up, or death, whichever occurred first (Up to 513 days).

Reporting group title	Phase 2: Golvatinib 200 mg + Sorafenib 400 mg

Reporting group description:

Subjects received golvatinib 200 mg, tablet, orally, once daily in combination with sorafenib 400 mg, tablet, orally, twice daily in 28-days treatment cycles until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the Investigator, lost to follow-up, or death, whichever occurred first (Up to 705 days).

Reporting group title	Phase 2: Sorafenib 400 mg

Reporting group description:

Subjects received sorafenib 400 mg, tablet, orally, twice daily in 28-days treatment cycles until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the Investigator, lost to follow-up, or death, whichever occurred first (Up to 705 days).

Serious adverse events	Phase 1b: Golvatinib 200 mg + Sorafenib 400 mg	Phase 1b: Golvatinib 300 mg + Sorafenib 400 mg	Phase 2: Golvatinib 200 mg + Sorafenib 400 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 7 (57.14%)	3 / 7 (42.86%)	20 / 42 (47.62%)
number of deaths (all causes)	7	6	32
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma Gastric			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (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
Malignant Neoplasm Progression			

subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Vascular disorders			
Aneurysm Ruptured			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hypertensive Crisis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General Physical Health Deterioration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema Peripheral			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (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%)	1 / 7 (14.29%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural Effusion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (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
Psychiatric disorders			
Confusional State			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Transaminases Increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (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			
Spinal Compression Fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (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			
Cardiac Arrest			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic Encephalopathy			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (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 / 7 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metabolic Encephalopathy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (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
Febrile Neutropenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
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 Distension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	3 / 42 (7.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (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
Diverticular Perforation			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (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 Ulcer			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (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
Haematemesis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (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
Haematochezia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal Varices Haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis Acute			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (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 Gastrointestinal Haemorrhage			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (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	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic Failure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hyperbilirubinaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (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
Liver Disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis Acneiform			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 42 (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
Dermatitis Psoriasiform			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (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
Palmar-Plantar Erythrodysaesthesia Syndrome			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal and urinary disorders			
Nephropathy Toxic			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (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 Failure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (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 Impairment			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (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			
Cellulitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (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 Urinary Tract Infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (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
Gastroenteritis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 42 (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
Infected Skin Ulcer			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective Exacerbation Of Chronic Obstructive Airways Disease			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Klebsiella Infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (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
Liver Abscess			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (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 / 7 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Scrotal Abscess			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (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 / 7 (0.00%)	3 / 42 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Septic Shock			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Urinary Tract Infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (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
Hypoalbuminaemia			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (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	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase 2: Sorafenib 400 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 42 (40.48%)		
number of deaths (all causes)	32		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma Gastric			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant Neoplasm Progression			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Vascular disorders			
Aneurysm Ruptured			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertensive Crisis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			

subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General Physical Health Deterioration			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oedema Peripheral			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural Effusion			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional State			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Transaminases Increased			

subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Spinal Compression Fracture			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac Arrest			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic Encephalopathy			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Ischaemic Stroke			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolic Encephalopathy			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	2 / 42 (4.76%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Febrile Neutropenia				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal Distension				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal Pain				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticular Perforation				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric Ulcer				
subjects affected / exposed	2 / 42 (4.76%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haematemesis				

subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematochezia				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal Varices Haemorrhage				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis Acute				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper Gastrointestinal Haemorrhage				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatic Failure				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperbilirubinaemia				

subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Liver Disorder				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Dermatitis Acneiform				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dermatitis Psoriasiform				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Palmar-Plantar Erythrodysaesthesia Syndrome				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Nephropathy Toxic				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal Failure				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Renal Impairment				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia Urinary Tract Infection			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infected Skin Ulcer			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infective Exacerbation Of Chronic Obstructive Airways Disease			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Klebsiella Infection			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Liver Abscess			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Scrotal Abscess				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic Shock				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary Tract Infection				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hyperkalaemia				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoalbuminaemia				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Phase 1b: Golvatinib 200 mg + Sorafenib 400 mg	Phase 1b: Golvatinib 300 mg + Sorafenib 400 mg	Phase 2: Golvatinib 200 mg + Sorafenib 400 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	6 / 7 (85.71%)	40 / 42 (95.24%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Keratoacanthoma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	7	0
Paraneoplastic syndrome			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Deep vein thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Flushing			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Haematoma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Hot flush			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	8 / 42 (19.05%)
occurrences (all)	0	1	13
Hypotension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 42 (4.76%)
occurrences (all)	0	0	2
Orthostatic hypotension			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Pallor			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Vascular insufficiency			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	12 / 42 (28.57%)
occurrences (all)	2	0	17
Chest Pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	1	0	0
Early satiety			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Face oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Facial pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	1 / 7 (14.29%)	4 / 7 (57.14%)	13 / 42 (30.95%)
occurrences (all)	1	6	21
Generalised Oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Hypothermia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Inflammation			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	2
Influenza like illness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Injection site haematoma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Localised oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Mucosal Inflammation			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	3 / 42 (7.14%)
occurrences (all)	1	1	4
Oedema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Oedema Peripheral			
subjects affected / exposed	2 / 7 (28.57%)	3 / 7 (42.86%)	5 / 42 (11.90%)
occurrences (all)	8	6	15
Pain			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	2	0	0
Pyrexia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	3 / 42 (7.14%)
occurrences (all)	4	1	3
Thirst			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Vessel Puncture Site Bruise			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Xerosis			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Drug Hypersensitivity			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Genital lesion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Nipple pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	3
Prostatic obstruction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Testicular pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Testicular swelling			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Vaginal Haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (0.00%)
occurrences (all)	0	3	0
Vaginal Polyp			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal Discomfort			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			

Asthma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	3
Dysphonia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	1 / 42 (2.38%)
occurrences (all)	1	1	1
Dyspnoea			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	1	0	1
Dyspnoea Exertional			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 42 (4.76%)
occurrences (all)	0	0	2
Epistaxis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	2 / 42 (4.76%)
occurrences (all)	1	0	2
Haemoptysis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 42 (4.76%)
occurrences (all)	0	0	2
Hiccups			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	1	0	0
Nasal dryness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 42 (2.38%)
occurrences (all)	0	1	1
Paranasal sinus hypersecretion			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	1	0	0
Pneumonitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1

Productive cough			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Pulmonary oedema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Throat tightness			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Anxiety			
subjects affected / exposed	3 / 7 (42.86%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	3	0	1
Confusional state			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Depressed mood			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Depression			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 42 (4.76%)
occurrences (all)	0	0	2
Insomnia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	5 / 42 (11.90%)
occurrences (all)	0	0	5
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 7 (14.29%)	4 / 7 (57.14%)	7 / 42 (16.67%)
occurrences (all)	1	15	12
Ammonia Increased			

subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 42 (2.38%)
occurrences (all)	0	1	1
Amylase Increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	2	0	6
Aspartate Aminotransferase Increased			
subjects affected / exposed	2 / 7 (28.57%)	5 / 7 (71.43%)	11 / 42 (26.19%)
occurrences (all)	3	22	17
Bacterial test positive			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Blood Bilirubin Increased			
subjects affected / exposed	3 / 7 (42.86%)	1 / 7 (14.29%)	3 / 42 (7.14%)
occurrences (all)	4	2	4
Blood Creatinine Increased			
subjects affected / exposed	3 / 7 (42.86%)	2 / 7 (28.57%)	1 / 42 (2.38%)
occurrences (all)	4	5	1
Blood Lactate Dehydrogenase Increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	1	0	1
Blood Thyroid Stimulating Hormone Increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (0.00%)
occurrences (all)	0	2	0
Blood albumin decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Blood urine present			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Body temperature increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Breath sounds abnormal			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Globulins increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Heart Rate Increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (0.00%)
occurrences (all)	0	2	0
Hepatitis C Virus Test Positive			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Lipase Increased			
subjects affected / exposed	1 / 7 (14.29%)	3 / 7 (42.86%)	1 / 42 (2.38%)
occurrences (all)	9	3	8
Liver Palpable Subcostal			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Oxygen saturation decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Platelet Count Decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (0.00%)
occurrences (all)	0	2	0
Protein urine present			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Serum ferritin increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Thyroxine increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Transaminases increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Urine analysis abnormal			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Weight Decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	6 / 42 (14.29%)
occurrences (all)	0	0	7
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	3 / 7 (42.86%)	4 / 7 (57.14%)	6 / 42 (14.29%)
occurrences (all)	6	15	10
Blood potassium increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Eye Contusion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	1	0	0
Spinal compression fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Subcutaneous haematoma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Wound			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Cardiac failure			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Sinus tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Aphonia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Balance disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Dementia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 42 (0.00%)
occurrences (all)	1	1	0
Dysgeusia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	4 / 42 (9.52%)
occurrences (all)	1	0	4
Headache			
subjects affected / exposed	0 / 7 (0.00%)	3 / 7 (42.86%)	8 / 42 (19.05%)
occurrences (all)	0	3	17
Hepatic Encephalopathy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	1	7	0
Lethargy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	4
Memory Impairment			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	1	0	1
Mental impairment			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0

Monoparesis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Neuropathy Peripheral			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	2 / 42 (4.76%)
occurrences (all)	1	1	2
Restless Legs Syndrome			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 7 (14.29%)	3 / 7 (42.86%)	6 / 42 (14.29%)
occurrences (all)	3	19	8
Anaemia Macrocytic			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Lymphadenopathy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Lymphopenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Neutropenia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 7 (28.57%)	1 / 42 (2.38%)
occurrences (all)	4	5	3
Thrombocytopenia			

subjects affected / exposed	1 / 7 (14.29%)	3 / 7 (42.86%)	4 / 42 (9.52%)
occurrences (all)	2	14	4
Leukopenia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	0 / 42 (0.00%)
occurrences (all)	0	5	0
Ear and labyrinth disorders			
Ear pruritus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
External ear inflammation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Dry Eye			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	2 / 42 (4.76%)
occurrences (all)	0	1	2
Eye pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Vision Blurred			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal Discomfort			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 42 (2.38%)
occurrences (all)	0	1	1
Abdominal Pain			
subjects affected / exposed	2 / 7 (28.57%)	5 / 7 (71.43%)	8 / 42 (19.05%)
occurrences (all)	5	10	8
Abdominal Pain Lower			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Abdominal Pain Upper			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	8 / 42 (19.05%)
occurrences (all)	0	1	9
Abdominal distension			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 42 (4.76%)
occurrences (all)	0	0	2
Abdominal hernia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Anal Fissure			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Anorectal Discomfort			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	1	0	0
Ascites			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	8 / 42 (19.05%)
occurrences (all)	0	0	12
Constipation			
subjects affected / exposed	3 / 7 (42.86%)	1 / 7 (14.29%)	7 / 42 (16.67%)
occurrences (all)	3	1	7
Diarrhoea			
subjects affected / exposed	2 / 7 (28.57%)	6 / 7 (85.71%)	26 / 42 (61.90%)
occurrences (all)	6	30	43
Dry Mouth			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	3 / 42 (7.14%)
occurrences (all)	1	1	3
Dysphagia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 42 (2.38%)
occurrences (all)	0	1	1
Enterocolitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Faecal incontinence			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Faeces soft			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Food poisoning			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	2
Gastric ulcer			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Gastrointestinal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	1 / 42 (2.38%)
occurrences (all)	0	2	1
Glossitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 42 (4.76%)
occurrences (all)	0	0	2
Hypoaesthesia Oral			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	1	0	0
Lip blister			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Malabsorption			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Melaena			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	6 / 7 (85.71%)	5 / 7 (71.43%)	15 / 42 (35.71%)
occurrences (all)	6	19	22
Rectal haemorrhage			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Retching			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 42 (2.38%)
occurrences (all)	0	2	1
Stomatitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	6 / 42 (14.29%)
occurrences (all)	1	0	7
Toothache			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Varices oesophageal			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	2 / 7 (28.57%)	5 / 7 (71.43%)	14 / 42 (33.33%)
occurrences (all)	9	14	20
Dyspepsia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	5 / 42 (11.90%)
occurrences (all)	1	0	5
Flatulence			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	1	0	1
Gastric hypomotility			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Hepatic cirrhosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Hepatic function abnormal			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0

Hepatic pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Hepatotoxicity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Hyperbilirubinaemia			
subjects affected / exposed	1 / 7 (14.29%)	4 / 7 (57.14%)	5 / 42 (11.90%)
occurrences (all)	11	10	8
Jaundice			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Liver disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Liver tenderness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Portal vein thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	8 / 42 (19.05%)
occurrences (all)	1	0	10
Blister			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Decubitus ulcer			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Dermatitis acneiform			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	3	0	0
Dermatitis psoriasiform			

subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (0.00%)
occurrences (all)	0	2	0
Diabetic ulcer			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	2 / 42 (4.76%)
occurrences (all)	1	0	2
Erythema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	3
Hyperhidrosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Hyperkeratosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	1	0	0
Pain of skin			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Palmar-Plantar Erythrodysaesthesia Syndrome			
subjects affected / exposed	2 / 7 (28.57%)	3 / 7 (42.86%)	15 / 42 (35.71%)
occurrences (all)	5	14	31
Plantar erythema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	9 / 42 (21.43%)
occurrences (all)	1	2	10
Rash			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	13 / 42 (30.95%)
occurrences (all)	0	1	19

Rash erythematous			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Rash generalised			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 42 (2.38%)
occurrences (all)	0	1	1
Rash maculo-papular			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	2 / 42 (4.76%)
occurrences (all)	1	4	2
Skin exfoliation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Skin fissures			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Skin irritation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	1	0	0
Skin toxicity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Skin ulcer			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Urticaria			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	1	0	1
Dermatitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 42 (4.76%)
occurrences (all)	0	0	2
Haematuria			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Nephrolithiasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Nocturia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	1	0	0
Pollakiuria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	2
Polyuria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Proteinuria			
subjects affected / exposed	2 / 7 (28.57%)	2 / 7 (28.57%)	1 / 42 (2.38%)
occurrences (all)	9	5	1
Renal Failure Chronic			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Renal failure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Renal failure acute			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Urinary Incontinence			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Hypothyroidism			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Arthropathy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Axillary mass			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Back Pain			
subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	3 / 42 (7.14%)
occurrences (all)	5	2	3
Bone Pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Bursitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Groin pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Joint swelling			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Muscle Spasms			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	3 / 42 (7.14%)
occurrences (all)	1	1	3
Muscular Weakness			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	0 / 42 (0.00%)
occurrences (all)	0	5	0
Musculoskeletal Chest Pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Musculoskeletal Pain			

subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	1	0	1
Musculoskeletal discomfort			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Myositis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	2
Neck Pain			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 42 (0.00%)
occurrences (all)	1	1	0
Pain In Extremity			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	2 / 42 (4.76%)
occurrences (all)	2	0	3
Spinal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Tenosynovitis stenosans			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Acid fast bacilli infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	2 / 42 (4.76%)
occurrences (all)	1	0	2
Cellulitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1

Fungal Skin Infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Gastroenteritis Viral			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Localised infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	1	0	0
Oesophageal Candidiasis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	2 / 42 (4.76%)
occurrences (all)	1	0	2
Oral candidiasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 42 (4.76%)
occurrences (all)	0	0	2
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 42 (2.38%)
occurrences (all)	0	1	1
Sinusitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Tooth abscess			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 42 (2.38%)
occurrences (all)	0	1	1
Urinary Tract Infection			
subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	2 / 42 (4.76%)
occurrences (all)	2	1	3

Viral diarrhoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Decreased Appetite			
subjects affected / exposed	1 / 7 (14.29%)	3 / 7 (42.86%)	13 / 42 (30.95%)
occurrences (all)	1	5	19
Dehydration			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	0 / 42 (0.00%)
occurrences (all)	0	6	0
Gout			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 7 (28.57%)	2 / 42 (4.76%)
occurrences (all)	1	4	2
Hyperkalaemia			
subjects affected / exposed	1 / 7 (14.29%)	4 / 7 (57.14%)	1 / 42 (2.38%)
occurrences (all)	2	8	1
Hyperlipasaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 42 (4.76%)
occurrences (all)	0	0	2
Hypermagnesaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	1	0	0
Hyperuricaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Hypervolaemia			

subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Hypoalbuminaemia			
subjects affected / exposed	3 / 7 (42.86%)	4 / 7 (57.14%)	1 / 42 (2.38%)
occurrences (all)	7	28	1
Hypocalcaemia			
subjects affected / exposed	3 / 7 (42.86%)	4 / 7 (57.14%)	3 / 42 (7.14%)
occurrences (all)	7	15	5
Hypokalaemia			
subjects affected / exposed	1 / 7 (14.29%)	4 / 7 (57.14%)	3 / 42 (7.14%)
occurrences (all)	5	5	3
Hypomagnesaemia			
subjects affected / exposed	2 / 7 (28.57%)	2 / 7 (28.57%)	2 / 42 (4.76%)
occurrences (all)	5	4	2
Hyponatraemia			
subjects affected / exposed	2 / 7 (28.57%)	2 / 7 (28.57%)	2 / 42 (4.76%)
occurrences (all)	4	10	4
Hypophosphataemia			
subjects affected / exposed	0 / 7 (0.00%)	3 / 7 (42.86%)	4 / 42 (9.52%)
occurrences (all)	0	3	5
Malnutrition			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 42 (2.38%)
occurrences (all)	0	0	1
Metabolic acidosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 42 (0.00%)
occurrences (all)	0	0	0
hypoproteinaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (0.00%)
occurrences (all)	0	1	0
Fluid Overload			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 42 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Phase 2: Sorafenib 400 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 42 (95.24%)		

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Keratoacanthoma			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Paraneoplastic syndrome			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Deep vein thrombosis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Flushing			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Haematoma			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Hot flush			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	9 / 42 (21.43%)		
occurrences (all)	12		
Hypotension			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	2		
Orthostatic hypotension			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Pallor			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Vascular insufficiency			

subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	12 / 42 (28.57%)		
occurrences (all)	19		
Chest Pain			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Early satiety			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Face oedema			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Facial pain			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	12 / 42 (28.57%)		
occurrences (all)	13		
Generalised Oedema			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Hypothermia			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Inflammation			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Influenza like illness			

subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Injection site haematoma			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Localised oedema			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Malaise			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Mucosal Inflammation			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Oedema			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Oedema Peripheral			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	6		
Pain			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	6 / 42 (14.29%)		
occurrences (all)	10		
Thirst			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Vessel Puncture Site Bruise			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Xerosis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Immune system disorders			

Drug Hypersensitivity			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Genital lesion			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Nipple pain			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Prostatic obstruction			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Testicular pain			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Testicular swelling			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	4		
Vaginal Haemorrhage			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Vaginal Polyp			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Vulvovaginal Discomfort			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Cough			

subjects affected / exposed	4 / 42 (9.52%)			
occurrences (all)	4			
Dysphonia				
subjects affected / exposed	5 / 42 (11.90%)			
occurrences (all)	5			
Dyspnoea				
subjects affected / exposed	7 / 42 (16.67%)			
occurrences (all)	7			
Dyspnoea Exertional				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Epistaxis				
subjects affected / exposed	4 / 42 (9.52%)			
occurrences (all)	4			
Haemoptysis				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Hiccups				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Nasal dryness				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Oropharyngeal pain				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Paranasal sinus hypersecretion				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Pneumonitis				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Productive cough				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Pulmonary oedema				

subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Sleep apnoea syndrome			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Throat tightness			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Anxiety			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Confusional state			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Depressed mood			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	8 / 42 (19.05%)		
occurrences (all)	11		
Ammonia Increased			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Amylase Increased			

subjects affected / exposed	4 / 42 (9.52%)			
occurrences (all)	7			
Aspartate Aminotransferase Increased				
subjects affected / exposed	13 / 42 (30.95%)			
occurrences (all)	20			
Bacterial test positive				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Blood Bilirubin Increased				
subjects affected / exposed	5 / 42 (11.90%)			
occurrences (all)	11			
Blood Creatinine Increased				
subjects affected / exposed	2 / 42 (4.76%)			
occurrences (all)	2			
Blood Lactate Dehydrogenase Increased				
subjects affected / exposed	2 / 42 (4.76%)			
occurrences (all)	2			
Blood Thyroid Stimulating Hormone Increased				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Blood albumin decreased				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Blood urine present				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Body temperature increased				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Breath sounds abnormal				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	2			
Globulins increased				

subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Heart Rate Increased				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Hepatitis C Virus Test Positive				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Lipase Increased				
subjects affected / exposed	7 / 42 (16.67%)			
occurrences (all)	16			
Liver Palpable Subcostal				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Oxygen saturation decreased				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Platelet Count Decreased				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Protein urine present				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Serum ferritin increased				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Thyroxine increased				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Transaminases increased				
subjects affected / exposed	2 / 42 (4.76%)			
occurrences (all)	2			
Urine analysis abnormal				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Weight Decreased				

subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	11 / 42 (26.19%)		
occurrences (all)	11		
Blood potassium increased			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	2		
Eye Contusion			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Spinal compression fracture			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Subcutaneous haematoma			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Wound			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	2		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Cardiac failure			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Sinus tachycardia			

subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Nervous system disorders			
Aphonia			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Balance disorder			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Dementia			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Dysgeusia			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Headache			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	5		
Hepatic Encephalopathy			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	5		
Lethargy			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Memory Impairment			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Mental impairment			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Monoparesis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		

Neuropathy Peripheral subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0			
Paraesthesia subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0			
Restless Legs Syndrome subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0			
Somnolence subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1			
Syncope subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0			
Blood and lymphatic system disorders				
Anaemia subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 8			
Anaemia Macrocytic subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0			
Lymphadenopathy subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1			
Lymphopenia subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 5			
Neutropenia subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1			
Thrombocytopenia subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 8			
Leukopenia				

subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Ear pruritus			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
External ear inflammation			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Eye disorders			
Dry Eye			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Eye pain			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Vision Blurred			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal Discomfort			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Abdominal Pain			
subjects affected / exposed	7 / 42 (16.67%)		
occurrences (all)	9		
Abdominal Pain Lower			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Abdominal Pain Upper			
subjects affected / exposed	5 / 42 (11.90%)		
occurrences (all)	8		
Abdominal distension			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	2		
Abdominal hernia			

subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Anal Fissure				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Anorectal Discomfort				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Ascites				
subjects affected / exposed	5 / 42 (11.90%)			
occurrences (all)	10			
Constipation				
subjects affected / exposed	5 / 42 (11.90%)			
occurrences (all)	6			
Diarrhoea				
subjects affected / exposed	22 / 42 (52.38%)			
occurrences (all)	41			
Dry Mouth				
subjects affected / exposed	3 / 42 (7.14%)			
occurrences (all)	4			
Dysphagia				
subjects affected / exposed	2 / 42 (4.76%)			
occurrences (all)	2			
Enterocolitis				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Faecal incontinence				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Faeces soft				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Food poisoning				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Gastric ulcer				

subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Gastritis				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Gastrointestinal pain				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Gastrooesophageal Reflux Disease				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Glossitis				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Haemorrhoids				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Hypoaesthesia Oral				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Lip blister				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Malabsorption				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Melaena				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Nausea				
subjects affected / exposed	12 / 42 (28.57%)			
occurrences (all)	16			
Rectal haemorrhage				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	2			
Retching				

subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Stomatitis			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	6		
Toothache			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Varices oesophageal			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	7 / 42 (16.67%)		
occurrences (all)	10		
Dyspepsia			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Flatulence			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Gastric hypomotility			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Hepatic cirrhosis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Hepatic function abnormal			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	2		
Hepatic pain			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		

Hepatotoxicity			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Hyperbilirubinaemia			
subjects affected / exposed	6 / 42 (14.29%)		
occurrences (all)	8		
Jaundice			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Liver disorder			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Liver tenderness			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Portal vein thrombosis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Blister			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	4		
Decubitus ulcer			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Dermatitis acneiform			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Dermatitis psoriasiform			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Diabetic ulcer			

subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Dry skin				
subjects affected / exposed	2 / 42 (4.76%)			
occurrences (all)	3			
Erythema				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Hyperhidrosis				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Hyperkeratosis				
subjects affected / exposed	3 / 42 (7.14%)			
occurrences (all)	3			
Night sweats				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Pain of skin				
subjects affected / exposed	4 / 42 (9.52%)			
occurrences (all)	5			
Palmar-Plantar Erythrodysaesthesia Syndrome				
subjects affected / exposed	9 / 42 (21.43%)			
occurrences (all)	16			
Plantar erythema				
subjects affected / exposed	2 / 42 (4.76%)			
occurrences (all)	2			
Pruritus				
subjects affected / exposed	3 / 42 (7.14%)			
occurrences (all)	3			
Rash				
subjects affected / exposed	9 / 42 (21.43%)			
occurrences (all)	13			
Rash erythematous				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			

Rash generalised subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0		
Rash maculo-papular subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0		
Skin exfoliation subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 5		
Skin fissures subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Skin irritation subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0		
Skin toxicity subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0		
Skin ulcer subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Urticaria subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0		
Dermatitis subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Haematuria subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0		
Nephrolithiasis			

subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Nocturia			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Pollakiuria			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Polyuria			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Proteinuria			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	3		
Renal Failure Chronic			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Renal failure			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Renal failure acute			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Urinary Incontinence			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Hypothyroidism			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			

Arthralgia				
subjects affected / exposed	2 / 42 (4.76%)			
occurrences (all)	2			
Arthropathy				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Axillary mass				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Back Pain				
subjects affected / exposed	7 / 42 (16.67%)			
occurrences (all)	7			
Bone Pain				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Bursitis				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Groin pain				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Joint swelling				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Muscle Spasms				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Muscular Weakness				
subjects affected / exposed	2 / 42 (4.76%)			
occurrences (all)	2			
Musculoskeletal Chest Pain				
subjects affected / exposed	5 / 42 (11.90%)			
occurrences (all)	7			
Musculoskeletal Pain				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			

Musculoskeletal discomfort				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Myalgia				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Myositis				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Neck Pain				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Pain In Extremity				
subjects affected / exposed	5 / 42 (11.90%)			
occurrences (all)	8			
Spinal pain				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Tenosynovitis stenosans				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Infections and infestations				
Acid fast bacilli infection				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Bronchitis				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Cellulitis				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	2			
Cystitis				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Fungal Skin Infection				

subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Gastroenteritis Viral				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Influenza				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Localised infection				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Nasopharyngitis				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Oesophageal Candidiasis				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Oral candidiasis				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Pneumonia				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Sinusitis				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Tooth abscess				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Upper Respiratory Tract Infection				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Urinary Tract Infection				
subjects affected / exposed	6 / 42 (14.29%)			
occurrences (all)	8			
Viral diarrhoea				

subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Decreased Appetite			
subjects affected / exposed	15 / 42 (35.71%)		
occurrences (all)	19		
Dehydration			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Gout			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Hyperglycaemia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Hyperkalaemia			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Hyperlipasaemia			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Hypermagnesaemia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Hyperuricaemia			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Hypervolaemia			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		

Hypoalbuminaemia subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 6		
Hypocalcaemia subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2		
Hypokalaemia subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 9		
Hypomagnesaemia subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0		
Hyponatraemia subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2		
Hypophosphataemia subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0		
Malnutrition subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0		
Metabolic acidosis subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
hypoproteinaemia subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0		
Fluid Overload subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 December 2010	Amendment 1: The purpose of this amendment was mainly to change planned upper dose for the Phase Ib portion of the study was from 360 mg daily to 400 mg daily.
22 February 2011	Amendment 2: The purpose of this amendment was mainly to add additional PK sampling times, continuing treatment from sorafenib with or without golvatinib to golvatinib with or without sorafenib for subjects who were experiencing clinical benefit after 6 cycles, added efficacy endpoints and removed history of portal vein thrombosis as an exclusion criterion.
20 June 2011	Amendment 3: The purpose of this amendment was mainly to allow subjects on golvatinib who experienced nausea to take golvatinib with food and antiemetic therapy per local guidelines and Investigator practice and updated definition of an SAE to reflect new FDA guidelines.
13 September 2012	Amendment 4: The purpose of this amendment was mainly to add disease progression to Section 4.4.3 "Patient Withdrawal and provided the dose for the Phase 2 portion of the study.
05 November 2014	Amendment 5: The purpose of this amendment was mainly to remove the long-term overall survival follow-up.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported