Clinical trial results:
A Multicenter, Global, Randomized, Double-Blind Study of Axitinib plus Best Supportive Care Versus Placebo plus Best Supportive Care in Patients with Advanced Hepatocellular Carcinoma Following Failure of One Prior Antiangiogenic Therapy

Summary

EudraCT number	2010-021590-37
Trial protocol	DE HU SK GB BE IT
Global end of trial date	20 December 2016

Results information

Result version number	v1 (current)
This version publication date	05 January 2018
First version publication date	05 January 2018

Trial information

Trial identification

Sponsor protocol code	A4061058

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01210495
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.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	20 March 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of non-randomized portion was to evaluate, in subjects with advanced hepatocellular carcinoma (HCC) following failure of one prior antiangiogenic therapy, the pharmacokinetics (PK) of axitinib, and the tolerability and starting dose in subjects with Child-Pugh Class B disease (Score 7); and the objective of randomized portion was to compare the overall survival (OS) of subjects with advanced HCC receiving axitinib+best supportive care (BSC) versus placebo+BSC following failure of one prior antiangiogenic therapy.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 December 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Hong Kong: 13
Country: Number of subjects enrolled	Japan: 44
Country: Number of subjects enrolled	Korea, Republic of: 44
Country: Number of subjects enrolled	United States: 19
Country: Number of subjects enrolled	China: 20
Country: Number of subjects enrolled	Taiwan: 19
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	France: 33
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Slovakia: 4
Country: Number of subjects enrolled	United Kingdom: 8
Worldwide total number of subjects	224
EEA total number of subjects	65

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)	131
From 65 to 84 years	93
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Total 224 subjects were enrolled in the study. Randomized portion enrolled 202 subjects in 2 arms (134 in axitinib, 68 in placebo) in 70 centres (13 countries). Non-randomized portion enrolled 22 subjects in 2 cohorts (15 in Child-Pugh Class A, 7 in Child-Pugh Class B score 7) according to Child-Pugh score in 13 centers (4 countries).

Pre-assignment

Screening details:

Subjects with Child-Pugh Class A (score 5 or 6) could have been enrolled into either non-randomized or to randomized portion. Subjects with Child-Pugh Class B (score 7) were initially enrolled into non-randomized portion but following determination of recommended axitinib starting dose they could have been enrolled in randomized portion.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Child-Pugh Class A

Arm description:

Subjects with Child-Pugh Class A disease (score 5 or 6) were enrolled into the non-randomized portion at selected sites only at a starting axitinib dose of 5 milligrams (mg) twice daily (BID).

Arm type	Experimental
Investigational medicinal product name	Axitinib
Investigational medicinal product code	AG-013736
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Axitinib will be administered as per the dose and schedule specified in the arm group description.

Arm title	Child-Pugh Class B

Arm description:

Subjects with Child-Pugh Class B disease (score 7) at selected sites were initially enrolled only into the non-randomized portion of this study to determine the recommended starting dose of axitinib for this population. The initial starting dose for this group was 2 mg BID.

Arm type	Experimental
Investigational medicinal product name	Axitinib
Investigational medicinal product code	AG-013736
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Axitinib will be administered as per the dose and schedule specified in the arm group description.

Arm title	Axitinib

Arm description:

Subjects in this group received axitinib + best supportive care. Subjects with Child-Pugh Class A disease (score 5 or 6) were enrolled into the randomized portion at a starting axitinib dose of 5 mg BID orally.

Subjects with Child-Pugh Class B disease (score 7) were to begin enrollment into the randomized portion of the study following determination of the recommended axitinib starting dose in the non-randomized portion. Study treatment was administered in cycles of 4 weeks in duration.

Arm type	Experimental
Investigational medicinal product name	Axitinib
Investigational medicinal product code	AG-013736
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Axitinib will be administered as per the dose and schedule specified in the arm group description.

Arm title	Placebo

Arm description:

Subjects in this group received placebo + best supportive care. Treatment was administered in cycles of 4 weeks in duration. The starting dose of placebo for subjects with Child Pugh Class A disease (score 5 or 6) was chosen as 5 mg BID. Subjects with Child-Pugh Class B, score 7 received placebo that was determined from the non-randomized portion of the study until the recommended starting dose was determined, subjects with Child-Pugh Class B, score 7, were not permitted to enter the randomized portion of the study.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	AG-013736
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to axitinib will be administered as per the dose and schedule specified in the arm group description.

Number of subjects in period 1	Child-Pugh Class A	Child-Pugh Class B	Axitinib
Started	15	7	134
Completed	0	0	0
Not completed	15	7	134
Other unspecified	-	-	6
Death	14	7	112
Subject Refused Further Follow-Up	1	-	11
Study Terminated by Sponsor	-	-	4
Lost to follow-up	-	-	1

Number of subjects in period 1	Placebo
Started	68
Completed	0
Not completed	68
Other unspecified	-
Death	54
Subject Refused Further Follow-Up	2

Study Terminated by Sponsor	11
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Child-Pugh Class A
Reporting group description:	
Subjects with Child-Pugh Class A disease (score 5 or 6) were enrolled into the non-randomized portion at selected sites only at a starting axitinib dose of 5 milligrams (mg) twice daily (BID).	
Reporting group title	Child-Pugh Class B
Reporting group description:	
Subjects with Child-Pugh Class B disease (score 7) at selected sites were initially enrolled only into the non-randomized portion of this study to determine the recommended starting dose of axitinib for this population. The initial starting dose for this group was 2 mg BID.	
Reporting group title	Axitinib
Reporting group description:	
Subjects in this group received axitinib + best supportive care. Subjects with Child-Pugh Class A disease (score 5 or 6) were enrolled into the randomized portion at a starting axitinib dose of 5 mg BID orally. Subjects with Child-Pugh Class B disease (score 7) were to begin enrollment into the randomized portion of the study following determination of the recommended axitinib starting dose in the non-randomized portion. Study treatment was administered in cycles of 4 weeks in duration.	
Reporting group title	Placebo
Reporting group description:	
Subjects in this group received placebo + best supportive care. Treatment was administered in cycles of 4 weeks in duration. The starting dose of placebo for subjects with Child Pugh Class A disease (score 5 or 6) was chosen as 5 mg BID. Subjects with Child-Pugh Class B, score 7 received placebo that was determined from the non-randomized portion of the study until the recommended starting dose was determined, subjects with Child-Pugh Class B, score 7, were not permitted to enter the randomized portion of the study.	

Reporting group values	Child-Pugh Class A	Child-Pugh Class B	Axitinib
Number of subjects	15	7	134
Age, Customized Units: Subjects			
<18 years|	0	0	0
18-44 years|	4	0	7
45-64 years|	5	5	74
>=65 years|	6	2	53
Sex: Female, Male Units: Subjects			
Female	3	2	24
Male	12	5	110

Reporting group values	Placebo	Total	
Number of subjects	68	224	
Age, Customized Units: Subjects			
<18 years|	0	0	
18-44 years|	4	15	
45-64 years|	32	116	
>=65 years|	32	93	
Sex: Female, Male Units: Subjects			
Female	12	41	

Male	56	183	

End points

End points reporting groups

Reporting group title	Child-Pugh Class A

Reporting group description:

Subjects with Child-Pugh Class A disease (score 5 or 6) were enrolled into the non-randomized portion at selected sites only at a starting axitinib dose of 5 milligrams (mg) twice daily (BID).

Reporting group title	Child-Pugh Class B

Reporting group description:

Subjects with Child-Pugh Class B disease (score 7) at selected sites were initially enrolled only into the non-randomized portion of this study to determine the recommended starting dose of axitinib for this population. The initial starting dose for this group was 2 mg BID.

Reporting group title	Axitinib

Reporting group description:

Subjects in this group received axitinib + best supportive care. Subjects with Child-Pugh Class A disease (score 5 or 6) were enrolled into the randomized portion at a starting axitinib dose of 5 mg BID orally. Subjects with Child-Pugh Class B disease (score 7) were to begin enrollment into the randomized portion of the study following determination of the recommended axitinib starting dose in the non-randomized portion. Study treatment was administered in cycles of 4 weeks in duration.

Reporting group title	Placebo

Reporting group description:

Subjects in this group received placebo + best supportive care. Treatment was administered in cycles of 4 weeks in duration. The starting dose of placebo for subjects with Child Pugh Class A disease (score 5 or 6) was chosen as 5 mg BID. Subjects with Child-Pugh Class B, score 7 received placebo that was determined from the non-randomized portion of the study until the recommended starting dose was determined, subjects with Child-Pugh Class B, score 7, were not permitted to enter the randomized portion of the study.

Primary: Overall Survival (OS) - Stratified Analysis, Randomized Portion

End point title	Overall Survival (OS) - Stratified Analysis, Randomized

End point description:

OS was defined as the time from the date of randomization to the date of death due to any cause. OS (in months) was calculated as (date of death − first randomization date +1)/30.4. For subjects still alive at the time of the analysis, the OS time was censored on the last date they were known to be alive. All subjects were followed up for survival at least every 3 months after discontinuing study treatment until at least two years after randomization of the last subjects. FAS included all randomized subjects, and subjects were classified according to the randomized treatment arm regardless of what treatment, if any, was received.

End point type	Primary

End point timeframe:

From randomization until at least two years after the last subject has been randomized (up to 6 years)

Notes:

[1] - 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: The endpoint was planned to be reported for Axitinib and Placebo arm only.

End point values	Axitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	68		
Units: months				
median (confidence interval 95%)	12.7 (10.2 to 14.9)	9.7 (5.9 to 11.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The study was designed to test the null hypothesis that the true median OS was 5 months vs. the alternative hypothesis that the true median OS was at least 8.3 months (i.e., 66 percent [%] improvement in median OS).

Comparison groups	Axitinib v Placebo
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.2872 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.907
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.646
upper limit	1.274

Notes:

[2] - Assuming proportional hazards, a hazard ratio less than (<) 1 indicated reduction in hazard rate to favor Axitinib; hazard ratio greater than (>) 1 indicated reduction to favor Placebo.
[3] - For the overall stratified analysis the p-value is from a 1-sided log-rank test of treatment stratified by tumor invasion and geographic region.

Secondary: Progression-Free Survival (PFS) - Stratified Analysis, Randomized Portion

End point title	Progression-Free Survival (PFS) - Stratified Analysis, Randomized Portion[4]

End point description:

PFS was defined as time from randomization to first documented objective tumor progression or to death due to any cause, whichever occurred first. PFS was calculated as(first event date − first randomization date +1)/30.4. Tumor progression was determined from oncologic assessment data (data meet the criteria for progressive disease [PD]), or from adverse event (AE) data (where outcome was death). As per response evaluation criteria in solid tumors (RECIST) 1.1, progression was defined as greater than or equal to (>=) 20% increase in sum of longest dimensions of target lesions or appearance of one or more new target lesions, unequivocal progression of existing non-target lesions, or appearance of 1 new non-target lesions. Subjects discontinuing study treatment without documented evidence of PD were to be followed up at least every 8 weeks after discontinuing study treatment until disease progression, or initiation of another anticancer treatment. FAS included all randomized subjects.

End point type	Secondary

End point timeframe:

Every 8 weeks until disease progression/death or start of new treatment or until at least two years after the last subject has been randomized, whatever occurs first

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be reported for Axitinib and Placebo arm only.

End point values	Axitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	68		
Units: months				
median (confidence interval 95%)	3.6 (2.3 to 4.6)	1.9 (1.9 to 3.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Assuming proportional hazards, a hazard ratio <1 indicated a reduction in hazard rate in favor of Axitinib; a hazard ratio >1 indicated a reduction in favor of Placebo.

Comparison groups	Axitinib v Placebo
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0039 [5]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.618
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.438
upper limit	0.871

Notes:

[5] - For the overall stratified analysis the p-value is from a 1-sided log-rank test of treatment stratified by tumor invasion and geographic region.

Secondary: Objective Response Rate (ORR) - Percentage of Subjects With Objective Response by Stratified Analysis, Randomized Portion

End point title	Objective Response Rate (ORR) - Percentage of Subjects With Objective Response by Stratified Analysis, Randomized Portion[6]

End point description:

ORR was defined as the percentage of subjects with confirmed complete response (CR) or confirmed partial response (PR) according to the RECIST 1.1. CR was defined as the disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must decrease to normal (short axis <10 millimetres [mm]). PR was defined as a 30% decrease in the sum of the longest dimensions of the target lesions taking as a reference the baseline sum longest dimensions. FAS included all randomized subjects, and subjects were classified according to the randomized treatment arm regardless of what treatment, if any, was received.

End point type	Secondary

End point timeframe:

Every 8 weeks until at least two years after the last subject has been randomized

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be reported for Axitinib and Placebo arm only.

End point values	Axitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	68		
Units: percentage of subjects				
number (confidence interval 95%)	9.7 (5.3 to 16.0)	2.9 (0.4 to 10.2)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Risk ratio and confidence interval (CI) were based on the Mantel-Haenszel estimator; risk ratio was adjusted for geographical region and vascular invasion and extra hepatic spread.

Comparison groups	Axitinib v Placebo
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0914 [7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	3.172
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.759
upper limit	13.265

Notes:

[7] - ORR for the 2 treatment arms was compared with a significance level of 0.025 using Cochran-Mantel-Haenszel (CMH) test for stratified analyses.

Secondary: Time to Tumor Progression (TTP) - Stratified Analysis, Randomized Portion

End point title	Time to Tumor Progression (TTP) - Stratified Analysis, Randomized Portion[8]

End point description:

TTP was defined as the time from randomization to first documentation of objective tumor progression. If tumor progression data included more than 1 date, the first date was used. TTP (in months) was calculated as (first event date − first randomization date +1)/30.4. FAS included all randomized subjects, and subjects were classified according to the randomized treatment arm regardless of what treatment, if any, was received.

End point type	Secondary

End point timeframe:

Every 8 weeks until disease progression/death or start of new treatment or until at least two years after the last subject has been randomized, whatever occurs first

Notes:

[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: The endpoint was planned to be reported for Axitinib and Placebo arm only.

End point values	Axitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	68		
Units: months				
median (confidence interval 95%)	3.7 (2.8 to 5.6)	1.9 (1.9 to 3.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Assuming proportional hazards, a hazard ratio <1 indicated a reduction in hazard rate in favor of Axitinib; a hazard ratio >1 indicated a reduction in favor of Placebo.

Comparison groups	Axitinib v Placebo
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006 [9]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.621
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.434
upper limit	0.889

Notes:

[9] - For the overall stratified analysis the p-value is from a 1-sided log-rank test of treatment stratified by tumor invasion and geographic region.

Secondary: Duration of Response (DR) by Unstratified Analysis, Randomized Portion

End point title	Duration of Response (DR) by Unstratified Analysis, Randomized Portion[10]

End point description:

DR was defined as the time from the first documentation of objective tumor response (CR or PR) that was subsequently confirmed to the first documentation of PD or to death due to any cause, whichever occurs first. If tumor progression data included more than 1 date, the first date was to be used. DR (in months) was to be calculated as (the end date for DR − first CR or PR that was subsequently confirmed +1)/30.4. FAS included all randomized subjects, and subjects were classified according to the randomized treatment arm regardless of what treatment, if any, was received. DR was calculated for the subgroup of FAS subjects with objective response. Here, '99999' represents 'value not reached'.

End point type	Secondary

End point timeframe:

From objective response to date of progression or death

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be reported for Axitinib and Placebo arm only.

End point values	Axitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	2		
Units: months				
median (confidence interval 95%)	6.4 (3.7 to 9.3)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Overall Clinical Benefit Response (CBR) - Stratified Analysis, Randomized Portion

End point title	Percentage of Subjects With Overall Clinical Benefit Response (CBR) - Stratified Analysis, Randomized Portion[11]

End point description:

CBR was defined as the percentage of subjects with confirmed CR or confirmed PR or a best response of stable disease >=8 weeks according to RECIST 1.1 criteria, relative to all randomized subjects who had baseline measurable disease. Confirmed responses were defined as those that persisted on repeat imaging study >=4 weeks after the initial documentation of response. Subjects who did not have on study radiographic tumor re-evaluation or who died, progressed, or dropped out for any reason prior to reaching a CR, PR, or stable disease were counted as non-responders in the assessment of CBR. A subject who initially met the criteria for a PR and then subsequently became a confirmed CR was to be assigned a best response of CR. FAS included all randomized subjects, and subjects were classified according to the randomized treatment arm regardless of what treatment, if any, was received.

End point type	Secondary

End point timeframe:

From Baseline up to end of treatment

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be reported for Axitinib and Placebo arm only.

End point values	Axitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	68		
Units: percentage of subjects				
number (confidence interval 95%)	31.3 (23.6 to 39.9)	11.8 (5.2 to 21.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Risk Ratio and CI based on the Mantel-Haenszel estimator; risk ratio was adjusted for geographical region and vascular invasion and extra hepatic spread.

Comparison groups	Axitinib v Placebo

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0025 [12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	2.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.319
upper limit	5.326

Notes:

[12] - For the overall stratified analysis the p-value is from Cochran-Mantel-Haenszel test of treatment stratified by geographical region and vascular invasion and extra hepatic spread.

Secondary: Axitinib Steady-State Pharmacokinetic (PK) Parameter - Maximum Observed Plasma Concentration (Cmax), Non-Randomized Portion

End point title	Axitinib Steady-State Pharmacokinetic (PK) Parameter - Maximum Observed Plasma Concentration (Cmax), Non-Randomized Portion[13]

End point description:

Axitinib samples were to be collected from all subjects on Cycle 1 Day 15 at the following time points: pre-dose, 1, 2, 3, 4, 6 and 8 hours after axitinib dosing. The PK concentration set included all subjects who were treated and had at least 1 measured concentration on at least 1 day of PK assessment. The PK parameter analysis set included all subjects treated who had at least 1 estimated PK parameter of primary interest.

End point type	Secondary

End point timeframe:

Cycle 1 Day 15

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be reported for Axitinib and Placebo arm only.

End point values	Child-Pugh Class A	Child-Pugh Class B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	7		
Units: nanograms per milliliter (ng/mL)				
geometric mean (confidence interval 95%)	35.74 (21.84 to 58.50)	21.16 (11.10 to 40.33)		

Statistical analyses

No statistical analyses for this end point

Secondary: Axitinib Steady-State PK Parameter - Area Under the Plasma Concentration Versus Time Curve From 0 to 24 Hour (AUC0-24), Non-Randomized Portion

End point title	Axitinib Steady-State PK Parameter - Area Under the Plasma Concentration Versus Time Curve From 0 to 24 Hour (AUC0-24), Non-Randomized Portion[14]

End point description:

Axitinib samples were to be collected from all subjects on Cycle 1 Day 15 at the following time points: pre-dose, 1, 2, 3, 4, 6 and 8 hours after axitinib dosing. In the below table, 4 subjects in Child-Pugh A and 1 subject in Child-Pugh B were not reported due to nonestimable half-life. The PK concentration set included all subjects who were treated and had at least 1 measured concentration on at least 1 day of PK assessment. The PK parameter analysis set included all subjects treated who had at least 1 estimated PK parameter of primary interest.

End point type	Secondary

End point timeframe:

Cycle 1 Day 15

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be reported for Axitinib and Placebo arm only.

End point values	Child-Pugh Class A	Child-Pugh Class B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	6		
Units: nanograms*hour per milliliter (ng*hr/mL)				
geometric mean (confidence interval 95%)	310.76 (175.02 to 551.75)	316.20 (162.96 to 613.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Axitinib Steady-State Pharmacokinetic Parameter - Time to First Occurrence of Cmax (Tmax), Non-Randomized Portion

End point title	Axitinib Steady-State Pharmacokinetic Parameter - Time to First Occurrence of Cmax (Tmax), Non-Randomized Portion[15]

End point description:

Axitinib samples were to be collected from all subjects on Cycle 1 Day 15 at the following time points: pre-dose, 1, 2, 3, 4, 6 and 8 hours after axitinib dosing. The PK concentration set included all subjects who were treated and had at least 1 measured concentration on at least 1 day of PK assessment. The PK parameter analysis set included all subjects treated who had at least 1 estimated PK parameter of primary interest.

End point type	Secondary

End point timeframe:

Cycle 1 Day 15

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be reported for Axitinib and Placebo arm only.

End point values	Child-Pugh Class A	Child-Pugh Class B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	7		
Units: hours				
median (full range (min-max))	2.50 (0.00 to 7.98)	1.05 (0.00 to 4.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Axitinib Steady-State Pharmacokinetic Parameter - Apparent Oral Clearance (CL/F), Non-Randomized Portion

End point title	Axitinib Steady-State Pharmacokinetic Parameter - Apparent Oral Clearance (CL/F), Non-Randomized Portion[16]

End point description:

Axitinib samples were to be collected from all subjects on Cycle 1 Day 15 at the following time points: pre-dose, 1, 2, 3, 4, 6 and 8 hours after axitinib dosing. In the below table, 4 subjects in Child-Pugh A and 1 subject in Child-Pugh B were not reported due to nonestimable half-life. The PK concentration set included all subjects who were treated and had at least 1 measured concentration on at least 1 day of PK assessment. The PK parameter analysis set included all subjects treated who had at least 1 estimated PK parameter of primary interest.

End point type	Secondary

End point timeframe:

Cycle 1 Day 15

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be reported for Axitinib and Placebo arm only.

End point values	Child-Pugh Class A	Child-Pugh Class B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	6		
Units: liters per hour (L/hr)				
geometric mean (confidence interval 95%)	32.18 (18.12 to 57.13)	12.65 (6.52 to 24.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Axitinib Steady-State Pharmacokinetic Parameter - Terminal Plasma Elimination Half-Life (t1/2), Non-Randomized Portion

End point title	Axitinib Steady-State Pharmacokinetic Parameter - Terminal Plasma Elimination Half-Life (t1/2), Non-Randomized Portion[17]

End point description:

Axitinib samples were to be collected from all subjects on Cycle 1 Day 15 at the following time points: pre-dose, 1, 2, 3, 4, 6 and 8 hours after axitinib dosing. In the below table, 4 subjects in Child-Pugh A and 1 subject in Child-Pugh B were not reported due to nonestimable half-life. The PK concentration set

included all subjects who were treated and had at least 1 measured concentration on at least 1 day of PK assessment. The PK parameter analysis set included all subjects treated who had at least 1 estimated PK parameter of primary interest.

End point type	Secondary

End point timeframe:

Cycle 1 Day 15

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be reported for Axitinib and Placebo arm only.

End point values	Child-Pugh Class A	Child-Pugh Class B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	6		
Units: hours				
arithmetic mean (standard deviation)	4.12 (± 3.55)	4.79 (± 2.42)		

Statistical analyses

No statistical analyses for this end point

Secondary: Axitinib Steady-State Pharmacokinetic Parameter - Apparent Oral Volume of Distribution of the Drug During the Elimination Phase (Vz/F), Non-Randomized Portion

End point title	Axitinib Steady-State Pharmacokinetic Parameter - Apparent Oral Volume of Distribution of the Drug During the Elimination Phase (Vz/F), Non-Randomized Portion[18]

End point description:

Axitinib samples were to be collected from all subjects on Cycle 1 Day 15 at the following time points: pre-dose, 1, 2, 3, 4, 6 and 8 hours after axitinib dosing. The PK parameter, Vz/F has been presented in this outcome measure. In the below table, 4 subjects in Child-Pugh A and 1 subject in Child-Pugh B were not reported due to nonestimable half-life. The PK concentration set included all subjects who were treated and had at least 1 measured concentration on at least 1 day of PK assessment. The PK parameter analysis set included all subjects treated who had at least 1 estimated PK parameter of primary interest.

End point type	Secondary

End point timeframe:

Cycle 1 Day 15

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be reported for Axitinib and Placebo arm only.

End point values	Child-Pugh Class A	Child-Pugh Class B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	6		
Units: liters				
geometric mean (confidence interval 95%)	150.01 (94.67 to 237.68)	81.16 (47.70 to 138.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration of Soluble Proteins at Baseline in Randomized Portion

End point title	Concentration of Soluble Proteins at Baseline in Randomized Portion[19]

End point description:

Plasma soluble proteins interleukin-6 (IL-6), E-Selectin, interleukin-8 (IL-8), hepatocyte growth factor (HGF), matrix metalloproteinase-2 (MMP-2), stem cell factor (SCF), angiopoietin-2 (Ang-2), vascular endothelial growth factor-A (VEGF-A), vascular endothelial growth factor-C (VEGF-C), soluble vascular endothelial growth factor receptor 2 (sVEGFR2), sVEGFR3, stromal cell-derived factor-1 (SDF1), neutrophil gelatinase-associated lipocalin (NGAL), migration inhibitory factor (MIF), c-MET, regulated upon activation normal T cell expressed and presumably secreted (RANTES), monocyte chemotactic protein-3 (MCP-3) were only measured in randomized subjects. Soluble protein analysis set included all subjects in safety analysis set who had a Baseline soluble protein assessment. Here, '99999' represents ‘data not available as % < lower limit of quantification (LLQ) was greater than 75%’.

End point type	Secondary

End point timeframe:

Baseline

Notes:

[19] - 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: The endpoint was planned to be reported for Axitinib and Placebo arm only.

End point values	Axitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	61		
Units: picograms per milliliter (pg/mL)				
arithmetic mean (standard deviation)				
IL-6	50.67 (± 102.86)	50.72 (± 106.74)		
E-Selectin	52313.94 (± 32603.18)	55430.76 (± 26723.43)		
IL-8	33.35 (± 47.72)	27.23 (± 44.46)		
HGF	478.84 (± 712.43)	406.06 (± 376.04)		
MMP-2	355715.66 (± 137663.04)	350979.72 (± 146323.29)		
SCF	1352.75 (± 1534.41)	1439.71 (± 2260.89)		
Ang-2	662.40 (± 623.87)	577.82 (± 354.42)		
VEGF-A	102.56 (± 128.09)	173.59 (± 472.19)		
VEGF-C	99999 (± 99999)	99999 (± 99999)		
sVEGFR2	17675.76 (± 7218.95)	18273.65 (± 6836.16)		

sVEGFR3	287429.28 (± 117583.24)	290338.69 (± 97830.36)		
SDF1	1190.08 (± 823.03)	1150.10 (± 681.04)		
NGAL	134861.80 (± 152492.96)	141383.00 (± 121747.35)		
MIF	33057.15 (± 28256.00)	32302.99 (± 21485.01)		
c-MET ELISA	1664.96 (± 834.36)	1641.08 (± 704.38)		
RANTES	26412.12 (± 38682.81)	26917.76 (± 27094.12)		
MCP-3	99999 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Specific Micro-Ribonucleic Acid (miRNA) Transcript Present in Circulation in Randomized Portion

End point title	Percentage of Subjects With Specific Micro-Ribonucleic Acid (miRNA) Transcript Present in Circulation in Randomized Portion[20]

End point description:

A 5 millilitres (mL) whole blood sample was collected from all randomized subjects to evaluate the miRNA transcripts. The miRNA analysis set included all subjects in the safety analysis set who had a baseline miRNA assessment. Safety analysis population included all randomized subjects who received at least 1 dose of study drug with treatment assignments designated according to actual study treatment received.

End point type	Secondary

End point timeframe:

Baseline

Notes:

[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: The endpoint was planned to be reported for Axitinib and Placebo arm only.

End point values	Axitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	59		
Units: percentage of subjects				
number (not applicable)				
hsa-let-7a-5p	100.0	100.0		
hsa-let-7b-5p	100.0	100.0		
hsa-let-7c	100.0	100.0		
hsa-let-7d-5p	100.0	100.0		
hsa-let-7f-5p	100.0	100.0		
hsa-let-7g-5p	100.0	100.0		
hsa-let-7i-5p	100.0	100.0		
hsa-miR-103a-3p	100.0	100.0		
hsa-miR-106b-5p	100.0	100.0		
hsa-miR-107	100.0	100.0		

hsa-miR-1202	100.0	100.0		
hsa-miR-1207-5p	100.0	100.0		
hsa-miR-1225-5p	100.0	100.0		
hsa-miR-1234-5p	100.0	100.0		
hsa-miR-1246	100.0	100.0		
hsa-miR-125b-5p	100.0	100.0		
hsa-miR-126-3p	100.0	100.0		
hsa-miR-1260a	100.0	100.0		
hsa-miR-1260b	100.0	100.0		
hsa-miR-1268a	100.0	100.0		
hsa-miR-1273g-3p	100.0	100.0		
hsa-miR-1275	100.0	100.0		
hsa-miR-128	100.0	100.0		
hsa-miR-130a-3p	100.0	100.0		
hsa-miR-130b-3p	100.0	100.0		
hsa-miR-140-3p	100.0	100.0		
hsa-miR-142-3p	100.0	100.0		
hsa-miR-145-5p	100.0	100.0		
hsa-miR-148a-3p	100.0	100.0		
hsa-miR-148b-3p	100.0	100.0		
hsa-miR-150-5p	100.0	100.0		
hsa-miR-151a-3p	100.0	100.0		
hsa-miR-151a-5p	100.0	100.0		
hsa-miR-151b	100.0	100.0		
hsa-miR-1587	100.0	100.0		
hsa-miR-15a-5p	100.0	100.0		
hsa-miR-15b-5p	100.0	100.0		
hsa-miR-16-5p	100.0	100.0		
hsa-miR-17-5p	100.0	100.0		
hsa-miR-181a-5p	100.0	100.0		
hsa-miR-182-5p	100.0	100.0		
hsa-miR-183-5p	100.0	100.0		
hsa-miR-185-5p	100.0	100.0		
hsa-miR-186-5p	100.0	100.0		
hsa-miR-191-5p	100.0	100.0		
hsa-miR-1914-3p	100.0	100.0		
hsa-miR-1915-3p	100.0	100.0		
hsa-miR-192-5p	100.0	100.0		
hsa-miR-194-5p	100.0	100.0		
hsa-miR-197-3p	100.0	100.0		
hsa-miR-197-5p	100.0	100.0		
hsa-miR-19a-3p	100.0	100.0		
hsa-miR-19b-3p	100.0	100.0		
hsa-miR-20a-5p	100.0	100.0		
hsa-miR-20b-5p	100.0	100.0		
hsa-miR-21-5p	100.0	100.0		
hsa-miR-210	100.0	100.0		
hsa-miR-215	100.0	100.0		
hsa-miR-22-3p	100.0	100.0		
hsa-miR-222-3p	100.0	100.0		
hsa-miR-223-3p	100.0	100.0		
hsa-miR-23a-3p	100.0	100.0		

hsa-miR-23b-3p	100.0	100.0		
hsa-miR-24-3p	100.0	100.0		
hsa-miR-25-3p	100.0	100.0		
hsa-miR-26a-5p	100.0	100.0		
hsa-miR-26b-5p	100.0	100.0		
hsa-miR-2861	100.0	100.0		
hsa-miR-29a-3p	100.0	100.0		
hsa-miR-29b-3p	100.0	100.0		
hsa-miR-29c-3p	100.0	100.0		
hsa-miR-29c-5p	100.0	100.0		
hsa-miR-30b-5p	100.0	100.0		
hsa-miR-30c-5p	100.0	100.0		
hsa-miR-30d-5p	100.0	100.0		
hsa-miR-30e-5p	100.0	100.0		
hsa-miR-3135b	100.0	100.0		
hsa-miR-3162-5p	100.0	100.0		
hsa-miR-3180-3p	100.0	100.0		
hsa-miR-3195	100.0	100.0		
hsa-miR-320a	100.0	100.0		
hsa-miR-320b	100.0	100.0		
hsa-miR-320c	100.0	100.0		
hsa-miR-320d	100.0	100.0		
hsa-miR-320e	100.0	100.0		
hsa-miR-324-3p	100.0	100.0		
hsa-miR-324-5p	100.0	100.0		
hsa-miR-331-3p	100.0	100.0		
hsa-miR-339-5p	100.0	100.0		
hsa-miR-342-3p	100.0	100.0		
hsa-miR-361-3p	100.0	100.0		
hsa-miR-361-5p	100.0	100.0		
hsa-miR-362-5p	100.0	100.0		
hsa-miR-363-3p	100.0	100.0		
hsa-miR-3651	100.0	100.0		
hsa-miR-3656	100.0	100.0		
hsa-miR-365a-3p	100.0	100.0		
hsa-miR-3665	100.0	100.0		
hsa-miR-3676-5p	100.0	100.0		
hsa-miR-374b-5p	100.0	100.0		
hsa-miR-378a-3p	100.0	100.0		
hsa-miR-378i	100.0	100.0		
hsa-miR-3940-5p	100.0	100.0		
hsa-miR-3960	100.0	100.0		
hsa-miR-423-3p	100.0	100.0		
hsa-miR-425-5p	100.0	100.0		
hsa-miR-4281	100.0	100.0		
hsa-miR-4284	100.0	100.0		
hsa-miR-4286	100.0	100.0		
hsa-miR-4299	100.0	100.0		
hsa-miR-4306	100.0	100.0		
hsa-miR-4318	100.0	100.0		
hsa-miR-4323	100.0	100.0		
hsa-miR-4428	100.0	100.0		

hsa-miR-4442	100.0	100.0		
hsa-miR-4443	100.0	100.0		
hsa-miR-4454	100.0	100.0		
hsa-miR-4459	100.0	100.0		
hsa-miR-4466	100.0	100.0		
hsa-miR-4497	100.0	100.0		
hsa-miR-4505	100.0	100.0		
hsa-miR-4507	100.0	100.0		
hsa-miR-4516	100.0	100.0		
hsa-miR-451a	100.0	100.0		
hsa-miR-4530	100.0	100.0		
hsa-miR-4687-3p	100.0	100.0		
hsa-miR-4713-3p	100.0	100.0		
hsa-miR-4721	100.0	100.0		
hsa-miR-4728-5p	100.0	100.0		
hsa-miR-4732-3p	100.0	100.0		
hsa-miR-4739	100.0	100.0		
hsa-miR-4763-3p	100.0	100.0		
hsa-miR-4787-5p	100.0	100.0		
hsa-miR-4788	100.0	100.0		
hsa-miR-484	100.0	100.0		
hsa-miR-486-5p	100.0	100.0		
hsa-miR-494	100.0	100.0		
hsa-miR-5001-5p	100.0	100.0		
hsa-miR-500a-3p	100.0	100.0		
hsa-miR-500a-5p	100.0	100.0		
hsa-miR-501-3p	100.0	100.0		
hsa-miR-501-5p	100.0	100.0		
hsa-miR-502-3p	100.0	100.0		
hsa-miR-505-5p	100.0	100.0		
hsa-miR-5100	100.0	100.0		
hsa-miR-532-3p	100.0	100.0		
hsa-miR-532-5p	100.0	100.0		
hsa-miR-550a-3-5p	100.0	100.0		
hsa-miR-550a-3p	100.0	100.0		
hsa-miR-5739	100.0	100.0		
hsa-miR-574-3p	100.0	100.0		
hsa-miR-574-5p	100.0	100.0		
hsa-miR-5787	100.0	100.0		
hsa-miR-584-5p	100.0	100.0		
hsa-miR-6085	100.0	100.0		
hsa-miR-6087	100.0	100.0		
hsa-miR-6088	100.0	100.0		
hsa-miR-6089	100.0	100.0		
hsa-miR-6090	100.0	100.0		
hsa-miR-6125	100.0	100.0		
hsa-miR-6127	100.0	100.0		
hsa-miR-625-5p	100.0	100.0		
hsa-miR-638	100.0	100.0		
hsa-miR-642a-3p	100.0	100.0		
hsa-miR-642b-3p	100.0	100.0		
hsa-miR-652-3p	100.0	100.0		

hsa-miR-660-5p	100.0	100.0		
hsa-miR-664a-3p	100.0	100.0		
hsa-miR-664b-3p	100.0	100.0		
hsa-miR-6717-5p	100.0	100.0		
hsa-miR-6724-5p	100.0	100.0		
hsa-miR-7-5p	100.0	100.0		
hsa-miR-762	100.0	100.0		
hsa-miR-766-3p	100.0	100.0		
hsa-miR-92a-3p	100.0	100.0		
hsa-miR-93-3p	100.0	100.0		
hsa-miR-93-5p	100.0	100.0		
hsa-miR-937-5p	100.0	100.0		
hsa-miR-940	100.0	100.0		
hsa-miR-1228-3p	99.1	100.0		
hsa-miR-1268b	99.1	100.0		
hsa-miR-142-5p	100.0	98.3		
hsa-miR-27a-3p	99.1	100.0		
hsa-miR-296-5p	99.1	100.0		
hsa-miR-3196	99.1	100.0		
hsa-miR-3198	99.1	100.0		
hsa-miR-342-5p	100.0	98.3		
hsa-miR-3653	100.0	98.3		
hsa-miR-4465	99.1	100.0		
hsa-miR-4515	99.1	100.0		
hsa-miR-4653-3p	99.1	100.0		
hsa-miR-4665-3p	99.1	100.0		
hsa-miR-4746-3p	99.1	100.0		
hsa-miR-505-3p	100.0	98.3		
hsa-miR-6073	99.1	100.0		
hsa-miR-6126	99.1	100.0		
hsa-miR-6132	99.1	100.0		
hsa-miR-6165	99.1	100.0		
hsa-miR-744-5p	100.0	98.3		
hsa-miR-874	99.1	100.0		
hsa-miR-942	100.0	98.3		
hsa-miR-96-5p	99.1	100.0		
hsa-miR-1238-3p	98.2	100.0		
hsa-miR-1285-3p	99.1	98.3		
hsa-miR-1305	98.2	100.0		
hsa-miR-146a-5p	98.2	100.0		
hsa-miR-15b-3p	99.1	98.3		
hsa-miR-17-3p	98.2	100.0		
hsa-miR-195-5p	99.1	98.3		
hsa-miR-199a-5p	99.1	98.3		
hsa-miR-28-5p	99.1	98.3		
hsa-miR-30a-5p	99.1	98.3		
hsa-miR-340-3p	99.1	98.3		
hsa-miR-3679-5p	99.1	98.3		
hsa-miR-374a-5p	99.1	98.3		
hsa-miR-378a-5p	99.1	98.3		
hsa-miR-4433-5p	98.2	100.0		
hsa-miR-454-3p	99.1	98.3		

hsa-miR-4685-5p	99.1	98.3		
hsa-miR-575	98.2	100.0		
hsa-miR-6068	98.2	100.0		
hsa-miR-6124	98.2	100.0		
hsa-miR-6131	98.2	100.0		
hsa-miR-939-5p	98.2	100.0		
hsa-miR-1234-3p	99.1	96.6		
hsa-miR-1249	98.2	98.3		
hsa-miR-132-3p	99.1	96.6		
hsa-miR-30e-3p	98.2	98.3		
hsa-miR-326	99.1	96.6		
hsa-miR-374c-5p	98.2	98.3		
hsa-miR-4270	97.3	100.0		
hsa-miR-4672	97.3	100.0		
hsa-miR-4741	98.2	98.3		
hsa-miR-6515-3p	97.3	100.0		
hsa-miR-371b-5p	97.3	98.3		
hsa-miR-4485	96.4	100.0		
hsa-miR-4513	98.2	96.6		
hsa-miR-454-5p	98.2	96.6		
hsa-miR-4716-3p	96.4	100.0		
hsa-miR-5006-5p	97.3	98.3		
hsa-miR-6069	98.2	96.6		
hsa-miR-101-3p	97.3	96.6		
hsa-miR-155-5p	97.3	96.6		
hsa-miR-16-2-3p	98.2	94.9		
hsa-miR-27b-3p	98.2	94.9		
hsa-miR-328	98.2	94.9		
hsa-miR-4486	96.4	98.3		
hsa-miR-513a-5p	96.4	98.3		
hsa-miR-92b-3p	98.2	94.9		
hsa-miR-98-5p	98.2	94.9		
hsa-miR-18b-5p	96.4	96.6		
hsa-miR-191-3p	97.3	94.9		
hsa-miR-3200-5p	97.3	94.9		
hsa-miR-4313	97.3	94.9		
hsa-miR-4532	96.4	96.6		
hsa-miR-4787-3p	97.3	94.9		
hsa-miR-513b	95.5	98.3		
hsa-miR-550a-5p	97.3	94.9		
hsa-miR-5581-5p	94.6	100.0		
hsa-miR-629-3p	97.3	94.9		
hsa-miR-629-5p	94.6	100.0		
hsa-miR-7-1-3p	98.2	93.2		
hsa-miR-125a-3p	94.6	98.3		
hsa-miR-1281	97.3	93.2		
hsa-miR-140-5p	95.5	96.6		
hsa-miR-144-5p	96.4	94.9		
hsa-let-7b-3p	96.4	93.2		
hsa-let-7f-1-3p	95.5	94.9		
hsa-miR-125a-5p	96.4	93.2		
hsa-miR-183-3p	96.4	93.2		

hsa-miR-3162-3p	97.3	91.5		
hsa-miR-33b-3p	97.3	91.5		
hsa-miR-4669	94.6	96.6		
hsa-miR-502-5p	96.4	93.2		
hsa-miR-1304-3p	97.3	89.8		
hsa-miR-1306-5p	95.5	93.2		
hsa-miR-221-3p	93.7	96.6		
hsa-miR-4649-3p	96.4	91.5		
hsa-miR-4690-5p	94.6	94.9		
hsa-miR-627	95.5	93.2		
hsa-miR-99a-5p	96.4	91.5		
hsa-miR-18a-5p	94.6	93.2		
hsa-miR-211-3p	94.6	93.2		
hsa-miR-4430	95.5	91.5		
hsa-miR-6508-5p	95.5	91.5		
hsa-miR-933	95.5	91.5		
hsa-miR-339-3p	94.6	91.5		
hsa-miR-624-5p	95.5	89.8		
hsa-miR-425-3p	95.5	88.1		
hsa-miR-5194	91.9	93.2		
hsa-miR-6511b-3p	92.8	91.5		
hsa-let-7d-3p	92.8	89.8		
hsa-miR-129-2-3p	92.8	89.8		
hsa-miR-1825	92.8	89.8		
hsa-miR-362-3p	93.7	88.1		
hsa-miR-665	91.0	93.2		
hsa-miR-149-5p	92.8	88.1		
hsa-miR-3620-5p	91.0	91.5		
hsa-miR-4478	90.1	91.5		
hsa-miR-4484	92.8	86.4		
hsa-miR-4656	90.1	91.5		
hsa-miR-602	91.9	88.1		
hsa-miR-1233-1-5p	89.2	91.5		
hsa-miR-3125	89.2	91.5		
hsa-miR-4725-5p	91.0	88.1		
hsa-miR-4732-5p	91.0	88.1		
hsa-miR-146b-5p	92.8	83.1		
hsa-miR-4659a-3p	91.0	86.4		
hsa-miR-6510-5p	88.3	91.5		
hsa-miR-1225-3p	91.0	84.7		
hsa-miR-1539	90.1	86.4		
hsa-miR-188-5p	88.3	89.8		
hsa-miR-4758-3p	91.0	84.7		
hsa-miR-550b-2-5p	91.9	83.1		
hsa-miR-144-3p	89.2	86.4		
hsa-miR-4310	89.2	84.7		
hsa-miR-4749-3p	89.2	84.7		
hsa-miR-1229-5p	87.4	86.4		
hsa-miR-1288	86.5	88.1		
hsa-miR-3156-5p	84.7	91.5		
hsa-miR-2116-3p	89.2	81.4		
hsa-miR-4664-3p	87.4	84.7		

hsa-miR-23c	87.4	83.1		
hsa-miR-3652	85.6	86.4		
hsa-miR-424-5p	88.3	81.4		
hsa-miR-4745-5p	85.6	86.4		
hsa-miR-1973	83.8	88.1		
hsa-miR-4291	84.7	86.4		
hsa-miR-3200-3p	86.5	81.4		
hsa-miR-4436b-5p	84.7	84.7		
hsa-miR-6512-5p	82.9	88.1		
hsa-miR-3613-3p	86.5	78.0		
hsa-miR-4793-5p	81.1	88.1		
hsa-miR-628-3p	83.8	83.1		
hsa-miR-1181	82.9	83.1		
hsa-miR-3646	82.0	84.7		
hsa-miR-4317	82.9	83.1		
hsa-miR-5684	83.8	81.4		
hsa-miR-1227-5p	81.1	84.7		
hsa-miR-3180-5p	84.7	78.0		
hsa-miR-4665-5p	82.9	81.4		
hsa-miR-129-1-3p	82.0	81.4		
hsa-miR-4652-3p	82.9	79.7		
hsa-miR-500b	82.0	79.7		
hsa-miR-181b-5p	83.8	74.6		
hsa-miR-3676-3p	82.9	76.3		
hsa-miR-671-5p	77.5	86.4		
hsa-miR-1185-1-3p	78.4	83.1		
hsa-miR-378d	78.4	83.1		
hsa-miR-1271-5p	81.1	76.3		
hsa-miR-4433-3p	78.4	81.4		
hsa-miR-564	81.1	76.3		
hsa-miR-6723-5p	81.1	76.3		
hsa-miR-100-5p	82.9	71.2		
hsa-miR-135a-3p	77.5	81.4		
hsa-miR-181a-2-3p	80.2	76.3		
hsa-miR-4666b	78.4	79.7		
hsa-miR-98-3p	79.3	76.3		
hsa-miR-3940-3p	77.5	74.6		
hsa-miR-513c-5p	74.8	79.7		
hsa-miR-634	79.3	71.2		
hsa-miR-4769-3p	77.5	72.9		
hsa-miR-6507-3p	76.6	72.9		
hsa-miR-3907	72.1	79.7		
hsa-miR-4634	73.0	78.0		
hsa-miR-563	73.9	74.6		
hsa-miR-892b	73.9	74.6		
hsa-miR-103a-2-5p	74.8	71.2		
hsa-miR-2392	73.9	72.9		
hsa-miR-3127-5p	72.1	76.3		
hsa-miR-338-5p	73.0	74.6		
hsa-miR-3614-5p	73.9	72.9		
hsa-miR-4499	70.3	79.7		
hsa-miR-3667-5p	74.8	69.5		

hsa-miR-1290	68.5	78.0		
hsa-miR-130b-5p	75.7	62.7		
hsa-miR-4449	73.0	67.8		
hsa-miR-4695-5p	70.3	67.8		
hsa-miR-4271	67.6	71.2		
hsa-miR-4651	69.4	67.8		
hsa-miR-340-5p	63.1	74.6		
hsa-miR-133b	67.6	61.0		
hsa-miR-199b-5p	70.3	55.9		
hsa-miR-200c-3p	67.6	61.0		
hsa-miR-4257	63.1	69.5		
hsa-miR-150-3p	62.2	69.5		
hsa-miR-30c-1-3p	68.5	57.6		
hsa-miR-139-3p	64.9	62.7		
hsa-miR-625-3p	62.2	67.8		
hsa-miR-106b-3p	67.6	54.2		
hsa-miR-409-3p	63.1	62.7		
hsa-miR-1237-3p	63.1	61.0		
hsa-miR-5571-5p	66.7	54.2		
hsa-miR-652-5p	63.1	61.0		
hsa-miR-196b-5p	61.3	62.7		
hsa-miR-22-5p	64.9	55.9		
hsa-miR-338-3p	64.0	55.9		
hsa-miR-26b-3p	62.2	55.9		
hsa-miR-4261	55.9	67.8		
hsa-miR-345-5p	60.4	57.6		
hsa-miR-10a-5p	58.6	59.3		
hsa-miR-3176	56.8	62.7		
hsa-miR-1224-5p	56.8	61.0		
hsa-miR-4462	55.9	62.7		
hsa-miR-4728-3p	58.6	57.6		
hsa-miR-193a-5p	59.5	54.2		
hsa-miR-664b-5p	55.9	61.0		
hsa-miR-3141	53.2	64.4		
hsa-miR-6075	55.9	59.3		
hsa-miR-6086	55.0	61.0		
hsa-miR-99b-5p	55.9	59.3		
hsa-miR-1307-3p	58.6	52.5		
hsa-miR-148b-5p	56.8	55.9		
hsa-miR-15a-3p	59.5	50.8		
hsa-miR-6513-3p	61.3	47.5		
hsa-miR-590-5p	54.1	57.6		
hsa-miR-199a-3p	52.3	59.3		
hsa-miR-301a-3p	55.0	52.5		
hsa-miR-4698	51.4	59.3		
hsa-miR-491-5p	56.8	49.2		
hsa-miR-4701-5p	53.2	54.2		
hsa-miR-572	53.2	54.2		
hsa-let-7e-5p	52.3	54.2		
hsa-miR-134	52.3	54.2		
hsa-miR-335-5p	51.4	54.2		
hsa-miR-4646-3p	54.1	49.2		

hsa-miR-4463	51.4	52.5		
hsa-miR-5690	56.8	39.0		
hsa-miR-1972	46.8	50.8		
hsa-miR-769-5p	48.6	47.5		
hsa-miR-126-5p	43.2	55.9		
hsa-miR-192-3p	52.3	39.0		
hsa-miR-4800-5p	42.3	52.5		
hsa-miR-212-3p	42.3	50.8		
hsa-miR-5010-3p	43.2	49.2		
hsa-miR-641	48.6	39.0		
hsa-miR-3648	40.5	50.8		
hsa-miR-548ai	45.9	40.7		
hsa-miR-3663-3p	42.3	44.1		
hsa-miR-4298	38.7	49.2		
hsa-miR-4707-3p	41.4	44.1		
hsa-miR-1273e	38.7	47.5		
hsa-miR-487b	36.9	49.2		
hsa-miR-1227-3p	40.5	40.7		
hsa-miR-18a-3p	43.2	35.6		
hsa-miR-769-3p	40.5	39.0		
hsa-miR-598	39.6	39.0		
hsa-miR-1273f	38.7	37.3		
hsa-miR-663a	38.7	37.3		
hsa-miR-2110	36.9	39.0		
hsa-miR-371a-5p	34.2	42.4		
hsa-miR-483-3p	36.0	39.0		
hsa-miR-5195-3p	37.8	35.6		
hsa-miR-654-3p	35.1	35.6		
hsa-miR-877-3p	34.2	37.3		
hsa-miR-3190-5p	34.2	35.6		
hsa-miR-4697-5p	34.2	35.6		
hsa-miR-617	36.0	32.2		
hsa-miR-4324	35.1	30.5		
hsa-miR-4534	31.5	35.6		
hsa-miR-4633-5p	28.8	39.0		
hsa-miR-4538	27.9	39.0		
hsa-miR-664a-5p	29.7	35.6		
hsa-miR-4312	26.1	37.3		
hsa-miR-6076	25.2	35.6		
hsa-miR-5585-3p	28.8	27.1		
hsa-miR-125b-1-3p	25.2	32.2		
hsa-miR-4632-5p	27.0	28.8		
hsa-miR-139-5p	27.9	25.4		
hsa-miR-4767	33.3	15.3		
hsa-miR-34a-5p	27.9	22.0		
hsa-miR-4455	25.2	27.1		
hsa-miR-330-3p	28.8	18.6		
hsa-miR-1180	25.2	23.7		
hsa-miR-193b-3p	28.8	16.9		
hsa-miR-4784	20.7	30.5		
hsa-miR-4667-5p	23.4	23.7		
hsa-miR-660-3p	23.4	23.7		

hsa-miR-4731-3p	22.5	23.7		
hsa-miR-503-5p	24.3	20.3		
hsa-miR-378g	18.0	27.1		
hsa-miR-4481	19.8	23.7		
hsa-miR-138-2-3p	18.9	23.7		
hsa-miR-1469	20.7	20.3		
hsa-miR-4327	21.6	18.6		
hsa-miR-1236-5p	17.1	23.7		
hsa-miR-152	18.0	22.0		
hsa-miR-21-3p	18.9	20.3		
hsa-miR-4697-3p	16.2	25.4		
hsa-miR-548aa	17.1	23.7		
hsa-miR-636	19.8	18.6		
hsa-miR-767-3p	18.0	22.0		
hsa-miR-4689	23.4	8.5		
hsa-miR-3679-3p	19.8	13.6		
hsa-miR-4326	15.3	22.0		
hsa-miR-2276	17.1	16.9		
hsa-miR-3137	17.1	16.9		
hsa-miR-4734	16.2	18.6		
hsa-miR-181c-5p	18.0	13.6		
hsa-miR-921	17.1	15.3		
hsa-miR-3688-3p	15.3	16.9		
hsa-miR-4274	15.3	16.9		
hsa-miR-4758-5p	16.2	13.6		
hsa-miR-5010-5p	15.3	15.3		
hsa-miR-4488	13.5	16.9		
hsa-miR-483-5p	14.4	15.3		
hsa-miR-542-5p	15.3	13.6		
hsa-miR-623	11.7	20.3		
hsa-miR-650	9.9	23.7		
hsa-miR-3188	11.7	18.6		
hsa-miR-378b	10.8	20.3		
hsa-miR-576-5p	12.6	16.9		
hsa-miR-20a-3p	15.3	10.2		
hsa-miR-4487	15.3	10.2		
hsa-miR-1976	12.6	13.6		
hsa-miR-3605-3p	12.6	13.6		
hsa-miR-4647	9.9	18.6		
hsa-miR-4700-3p	11.7	15.3		
hsa-miR-6503-3p	12.6	13.6		
hsa-miR-3615	10.8	13.6		
hsa-miR-424-3p	10.8	13.6		
hsa-miR-4636	11.7	11.9		
hsa-miR-4646-5p	9.0	16.9		
hsa-miR-3610	12.6	8.5		
hsa-miR-557	9.9	13.6		
hsa-miR-718	14.4	5.1		
hsa-miR-193b-5p	9.0	13.6		
hsa-miR-3692-5p	12.6	6.8		
hsa-miR-509-3-5p	11.7	8.5		
hsa-miR-1470	10.8	8.5		

hsa-miR-28-3p	8.1	13.6		
hsa-miR-378f	10.8	8.5		
hsa-miR-4252	6.3	16.9		
hsa-miR-4417	11.7	6.8		
hsa-miR-4498	10.8	8.5		
hsa-miR-491-3p	8.1	13.6		
hsa-miR-495-3p	7.2	15.3		
hsa-miR-5096	12.6	5.1		
hsa-miR-1229-3p	6.3	15.3		
hsa-miR-299-5p	6.3	15.3		
hsa-miR-3138	6.3	15.3		
hsa-miR-335-3p	8.1	11.9		
hsa-miR-3682-3p	8.1	11.9		
hsa-miR-485-3p	8.1	11.9		
hsa-miR-630	7.2	13.6		
hsa-miR-936	9.0	10.2		
hsa-miR-101-5p	10.8	5.1		
hsa-miR-122-5p	9.9	6.8		
hsa-miR-4446-3p	5.4	15.3		
hsa-miR-4518	8.1	10.2		
hsa-miR-4640-3p	6.3	13.6		
hsa-miR-5189	8.1	10.2		
hsa-miR-6129	8.1	10.2		
hsa-miR-1471	8.1	8.5		
hsa-miR-29b-2-5p	8.1	8.5		
hsa-miR-5003-5p	5.4	13.6		
hsa-miR-1273c	6.3	10.2		
hsa-miR-190a	9.0	5.1		
hsa-miR-3675-3p	8.1	6.8		
hsa-miR-6511b-5p	5.4	11.9		
hsa-miR-1291	4.5	11.9		
hsa-miR-3934-5p	4.5	11.9		
hsa-miR-4737	7.2	6.8		
hsa-miR-486-3p	6.3	8.5		
hsa-miR-5580-3p	2.7	15.3		
hsa-miR-671-3p	7.2	6.8		
hsa-miR-154-5p	6.3	6.8		
hsa-miR-3158-5p	7.2	5.1		
hsa-miR-337-3p	3.6	11.9		
hsa-miR-363-5p	4.5	10.2		
hsa-miR-376a-3p	3.6	11.9		
hsa-miR-5190	3.6	11.9		
hsa-miR-5701	6.3	6.8		
hsa-miR-770-5p	3.6	11.9		
hsa-miR-1226-5p	3.6	10.2		
hsa-miR-1267	6.3	5.1		
hsa-miR-1306-3p	6.3	5.1		
hsa-miR-3154	4.5	8.5		
hsa-miR-329	3.6	10.2		
hsa-miR-4659b-3p	7.2	3.4		
hsa-miR-6134	3.6	10.2		
hsa-miR-181a-3p	4.5	6.8		

hsa-miR-1827	5.4	5.1		
hsa-miR-3926	2.7	10.2		
hsa-miR-662	4.5	6.8		
hsa-miR-127-3p	4.5	5.1		
hsa-miR-148a-5p	3.6	6.8		
hsa-miR-18b-3p	3.6	6.8		
hsa-miR-202-3p	2.7	8.5		
hsa-miR-4325	2.7	8.5		
hsa-miR-4673	5.4	3.4		
hsa-miR-4730	6.3	1.7		
hsa-miR-489	4.5	5.1		
hsa-miR-584-3p	4.5	5.1		
hsa-miR-6720-3p	1.8	10.2		
hsa-let-7i-3p	5.4	1.7		
hsa-miR-1307-5p	3.6	5.1		
hsa-miR-204-5p	4.5	3.4		
hsa-miR-218-5p	4.5	3.4		
hsa-miR-378e	3.6	5.1		
hsa-miR-3911	2.7	6.8		
hsa-miR-543	3.6	5.1		
hsa-miR-5703	3.6	5.1		
hsa-miR-589-3p	3.6	5.1		
hsa-miR-885-5p	1.8	8.5		
hsa-let-7g-3p	3.6	3.4		
hsa-miR-1185-2-3p	4.5	1.7		
hsa-miR-1238-5p	3.6	3.4		
hsa-miR-19b-1-5p	3.6	3.4		
hsa-miR-3130-5p|	2.7	5.1		
hsa-miR-3163	3.6	3.4		
hsa-miR-377-3p	2.7	5.1		
hsa-miR-421	2.7	5.1		
hsa-miR-4419a	2.7	5.1		
hsa-miR-4425	3.6	3.4		
hsa-miR-4470	3.6	3.4		
hsa-miR-4539	2.7	5.1		
hsa-miR-516a-5p	3.6	3.4		
hsa-miR-610	4.5	1.7		
hsa-miR-628-5p	3.6	3.4		
hsa-miR-99b-3p	2.7	5.1		
hsa-let-7f-2-3p	2.7	3.4		
hsa-miR-193a-3p	0.9	6.8		
hsa-miR-195-3p	2.7	3.4		
hsa-miR-221-5p	3.6	1.7		
hsa-miR-223-5p	4.5	0.0		
hsa-miR-23a-5p	1.8	5.1		
hsa-miR-25-5p	1.8	5.1		
hsa-miR-3616-3p	0.9	6.8		
hsa-miR-376c-3p	1.8	5.1		
hsa-miR-4701-3p	2.7	3.4		
hsa-miR-4743-5p	1.8	5.1		
hsa-miR-5008-5p	1.8	5.1		
hsa-miR-570-3p	2.7	3.4		

hsa-miR-595	1.8	5.1		
hsa-miR-6716-3p	3.6	1.7		
hsa-miR-887	2.7	3.4		
hsa-miR-1299	0.9	5.1		
hsa-miR-133a	2.7	1.7		
hsa-miR-198	1.8	3.4		
hsa-miR-3622b-5p	0.9	5.1		
hsa-miR-373-5p	3.6	0.0		
hsa-miR-3917	0.9	5.1		
hsa-miR-409-5p	1.8	3.4		
hsa-miR-4440	2.7	1.7		
hsa-miR-4514	0.9	5.1		
hsa-miR-4535	0.9	5.1		
hsa-miR-4668-5p	0.9	5.1		
hsa-miR-4776-5p	0.9	5.1		
hsa-miR-4793-3p	2.7	1.7		
hsa-miR-542-3p	0.9	5.1		
hsa-miR-548am-5p	1.8	3.4		
hsa-miR-548q	1.8	3.4		
hsa-miR-582-5p	2.7	1.7		
hsa-miR-654-5p	1.8	3.4		
hsa-miR-758-3p	2.7	1.7		
hsa-miR-760	0.0	6.8		
hsa-miR-765	1.8	3.4		
hsa-miR-875-5p	1.8	3.4		
hsa-miR-106a-3p	2.7	0.0		
hsa-miR-1236-3p	0.0	5.1		
hsa-miR-1255b-5p	1.8	1.7		
hsa-miR-181c-3p	2.7	0.0		
hsa-miR-26a-2-3p	0.9	3.4		
hsa-miR-298	0.9	3.4		
hsa-miR-3194-5p	0.9	3.4		
hsa-miR-3620-3p	1.8	1.7		
hsa-miR-374a-3p	1.8	1.7		
hsa-miR-411-3p	1.8	1.7		
hsa-miR-4475	0.9	3.4		
hsa-miR-4476	0.9	3.4		
hsa-miR-4716-5p	1.8	1.7		
hsa-miR-4762-3p	1.8	1.7		
hsa-miR-544a	1.8	1.7		
hsa-miR-548d-5p	1.8	1.7		
hsa-miR-561-3p	1.8	1.7		
hsa-miR-5695	2.7	0.0		
hsa-miR-580	1.8	1.7		
hsa-miR-612	1.8	1.7		
hsa-miR-622	0.9	3.4		
hsa-miR-670	1.8	1.7		
hsa-miR-744-3p	1.8	1.7		
hsa-let-7a-3p	0.9	1.7		
hsa-miR-1255a	0.9	1.7		
hsa-miR-1270	0.9	1.7		
hsa-miR-185-3p	0.0	3.4		

hsa-miR-186-3p	0.0	3.4		
hsa-miR-187-5p	0.9	1.7		
hsa-miR-194-3p	1.8	0.0		
hsa-miR-200b-5p	0.9	1.7		
hsa-miR-2052	0.0	3.4		
hsa-miR-224-5p	0.9	1.7		
hsa-miR-2964a-5p	0.9	1.7		
hsa-miR-29b-1-5p	0.9	1.7		
hsa-miR-30d-3p	0.0	3.4		
hsa-miR-3150b-5p	1.8	0.0		
hsa-miR-3184-3p	0.9	1.7		
hsa-miR-32-3p	0.9	1.7		
hsa-miR-323a-3p	1.8	0.0		
hsa-miR-3663-5p	1.8	0.0		
hsa-miR-370	0.9	1.7		
hsa-miR-376a-5p	0.9	1.7		
hsa-miR-381-3p	0.9	1.7		
hsa-miR-3924	0.0	3.4		
hsa-miR-3945	0.9	1.7		
hsa-miR-422a	1.8	0.0		
hsa-miR-4289	0.9	1.7		
hsa-miR-432-3p	0.0	3.4		
hsa-miR-4468	0.9	1.7		
hsa-miR-452-3p	0.9	1.7		
hsa-miR-452-5p	0.0	3.4		
hsa-miR-4714-5p	0.9	1.7		
hsa-miR-504	1.8	0.0		
hsa-miR-5088	0.0	3.4		
hsa-miR-518b	0.9	1.7		
hsa-miR-545-3p	0.9	1.7		
hsa-miR-545-5p	0.9	1.7		
hsa-miR-548at-5p	0.9	1.7		
hsa-miR-556-3p	0.9	1.7		
hsa-miR-559	0.0	3.4		
hsa-miR-5686	0.9	1.7		
hsa-miR-5692a	0.0	3.4		
hsa-miR-586	0.9	1.7		
hsa-miR-590-3p	1.8	0.0		
hsa-miR-601	0.9	1.7		
hsa-miR-607	0.9	1.7		
hsa-miR-619	0.0	3.4		
hsa-miR-624-3p	1.8	0.0		
hsa-miR-642a-5p	0.9	1.7		
hsa-miR-645	0.9	1.7		
hsa-miR-668	0.9	1.7		
hsa-miR-6722-3p	1.8	0.0		
hsa-miR-675-5p	0.9	1.7		
hsa-miR-888-3p	0.9	1.7		
hsa-miR-937-3p	0.9	1.7		
hsa-miR-939-3p	0.9	1.7		
hsa-miR-10b-3p	0.0	1.7		
hsa-miR-10b-5p	0.0	1.7		

hsa-miR-1183	0.0	1.7		
hsa-miR-1208	0.0	1.7		
hsa-miR-1226-3p	0.0	1.7		
hsa-miR-1228-5p	0.0	1.7		
hsa-miR-124-3p	0.9	0.0		
hsa-miR-124-5p	0.0	1.7		
hsa-miR-1247-3p	0.9	0.0		
hsa-miR-1261	0.0	1.7		
hsa-miR-1269a	0.0	1.7		
hsa-miR-1273d	0.9	0.0		
hsa-miR-1285-5p	0.0	1.7		
hsa-miR-1287	0.0	1.7		
hsa-miR-1296	0.0	1.7		
hsa-miR-143-3p	0.9	0.0		
hsa-miR-1538	0.0	1.7		
hsa-miR-16-1-3p	0.9	0.0		
hsa-miR-184	0.9	0.0		
hsa-miR-188-3p	0.9	0.0		
hsa-miR-1909-5p	0.0	1.7		
hsa-miR-1910	0.0	1.7		
hsa-miR-196a-3p	0.9	0.0		
hsa-miR-19a-5p	0.0	1.7		
hsa-miR-19b-2-5p	0.9	0.0		
hsa-miR-205-5p	0.9	0.0		
hsa-miR-206	0.0	1.7		
hsa-miR-20b-3p	0.9	0.0		
hsa-miR-2115-5p	0.9	0.0		
hsa-miR-218-1-3p	0.0	1.7		
hsa-miR-218-2-3p	0.9	0.0		
hsa-miR-2277-3p	0.0	1.7		
hsa-miR-2681-3p	0.9	0.0		
hsa-miR-26a-1-3p	0.9	0.0		
hsa-miR-27b-5p	0.0	1.7		
hsa-miR-297	0.0	1.7		
hsa-miR-29a-5p	0.0	1.7		
hsa-miR-300	0.9	0.0		
hsa-miR-301b	0.9	0.0		
hsa-miR-302b-3p	0.0	1.7		
hsa-miR-30a-3p	0.9	0.0		
hsa-miR-3132	0.0	1.7		
hsa-miR-3149	0.0	1.7		
hsa-miR-3157-5p	0.0	1.7		
hsa-miR-3161	0.0	1.7		
hsa-miR-32-5p	0.9	0.0		
hsa-miR-330-5p	0.9	0.0		
hsa-miR-33a-3p	0.9	0.0		
hsa-miR-33b-5p	0.0	1.7		
hsa-miR-34c-3p	0.0	1.7		
hsa-miR-3591-3p	0.0	1.7		
hsa-miR-3607-3p	0.9	0.0		
hsa-miR-3654	0.0	1.7		
hsa-miR-3666	0.0	1.7		

hsa-miR-367-5p	0.9	0.0		
hsa-miR-374b-3p	0.9	0.0		
hsa-miR-379-3p	0.9	0.0		
hsa-miR-380-5p	0.9	0.0		
hsa-miR-3935	0.0	1.7		
hsa-miR-3937	0.0	1.7		
hsa-miR-3942-3p	0.9	0.0		
hsa-miR-3976	0.0	1.7		
hsa-miR-410	0.0	1.7		
hsa-miR-4259	0.0	1.7		
hsa-miR-4272	0.0	1.7		
hsa-miR-4290	0.0	1.7		
hsa-miR-4294	0.0	1.7		
hsa-miR-431-5p	0.0	1.7		
hsa-miR-4420	0.9	0.0		
hsa-miR-4422	0.0	1.7		
hsa-miR-4489	0.0	1.7		
hsa-miR-4500	0.9	0.0		
hsa-miR-450a-5p	0.9	0.0		
hsa-miR-450b-3p	0.0	1.7		
hsa-miR-451b	0.9	0.0		
hsa-miR-4520b-3p	0.0	1.7		
hsa-miR-4639-3p	0.9	0.0		
hsa-miR-4648	0.0	1.7		
hsa-miR-4657	0.0	1.7		
hsa-miR-4677-3p	0.9	0.0		
hsa-miR-4677-5p	0.9	0.0		
hsa-miR-4685-3p	0.9	0.0		
hsa-miR-4694-3p	0.0	1.7		
hsa-miR-4695-3p	0.0	1.7		
hsa-miR-4707-5p	0.0	1.7		
hsa-miR-4710	0.0	1.7		
hsa-miR-4723-3p	0.9	0.0		
hsa-miR-4726-5p	0.0	1.7		
hsa-miR-4733-3p	0.0	1.7		
hsa-miR-4733-5p	0.9	0.0		
hsa-miR-4736	0.0	1.7		
hsa-miR-4740-5p	0.0	1.7		
hsa-miR-4755-3p	0.0	1.7		
hsa-miR-4762-5p	0.0	1.7		
hsa-miR-4763-5p	0.0	1.7		
hsa-miR-4785	0.0	1.7		
hsa-miR-4792	0.9	0.0		
hsa-miR-4800-3p	0.9	0.0		
hsa-miR-493-5p	0.0	1.7		
hsa-miR-5007-3p	0.9	0.0		
hsa-miR-5011-5p	0.9	0.0		
hsa-miR-5087	0.0	1.7		
hsa-miR-5093	0.0	1.7		
hsa-miR-513a-3p	0.0	1.7		
hsa-miR-513c-3p	0.0	1.7		
hsa-miR-517c-3p	0.0	1.7		

hsa-miR-518a-5p	0.0	1.7		
hsa-miR-5196-3p	0.9	0.0		
hsa-miR-520c-3p	0.9	0.0		
hsa-miR-541-3p	0.0	1.7		
hsa-miR-548a-3p	0.9	0.0		
hsa-miR-548ap-3p	0.9	0.0		
hsa-miR-548d-3p	0.9	0.0		
hsa-miR-548e	0.9	0.0		
hsa-miR-552	0.9	0.0		
hsa-miR-558	0.0	1.7		
hsa-miR-5591-3p	0.0	1.7		
hsa-miR-5681b	0.9	0.0		
hsa-miR-5692b	0.9	0.0		
hsa-miR-5692c	0.9	0.0		
hsa-miR-571	0.0	1.7		
hsa-miR-588	0.9	0.0		
hsa-miR-589-5p	0.9	0.0		
hsa-miR-593-3p	0.9	0.0		
hsa-miR-597	0.0	1.7		
hsa-miR-609	0.9	0.0		
hsa-miR-615-3p	0.0	1.7		
hsa-miR-615-5p	0.0	1.7		
hsa-miR-616-5p	0.9	0.0		
hsa-miR-618	0.0	1.7		
hsa-miR-621	0.9	0.0		
hsa-miR-631	0.0	1.7		
hsa-miR-633	0.0	1.7		
hsa-miR-637	0.0	1.7		
hsa-miR-639	0.9	0.0		
hsa-miR-642b-5p	0.9	0.0		
hsa-miR-646	0.9	0.0		
hsa-miR-6509-3p	0.9	0.0		
hsa-miR-651	0.9	0.0		
hsa-miR-6511a-3p	0.0	1.7		
hsa-miR-657	0.9	0.0		
hsa-miR-6722-5p	0.0	1.7		
hsa-miR-708-5p	0.9	0.0		
hsa-miR-767-5p	0.9	0.0		
hsa-miR-875-3p	0.0	1.7		
hsa-miR-876-5p	0.9	0.0		
hsa-miR-877-5p	0.9	0.0		
hsa-miR-891a	0.9	0.0		
hsa-miR-920	0.9	0.0		
hsa-miR-922	0.9	0.0		
hsa-miR-924	0.0	1.7		
hsa-miR-92a-2-5p	0.9	0.0		
hsa-miR-935	0.9	0.0		
hsa-miR-938	0.0	1.7		
hsa-miR-943	0.9	0.0		
hsa-miR-423-5p	100.0	100.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Functional Assessment of Cancer Therapy – Hepatobiliary Questionnaire (FACT-Hep) in Randomized portion: Overall Between-Treatment Comparison Based on the Repeated Measures Mixed Effects Model

End point title	Functional Assessment of Cancer Therapy – Hepatobiliary Questionnaire (FACT-Hep) in Randomized portion: Overall Between-Treatment Comparison Based on the Repeated Measures Mixed Effects Model[21]

End point description:

FACT-Hep consists of 27-item FACT-G, and 18-item Hepatobiliary Subscale. FACT-Hep questionnaire uses 5-point Likert rating scale, range '0'-not at all to '4'. FACT-Hep total score ranges from 0 to 180, where highest score represents maximum achievable quality of life. Domains of FACT-G include Physical Well-Being (PWB), Social/Family Well-Being (SWB), Emotional Well-Being (EWB) and Functional Well-Being (FWB). Hepatobiliary disease specific items include: swelling or cramps, losing weight, gastrointestinal (GI)-related questions, lack of energy, side effects, pain, fatigue, usual activities, jaundice, fevers, itching, taste of food and chills. Eight of the items (pain, back pain, stomach pain/discomfort, lack of energy, fatigue, nausea, weight loss and jaundice) make up FACT-Hepatobiliary Symptom Index (FHSI-8), and are considered to be symptoms specific to hepatobiliary cancer. FAS included all randomized subjects.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 pre-dose and before any other clinical assessments, every 4 weeks thereafter while on study, at end of study treatment/withdrawal, and follow-up and at Day 28 after last dose date

Notes:

[21] - 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: The endpoint was planned to be reported for Axitinib and Placebo arm only.

End point values	Axitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	68		
Units: units on a scale				
least squares mean (confidence interval 95%)	123.33 (120.17 to 126.50)	135.22 (129.17 to 141.27)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Axitinib v Placebo

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006 [22]
Method	Longitudinal mixed effect analysis
Parameter estimate	Mean difference (final values)
Point estimate	-11.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.7
upper limit	-5.08

Notes:

[22] - No adjustment made for multiple comparisons.

Secondary: Functional Assessment of Cancer Therapy - General (FACT-G) in Randomized Portion: Overall Between-Treatment Comparison Based on the Repeated Measures Mixed Effects Model

End point title	Functional Assessment of Cancer Therapy - General (FACT-G) in Randomized Portion: Overall Between-Treatment Comparison Based on the Repeated Measures Mixed Effects Model[23]

End point description:

FACT-G is core questionnaire of Functional Assessment of Chronic Illness Therapy (FACIT) measurement system to evaluate QoL in cancer population. FACT-G consisted of 27 questions grouped in 4 domains of general Health-Related QoL (HRQoL): PWB, SWB, EWB and FWB; each ranging from 0 (not at all) to 4 (very much). FACT-G ranged between 0 and 108. Since questions could be reversed coded, as appropriate, before calculating FACT-G, 0 and 108 could be considered worst and best health states. The below table included the model estimated average based on all the observed values/time points. The mixed effect model was used. FAS included all randomized subjects, and subjects were classified according to the randomized treatment arm regardless of what treatment, if any, was received.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 pre-dose and before any other clinical assessments, every 4 weeks thereafter while on study, at end of study treatment/withdrawal, and follow-up and at Day 28 after last dose date

Notes:

[23] - 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: The endpoint was planned to be reported for Axitinib and Placebo arm only.

End point values	Axitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	68		
Units: units on a scale				
least squares mean (confidence interval 95%)	71.20 (69.00 to 73.41)	78.81 (74.68 to 82.93)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time,

treatment-by-time, and baseline as covariate.

Comparison groups	Axitinib v Placebo
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0014 [24]
Method	Longitudinal mixed effect analysis
Parameter estimate	Mean difference (final values)
Point estimate	-7.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.27
upper limit	-2.94

Notes:

[24] - No adjustment made for multiple comparisons.

Secondary: Functional Assessment of Cancer Therapy (FACT)-Hepatobiliary Symptom Index-8 (FHSI-8) in Randomized Portion: Overall Between-Treatment Comparison Based on the Repeated Measures Mixed Effects Model

End point title	Functional Assessment of Cancer Therapy (FACT)-Hepatobiliary Symptom Index-8 (FHSI-8) in Randomized Portion: Overall Between-Treatment Comparison Based on the Repeated Measures Mixed Effects Model[25]

End point description:

The FACT-Hep includes the FACT-G and a hepatobiliary module. The hepatobiliary disease specific items include: swelling or cramps, losing weight, GI related questions, lack of energy, side effects, pain, fatigue, usual activities, jaundice, fevers, itching, taste of food and chills. Eight of the items (pain, back pain, stomach pain/discomfort, lack of energy, fatigue, nausea, weight loss, and jaundice) make up the FHSI-8, and are considered to be symptoms specific to hepatobiliary cancer. FHSI-8 total score ranges from 0 to 32 where "0" is a severely symptomatic subject and the highest score indicates an asymptomatic subject. The below table included the model estimated average based on all the observed values/time points. The mixed effect model was used. FAS included all randomized subjects, and subjects were classified according to the randomized treatment arm regardless of what treatment, if any, was received.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 pre-dose and before any other clinical assessments, every 4 weeks thereafter while on study, at end of study treatment/withdrawal, and follow-up and at Day 28 after last dose date

Notes:

[25] - 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: The endpoint was planned to be reported for Axitinib and Placebo arm only.

End point values	Axitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	68		
Units: units on a scale				
least squares mean (confidence interval 95%)	23.42 (22.77 to 24.07)	26.69 (25.35 to 28.03)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Axitinib v Placebo
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [26]
Method	Longitudinal mixed effect analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.76
upper limit	-1.78

Notes:

[26] - No adjustment made for multiple comparisons.

Secondary: Functional Assessment of Cancer Therapy-G (FACT-G) Subscales in Randomized Portion: Overall Between-Treatment Comparison Based on the Repeated Measures Mixed Effects Model

End point title	Functional Assessment of Cancer Therapy-G (FACT-G) Subscales in Randomized Portion: Overall Between-Treatment Comparison Based on the Repeated Measures Mixed Effects Model[27]

End point description:

FACT-G is core questionnaire of Functional Assessment of Chronic Illness Therapy (FACIT) measurement system to evaluate QoL in cancer population. FACT-G consisted of 27 questions grouped in 4 domains of general HRQoL: PWB, SWB, EWB and FWB. Each of the individual subscale, except EWB has 7 items and each integer scored 0 to 4 making a maximum possible score of 28 (range 0 to 28). EWB has 6 items and each integer scored 0 to 4 making a maximum possible score of 24 (range 0 to 24). For all the 4 scales, higher values correspond to better health. The below table included the model estimated average based on all the observed values/time points. The mixed effect model was used. FAS included all randomized subjects, and subjects were classified according to the randomized treatment arm regardless of what treatment, if any, was received.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 pre-dose and before any other clinical assessments, every 4 weeks thereafter while on study, at end of study treatment/withdrawal, and follow-up and at Day 28 after last dose date

Notes:

[27] - 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: The endpoint was planned to be reported for Axitinib and Placebo arm only.

End point values	Axitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	68		
Units: units on a scale				
least squares mean (confidence interval 95%)				
PWB	19.39 (18.72 to 20.07)	23.13 (21.76 to 24.50)		

SWB	18.94 (18.05 to 19.83)	20.21 (18.66 to 21.77)		
EWB	17.23 (16.63 to 17.84)	17.71 (16.54 to 18.89)		
FWB	15.76 (14.88 to 16.65)	17.83 (16.19 to 19.47)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Analysis presented above is for FACT-G PWB. Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.	
Comparison groups	Axitinib v Placebo
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [28]
Method	Longitudinal mixed effect analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.26
upper limit	-2.21

Notes:

[28] - No adjustment made for multiple comparisons.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Analysis presented above is for FACT-G SWB. Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.	
Comparison groups	Axitinib v Placebo
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1642 [29]
Method	Longitudinal mixed effect analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.07
upper limit	0.52

Notes:

[29] - No adjustment made for multiple comparisons.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Analysis presented above is for FACT-G EWB. Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Axitinib v Placebo
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4759 [30]
Method	Longitudinal mixed effect analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	0.84

Notes:

[30] - No adjustment made for multiple comparisons.

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Analysis presented above is for FACT-G FWB. Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Axitinib v Placebo
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0288 [31]
Method	Longitudinal mixed effect analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.92
upper limit	-0.21

Notes:

[31] - No adjustment made for multiple comparisons.

Secondary: Functional Assessment of Cancer Therapy - Hepatobiliary Cancer Subscale (FACT Hep-CS18) Questionnaire in Randomized Portion: Overall Between-Treatment Comparison Based on the Repeated Measures Mixed Effects Model

End point title	Functional Assessment of Cancer Therapy - Hepatobiliary Cancer Subscale (FACT Hep-CS18) Questionnaire in Randomized Portion: Overall Between-Treatment Comparison Based on the Repeated Measures Mixed Effects Model[32]

End point description:

This subscale consists of 18 items rated on a scale from '0' - not at all to '4' - very much regarding how much each item was present in the last 7 days. FACT-Hep-CS18 total score ranges from 0 to 72. The higher score reflects better QoL or fewer symptoms. The 18 items of this scale are associated with hepatocellular carcinoma. The below table included the model estimated average based on all the observed values/time points. The mixed effect model was used. FAS included all randomized subjects, and subjects were classified according to the randomized treatment arm regardless of what treatment, if any, was received.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 pre-dose and before any other clinical assessments, every 4 weeks thereafter while on study, at end of study treatment/withdrawal, and follow-up and at Day 28 after last dose date

Notes:

[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: The endpoint was planned to be reported for Axitinib and Placebo arm only.

End point values	Axitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	68		
Units: units on a scale				
least squares mean (confidence interval 95%)	51.78 (50.46 to 53.10)	56.74 (54.08 to 59.39)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Axitinib v Placebo
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0011 [33]
Method	Longitudinal mixed effect analysis
Parameter estimate	Mean difference (final values)
Point estimate	-4.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.93
upper limit	-1.99

Notes:

[33] - No adjustment made for multiple comparisons.

Secondary: Functional Assessment of Cancer Therapy - Hepatobiliary Cancer Trial Outcome Index (FACT Hep-TOI) Questionnaire in Randomized Portion: Overall Between-Treatment Comparison Based on the Repeated Measures Mixed Effects Model

End point title	Functional Assessment of Cancer Therapy - Hepatobiliary Cancer Trial Outcome Index (FACT Hep-TOI) Questionnaire in Randomized Portion: Overall Between-Treatment Comparison Based on the Repeated Measures Mixed Effects Model[34]

End point description:

The trial outcome index is defined to be the sum (PWB+FWB+HepCS), making it 32 items altogether. Each ranges from '0' – not at all to '4' - very much regarding how much each item was present in the last 7 days. FACT Hep –TOI total score ranges from 0 to 128, where the highest score represents a maximum achievable quality of life. The below table included the model estimated average based on all the observed values/time points. The mixed effect model was used. FAS included all randomized

subjects, and subjects were classified according to the randomized treatment arm regardless of what treatment, if any, was received.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 pre-dose and before any other clinical assessments, every 4 weeks thereafter while on study, at end of study treatment/withdrawal, and follow-up and at Day 28 after last dose date

Notes:

[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: The endpoint was planned to be reported for Axitinib and Placebo arm only.

End point values	Axitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	68		
Units: units on a scale				
least squares mean (confidence interval 95%)	87.28 (84.98 to 89.58)	97.73 (93.24 to 102.23)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Axitinib v Placebo
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [35]
Method	Longitudinal mixed effect analysis
Parameter estimate	Mean difference (final values)
Point estimate	-10.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.49
upper limit	-5.42

Notes:

[35] - No adjustment made for multiple comparisons.

Secondary: Time to Deterioration (TTD) Based on the Composite Endpoint in Randomized Portion: Overall Between-Treatment Comparison Based on the Repeated Measures Mixed Effects Model

End point title	Time to Deterioration (TTD) Based on the Composite Endpoint in Randomized Portion: Overall Between-Treatment Comparison Based on the Repeated Measures Mixed Effects Model[36]

End point description:

A time to deterioration (TTD) analysis was performed for FHSI-8. Time to deterioration was defined as the time between date of randomization and date of the event. FAS included all randomized subjects, and subjects were classified according to the randomized treatment arm regardless of what treatment, if

any, was received.

End point type	Secondary

End point timeframe:

From randomization to death or tumor progression or FHSI-8 mean score decrease >=3 points, whichever comes first

Notes:

[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: The endpoint was planned to be reported for Axitinib and Placebo arm only.

End point values	Axitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	68		
Units: months				
median (confidence interval 95%)	1.9 (1.8 to 1.9)	1.9 (1.8 to 2.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Assuming proportional hazards, a hazard ratio <1 indicates reduction in hazard rate to favor Axitinib, hazard ratio >1 indicates reduction to favor Placebo.

Comparison groups	Axitinib v Placebo
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9182 [37]
Method	1-sided, unstratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.252
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.923
upper limit	1.698

Notes:

[37] - The p-value is from a 1-sided log-rank test.

Secondary: EuroQoL (EQ-5D)- Health State Profile Utility Score in Randomized Portion: Overall Between-Treatment Comparison Based on the Repeated Measures Mixed Effects Model

End point title	EuroQoL (EQ-5D)- Health State Profile Utility Score in Randomized Portion: Overall Between-Treatment Comparison Based on the Repeated Measures Mixed Effects Model[38]

End point description:

EQ-5D: subject rated questionnaire to assess health-related quality of life in terms of a single utility score. Health State Profile component assesses level of current health for 5 domains: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression; 1 indicates better health state (no problems); 3 indicates worst health state. Scoring formula developed by EuroQol Group assigns a utility value for each domain in the profile. Score is transformed and results in a total score range -0.594 to 1.000; higher score indicates a better health state. The below table included the model estimated

average based on all the observed values/time points. The mixed effect model was used. FAS included all randomized subjects, and subjects were classified according to the randomized treatment arm regardless of what treatment, if any, was received.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 pre-dose and before any other clinical assessments, every 4 weeks thereafter while on study, at end of study treatment/withdrawal, and follow-up and at Day 28 after last dose date

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: The endpoint was planned to be reported for Axitinib and Placebo arm only.

End point values	Axitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	68		
Units: units on a scale				
least squares mean (confidence interval 95%)	0.67 (0.63 to 0.70)	0.79 (0.72 to 0.86)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Axitinib v Placebo
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0024
Method	Longitudinal mixed effect analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	-0.04

Secondary: EuroQoL Visual Analogue Scale (EQ-VAS) in Randomized Portion: Overall Between-Treatment Comparison Based on the Repeated Measures Mixed Effects Model

End point title	EuroQoL Visual Analogue Scale (EQ-VAS) in Randomized Portion: Overall Between-Treatment Comparison Based on the Repeated Measures Mixed Effects Model[39]

End point description:

EQ-5D VAS in rates the subject's overall health status using values from 0 (worst imaginable) to 100 (best imaginable). The below table included the model estimated average based on all the observed values/time points. The mixed effect model was used. FAS included all randomized subjects, and

subjects were classified according to the randomized treatment arm regardless of what treatment, if any, was received.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 pre-dose and before any other clinical assessments, every 4 weeks thereafter while on study, at end of study treatment/withdrawal, and follow-up and at Day 28 after last dose date

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: The endpoint was planned to be reported for Axitinib and Placebo arm only.

End point values	Axitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	68		
Units: units on a scale				
least squares mean (confidence interval 95%)	68.67 (66.11 to 71.23)	75.70 (70.40 to 81.00)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Axitinib v Placebo
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0193
Method	Longitudinal mixed effect analysis
Parameter estimate	Mean difference (final values)
Point estimate	-7.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.91
upper limit	-1.15

Secondary: Number of Subjects With Dose-Limiting Toxicities (DLTs) in Non-Randomized Portion

End point title	Number of Subjects With Dose-Limiting Toxicities (DLTs) in Non-Randomized Portion[40]

End point description:

Number of Child-Pugh Class B (score 7) subjects with DLT was evaluated during Cycle 1 of treatment in the non-randomized portion of the study. Subjects with Child-Pugh Class B, score 7 are only included in this analysis.

End point type	Secondary

End point timeframe:

Cycle 1 (4 weeks)

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: The endpoint was planned to be reported for Axitinib and Placebo arm only.

End point values	Child-Pugh Class B			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: subjects	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (AEs) in Non-Randomized Portion

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs) in Non-Randomized Portion[41]

End point description:

An AE was an untoward medical occurrence in a subject who received study treatment without regard to possibility of causal relationship. Serious adverse event (SAE) was an AE resulting in any of the following outcomes: death, initial or prolonged inpatient hospitalization, life-threatening experience, persistent or significant disability/incapacity, congenital anomaly. Treatment-emergent AEs were those with initial onset or that worsen in severity after the first dose of study medication. The grade of an AE was determined according to Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. The safety analysis population included subjects who received at least 1 dose of study medication with treatment assignments designated according to actual study treatment received.

End point type	Secondary

End point timeframe:

Up to 28 days after last dose of study drug (up to 6 years)

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: The endpoint was planned to be reported for Axitinib and Placebo arm only.

End point values	Child-Pugh Class A	Child-Pugh Class B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	7		
Units: subjects				
Subjects with AEs	15	7		
Subjects with SAEs	10	3		
Subjects ≥Grade 3 AEs	13	5		
Subjects Grade 5 AEs	4	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Related Adverse Events (AEs) in Non-Randomized Portion

End point title	Number of Subjects With Treatment-Related Adverse Events (AEs) in Non-Randomized Portion[42]

End point description:

Treatment-related AE was any untoward medical occurrence in a subject with causal relationship to the study drug. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. The grade of an AE was determined according to CTCAE Version 3.0. The safety analysis population included subjects who received at least 1 dose of study medication with treatment assignments designated according to actual study treatment received.

End point type	Secondary

End point timeframe:

Up to 28 days after last dose of study drug (up to 6 years)

Notes:

[42] - 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: The endpoint was planned to be reported for Axitinib and Placebo arm only.

End point values	Child-Pugh Class A	Child-Pugh Class B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	7		
Units: subjects				
Subjects with AEs	14	6		
Subjects with SAEs	2	2		
Subjects ≥Grade 3 AEs	9	4		
Subjects Grade 5 AEs	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (AEs) in Randomized Portion

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs) in Randomized Portion[43]

End point description:

An AE was an untoward medical occurrence in a subject who received study treatment without regard to possibility of causal relationship. SAE was an AE resulting in any of the following outcomes: death, initial or prolonged inpatient hospitalization, life-threatening experience, persistent or significant disability/incapacity, congenital anomaly. Treatment-emergent AEs were those with initial onset or that worsen in severity after the first dose of study medication. The grade of an AE was determined according to CTCAE Version 3.0. The safety analysis population included all randomized subjects who received at least 1 dose of study medication with treatment assignments designated according to actual study treatment received.

End point type	Secondary

End point timeframe:

Up to 28 days after last dose of study drug (up to 6 years)

Notes:

[43] - 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: The endpoint was planned to be reported for Axitinib and Placebo arm only.

End point values	Axitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	68		
Units: subjects				
Subjects with AEs	131	63		
Subjects with SAEs	62	16		
Subjects with Grade ≥3 AEs	109	26		
Subjects with Grade 5 AEs	16	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Related Adverse Events (AEs) in Randomized Portion

End point title	Number of Subjects With Treatment-Related Adverse Events (AEs) in Randomized Portion[44]

End point description:

Treatment-related AE was any untoward medical occurrence in a subject with causal relationship to the study drug. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. The grade of an AE was determined according to CTCAE Version 3.0. The safety analysis population included all randomized subjects who received at least 1 dose of study medication with treatment assignments designated according to actual study treatment received.

End point type	Secondary

End point timeframe:

Up to 28 days after last dose of study drug (up to 6 years)

Notes:

[44] - 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: The endpoint was planned to be reported for Axitinib and Placebo arm only.

End point values	Axitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	68		
Units: subjects				
Subjects with AEs	128	40		
Subjects with SAEs	24	1		
Subjects with Grade ≥3 AEs	90	12		
Subjects with Grade 5 AEs	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to follow-up visit (up to 6 years)

Adverse event reporting additional description:

The same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as nonserious in another subject, or one subject may have experienced both a serious and nonserious event during the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Child-Pugh Class A

Reporting group description:

Subjects with Child-Pugh Class A disease (score 5 or 6) were enrolled into the non-randomized portion at selected sites only at a starting axitinib dose of 5 mg BID.

Reporting group title	Axitinib

Reporting group description:

Subjects in this group received axitinib + best supportive care. Subjects with Child-Pugh Class A disease (score 5 or 6) were enrolled into the randomized portion at a starting axitinib dose of 5 mg BID orally. Subjects with Child-Pugh Class B disease (score 7) were to begin enrollment into the randomized portion of the study following determination of the recommended axitinib starting dose in the non-randomized portion. Study treatment was administered in cycles of 4 weeks in duration.

Reporting group title	Placebo

Reporting group description:

Subjects in this group received placebo + best supportive care. Treatment was administered in cycles of 4 weeks in duration. The starting dose of placebo for subjects with Child Pugh Class A disease (score 5 or 6) was chosen as 5 mg BID. Subjects with Child-Pugh Class B, score 7 received placebo that was determined from the non-randomized portion of the study until the recommended starting dose was determined, subjects with Child-Pugh Class B, score 7, were not permitted to enter the randomized portion of the study.

Reporting group title	Child-Pugh Class B

Reporting group description:

Subjects with Child-Pugh Class B disease (score 7) at selected sites were initially enrolled only into the non randomized portion of this study to determine the recommended starting dose of axitinib for this population.

Serious adverse events	Child-Pugh Class A	Axitinib	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 15 (66.67%)	62 / 133 (46.62%)	16 / 68 (23.53%)
number of deaths (all causes)	14	100	52
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			

subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Malignant neoplasm progression			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Tumour rupture			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (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
Hypotension			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 15 (0.00%)	4 / 133 (3.01%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	3 / 15 (20.00%)	8 / 133 (6.02%)	4 / 68 (5.88%)
occurrences causally related to treatment / all	0 / 3	0 / 8	0 / 5
deaths causally related to treatment / all	0 / 3	0 / 12	0 / 6
General physical health deterioration			
subjects affected / exposed	0 / 15 (0.00%)	3 / 133 (2.26%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1

Inflammation			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (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
Oedema peripheral			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 15 (6.67%)	3 / 133 (2.26%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Obstructive airways disorder			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pulmonary alveolar haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (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
Respiratory failure			
subjects affected / exposed	0 / 15 (0.00%)	2 / 133 (1.50%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (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
Dysthymic disorder			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (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
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (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			
Femur fracture			

subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (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
Humerus fracture			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (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
Road traffic accident			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (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
Bradycardia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (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
Ventricular tachycardia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (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
Nervous system disorders			
Brain stem infarction			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (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
Coma hepatic			

subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (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
Dizziness			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 15 (0.00%)	2 / 133 (1.50%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	0 / 15 (0.00%)	4 / 133 (3.01%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	2 / 6	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Quadriparesis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			

subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (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
Eye disorders			
Cataract			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal vein occlusion			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 15 (6.67%)	3 / 133 (2.26%)	2 / 68 (2.94%)
occurrences causally related to treatment / all	1 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	2 / 68 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 15 (0.00%)	7 / 133 (5.26%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	7 / 9	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis haemorrhagic			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (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
Gastric ulcer			

subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (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
Gastrointestinal disorder			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Haematochezia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (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
Rectal haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varices oesophageal			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	0 / 68 (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 / 15 (0.00%)	1 / 133 (0.75%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (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
Cholangitis			

subjects affected / exposed	0 / 15 (0.00%)	4 / 133 (3.01%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	2 / 15 (13.33%)	1 / 133 (0.75%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	0 / 15 (0.00%)	2 / 133 (1.50%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 2	0 / 0
Hepatic function abnormal			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hepatorenal syndrome			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Jaundice cholestatic			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stone			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (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
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Renal failure			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Renal impairment			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (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
Ureteric obstruction			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (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
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (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
Necrotising myositis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (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
Osteoporotic fracture			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess rupture			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (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

Gastroenteritis			
subjects affected / exposed	0 / 15 (0.00%)	2 / 133 (1.50%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (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
Ovarian abscess			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis bacterial			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	0 / 68 (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	1 / 15 (6.67%)	1 / 133 (0.75%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Sepsis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 15 (0.00%)	3 / 133 (2.26%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Cachexia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (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
Decreased appetite			
subjects affected / exposed	1 / 15 (6.67%)	1 / 133 (0.75%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 15 (0.00%)	3 / 133 (2.26%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Electrolyte imbalance			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	0 / 68 (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
Hyperkalaemia			
subjects affected / exposed	0 / 15 (0.00%)	2 / 133 (1.50%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	0 / 68 (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
Hypovolaemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 133 (0.75%)	0 / 68 (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

Serious adverse events	Child-Pugh Class B		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 7 (42.86%)		
number of deaths (all causes)	6		
number of deaths resulting from adverse events			

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Malignant neoplasm progression			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tumour rupture			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Disease progression			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			

subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Inflammation				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Bronchospasm				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung disorder				

subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Obstructive airways disorder				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary alveolar haemorrhage				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Completed suicide				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dysthymic disorder				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ventricular tachycardia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Brain stem infarction			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebral infarction			

subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coma hepatic				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic encephalopathy				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Quadriparesis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				

subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Cataract				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Retinal vein occlusion				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enterocolitis haemorrhagic				

subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorder				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematochezia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Varices oesophageal				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Bile duct stenosis				

subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholangitis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis acute				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic failure				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic function abnormal				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatorenal syndrome				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Jaundice cholestatic				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bile duct stone				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Drug eruption				

subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal impairment			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ureteric obstruction			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Necrotising myositis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteoporotic fracture			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess rupture			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Appendicitis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Otitis media				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ovarian abscess				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peritonitis bacterial				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	0 / 7 (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 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Decreased appetite			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Electrolyte imbalance			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypovolaemia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Child-Pugh Class A	Axitinib	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)	130 / 133 (97.74%)	55 / 68 (80.88%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour associated fever			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 15 (46.67%)	72 / 133 (54.14%)	9 / 68 (13.24%)
occurrences (all)	10	128	9
Hypotension			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	2	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 15 (0.00%)	27 / 133 (20.30%)	3 / 68 (4.41%)
occurrences (all)	0	59	3
Chest discomfort			
subjects affected / exposed	2 / 15 (13.33%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	6	0	0
Chest pain			
subjects affected / exposed	2 / 15 (13.33%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	7	0	0
Chills			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Face oedema			
subjects affected / exposed	2 / 15 (13.33%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	2	0	0
Fatigue			
subjects affected / exposed	12 / 15 (80.00%)	46 / 133 (34.59%)	18 / 68 (26.47%)
occurrences (all)	23	81	25
Influenza like illness			

subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	4	0	0
Malaise			
subjects affected / exposed	0 / 15 (0.00%)	13 / 133 (9.77%)	1 / 68 (1.47%)
occurrences (all)	0	19	1
Mucosal inflammation			
subjects affected / exposed	1 / 15 (6.67%)	8 / 133 (6.02%)	0 / 68 (0.00%)
occurrences (all)	1	11	0
Oedema			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			
subjects affected / exposed	4 / 15 (26.67%)	14 / 133 (10.53%)	10 / 68 (14.71%)
occurrences (all)	6	21	13
Pain			
subjects affected / exposed	5 / 15 (33.33%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	6	0	0
Pyrexia			
subjects affected / exposed	3 / 15 (20.00%)	16 / 133 (12.03%)	3 / 68 (4.41%)
occurrences (all)	5	21	3
Catheter site pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 15 (20.00%)	16 / 133 (12.03%)	6 / 68 (8.82%)
occurrences (all)	7	17	7
Dysphonia			
subjects affected / exposed	6 / 15 (40.00%)	33 / 133 (24.81%)	0 / 68 (0.00%)
occurrences (all)	11	48	0
Dyspnoea			
subjects affected / exposed	3 / 15 (20.00%)	13 / 133 (9.77%)	6 / 68 (8.82%)
occurrences (all)	8	15	6
Epistaxis			

subjects affected / exposed	1 / 15 (6.67%)	10 / 133 (7.52%)	2 / 68 (2.94%)
occurrences (all)	4	10	2
Haemoptysis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Interstitial lung disease			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Nasal congestion			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Nasal inflammation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	2 / 15 (13.33%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	2	0	0
Productive cough			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract inflammation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Confusional state			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Depression			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	2 / 15 (13.33%)	12 / 133 (9.02%)	3 / 68 (4.41%)
occurrences (all)	2	16	5

Irritability			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 15 (13.33%)	8 / 133 (6.02%)	2 / 68 (2.94%)
occurrences (all)	2	10	3
Alpha 1 foetoprotein increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Ammonia increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 15 (26.67%)	10 / 133 (7.52%)	4 / 68 (5.88%)
occurrences (all)	6	13	6
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 15 (13.33%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	3	0	0
Blood bilirubin increased			
subjects affected / exposed	1 / 15 (6.67%)	7 / 133 (5.26%)	0 / 68 (0.00%)
occurrences (all)	2	19	0
Blood creatinine increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 15 (6.67%)	9 / 133 (6.77%)	0 / 68 (0.00%)
occurrences (all)	2	10	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 15 (20.00%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	3	0	0
Neutrophil count decreased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Platelet count decreased			

subjects affected / exposed	2 / 15 (13.33%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	2	0	0
Weight decreased			
subjects affected / exposed	5 / 15 (33.33%)	36 / 133 (27.07%)	2 / 68 (2.94%)
occurrences (all)	12	77	2
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Fall			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Laceration			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Procedural pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	0 / 15 (0.00%)	9 / 133 (6.77%)	0 / 68 (0.00%)
occurrences (all)	0	9	0
Dizziness			
subjects affected / exposed	6 / 15 (40.00%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	8	0	0
Headache			
subjects affected / exposed	5 / 15 (33.33%)	21 / 133 (15.79%)	3 / 68 (4.41%)
occurrences (all)	10	21	4

Hepatic encephalopathy			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 15 (13.33%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	2	0	0
Tremor			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 15 (0.00%)	8 / 133 (6.02%)	0 / 68 (0.00%)
occurrences (all)	0	13	0
Ear and labyrinth disorders			
Ear disorder			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Ocular surface disease			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 15 (13.33%)	5 / 133 (3.76%)	7 / 68 (10.29%)
occurrences (all)	3	6	7
Abdominal pain			
subjects affected / exposed	6 / 15 (40.00%)	45 / 133 (33.83%)	12 / 68 (17.65%)
occurrences (all)	12	72	16
Abdominal pain upper			
subjects affected / exposed	2 / 15 (13.33%)	17 / 133 (12.78%)	3 / 68 (4.41%)
occurrences (all)	9	20	4

Anal inflammation			
subjects affected / exposed	2 / 15 (13.33%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	2	0	0
Ascites			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	5 / 15 (33.33%)	21 / 133 (15.79%)	8 / 68 (11.76%)
occurrences (all)	6	25	9
Diarrhoea			
subjects affected / exposed	9 / 15 (60.00%)	71 / 133 (53.38%)	8 / 68 (11.76%)
occurrences (all)	30	201	10
Dry mouth			
subjects affected / exposed	1 / 15 (6.67%)	7 / 133 (5.26%)	2 / 68 (2.94%)
occurrences (all)	1	7	2
Dyspepsia			
subjects affected / exposed	5 / 15 (33.33%)	10 / 133 (7.52%)	6 / 68 (8.82%)
occurrences (all)	9	14	6
Enterocolitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Gastritis erosive			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Glossitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	5 / 15 (33.33%)	35 / 133 (26.32%)	7 / 68 (10.29%)
occurrences (all)	7	54	8
Stomatitis			
subjects affected / exposed	3 / 15 (20.00%)	19 / 133 (14.29%)	0 / 68 (0.00%)
occurrences (all)	9	34	0
Varices oesophageal			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0

Vomiting			
subjects affected / exposed	3 / 15 (20.00%)	26 / 133 (19.55%)	7 / 68 (10.29%)
occurrences (all)	3	41	13
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 15 (0.00%)	6 / 133 (4.51%)	7 / 68 (10.29%)
occurrences (all)	0	6	8
Blister			
subjects affected / exposed	2 / 15 (13.33%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	2	0	0
Dry skin			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Facial wasting			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Nail disorder			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Night sweats			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	8 / 15 (53.33%)	45 / 133 (33.83%)	4 / 68 (5.88%)
occurrences (all)	33	135	4
Petechiae			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	0 / 15 (0.00%)	11 / 133 (8.27%)	8 / 68 (11.76%)
occurrences (all)	0	12	10

Rash			
subjects affected / exposed	2 / 15 (13.33%)	23 / 133 (17.29%)	2 / 68 (2.94%)
occurrences (all)	2	32	2
Skin ulcer			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Dysuria			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Pollakiuria			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Proteinuria			
subjects affected / exposed	4 / 15 (26.67%)	27 / 133 (20.30%)	1 / 68 (1.47%)
occurrences (all)	9	79	1
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	4 / 15 (26.67%)	33 / 133 (24.81%)	0 / 68 (0.00%)
occurrences (all)	8	40	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 15 (13.33%)	7 / 133 (5.26%)	1 / 68 (1.47%)
occurrences (all)	4	9	1
Arthropathy			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	4 / 15 (26.67%)	11 / 133 (8.27%)	11 / 68 (16.18%)
occurrences (all)	7	12	13
Bone pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0

Flank pain			
subjects affected / exposed	4 / 15 (26.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	8	0	0
Muscle spasms			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Muscular weakness			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	2 / 15 (13.33%)	8 / 133 (6.02%)	4 / 68 (5.88%)
occurrences (all)	2	9	6
Musculoskeletal chest pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal discomfort			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal stiffness			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Neck pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	2 / 15 (13.33%)	7 / 133 (5.26%)	1 / 68 (1.47%)
occurrences (all)	5	8	2
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Cystitis			

subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	2	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 15 (0.00%)	9 / 133 (6.77%)	8 / 68 (11.76%)
occurrences (all)	0	12	9
Pneumonia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 15 (40.00%)	62 / 133 (46.62%)	14 / 68 (20.59%)
occurrences (all)	12	138	26
Dehydration			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 15 (0.00%)	9 / 133 (6.77%)	0 / 68 (0.00%)
occurrences (all)	0	10	0
Hypercalcaemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 15 (0.00%)	9 / 133 (6.77%)	2 / 68 (2.94%)
occurrences (all)	0	10	5
Hypoalbuminaemia			
subjects affected / exposed	4 / 15 (26.67%)	8 / 133 (6.02%)	1 / 68 (1.47%)
occurrences (all)	4	9	2
Hypocalcaemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Hyponatraemia			
subjects affected / exposed	1 / 15 (6.67%)	8 / 133 (6.02%)	3 / 68 (4.41%)
occurrences (all)	1	10	4
Hypophosphataemia			

subjects affected / exposed	1 / 15 (6.67%)	0 / 133 (0.00%)	0 / 68 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Child-Pugh Class B		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour associated fever			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 7 (42.86%)		
occurrences (all)	5		
Hypotension			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	5		
Chest discomfort			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Chest pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Chills			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Face oedema			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		

Influenza like illness subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Malaise subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 3		
Mucosal inflammation subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Oedema subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Oedema peripheral subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Pyrexia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Catheter site pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Dysphonia subjects affected / exposed occurrences (all)	3 / 7 (42.86%) 3		
Dyspnoea subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Epistaxis			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Haemoptysis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Interstitial lung disease			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Nasal congestion			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Nasal inflammation			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Productive cough			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Upper respiratory tract inflammation			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Confusional state			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		

Irritability			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Alpha 1 foetoprotein increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Ammonia increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Blood bilirubin increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Blood creatinine increased			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Neutrophil count decreased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Platelet count decreased			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	3 / 7 (42.86%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Laceration			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Procedural pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	3		

Hepatic encephalopathy subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Neuropathy peripheral subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Tremor subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Ear and labyrinth disorders Ear disorder subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Eye disorders Ocular surface disease subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Abdominal pain subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		

Anal inflammation				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Ascites				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences (all)	1			
Constipation				
subjects affected / exposed	2 / 7 (28.57%)			
occurrences (all)	2			
Diarrhoea				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences (all)	1			
Dry mouth				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Dyspepsia				
subjects affected / exposed	2 / 7 (28.57%)			
occurrences (all)	3			
Enterocolitis				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences (all)	1			
Gastritis erosive				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences (all)	2			
Glossitis				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences (all)	1			
Nausea				
subjects affected / exposed	3 / 7 (42.86%)			
occurrences (all)	4			
Stomatitis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences (all)	0			
Varices oesophageal				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences (all)	1			

Vomiting			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Alopecia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Blister			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Dry skin			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Facial wasting			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Nail disorder			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Night sweats			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Petechiae			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		

Rash			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Skin ulcer			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Dysuria			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Pollakiuria			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Proteinuria			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	5		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Arthropathy			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Bone pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		

Flank pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Muscular weakness			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Musculoskeletal discomfort			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Musculoskeletal stiffness			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Neck pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Cystitis			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 7 (71.43%)		
occurrences (all)	8		
Dehydration			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypercalcaemia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Hyperkalaemia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	3		
Hypoalbuminaemia			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Hypocalcaemia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
Hyponatraemia			
subjects affected / exposed	3 / 7 (42.86%)		
occurrences (all)	4		
Hypophosphataemia			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 April 2011	- Inclusion criterion was revised to remove "subjects must have received at least 4 weeks of prior therapy". - Inclusion criterion was revised to allow enrollment of subjects with mild and clinically irrelevant ascites (i.e., Child-Pugh score of 2). - Exclusion criterion was removed to allow enrollment of subjects with prior history of liver transplant. - Exclusion criterion was revised to be consistent with inclusion criterion to allow enrollment of subjects with mild and clinically irrelevant ascites (i.e., Child-Pugh score of 2). - Exclusion criterion was revised to clarify that subjects with invasion to 1st or 2nd branch of portal vein are allowed. - Exclusion criterion was revised to allow enrollment of subjects whose ulcer is completely healed confirmed by endoscopy prior to study treatment. - One DLT criterion was added "Compliance with taking the drug through the end of Cycle 1 is <75% because of treatment-related toxicity, regarded as a DLT by both investigator and sponsor". – "Management of Axitinib-Related Adverse Events" section was revised to emphasize that "Subjects should continue study treatment unless they experience intolerable AEs or if the subject is no longer benefiting from the treatment. In case of drug-related AEs, toxicity should be managed by introducing medication or dose reduction if necessary". – "SAE" section was revised; added the definition and reporting requirement of potential cases of drug-induced liver injury.
11 June 2012	- "AE Follow-up" was clarified when follow-up of an AE by the investigator was required, to reflect current regulatory guidance. - Language about active reporting period was clarified and added necessity to report all SAEs post-active reporting period, to reflect current regulatory requirement. - Definition of AE was updated, including addition of medication error, and clarified that drug abuse and drug dependency are to be considered AEs, to reflect current regulatory requirement. - The definition of persistent or significant disability/incapacity in the context of SAE criteria was clarified to indicate that it includes substantial disruption of the ability to conduct normal life functions. - Clarification of the criteria for laboratory abnormalities that required further evaluation in the context of potential cases of drug-induced liver injury. The recommended list of repeated laboratory tests was updated to include prothrombin time. – "Causality Assessment" was clarified that generally the facts (evidence) or arguments to suggest a causal relationship were to be provided by the investigator.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported