Clinical trial results:
A Phase 3, Randomized, Double-Blind Study of Tivantinib (ARQ 197) in Subjects with MET Diagnostic-High Inoperable Hepatocellular Carcinoma (HCC) Treated with One Prior Systemic Therapy

Summary

EudraCT number	2012-003308-10
Trial protocol	IT SE BE DE AT PT NL ES FR
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	19 April 2018
First version publication date	19 April 2018

Trial information

Trial identification

Sponsor protocol code	ARQ197-A-U303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01755767
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Daiichi Sankyo, Inc.
Sponsor organisation address	211 Mt. Airy Road, Basking Ridge, United States, 07920
Public contact	Clinical Trial Information, DAIICHI SANKYO DEVELOPMENT LIMITED, +44 1753482800, info@dsd-eu.com
Scientific contact	Clinical Trial Information, DAIICHI SANKYO DEVELOPMENT LIMITED, +44 1753482800, info@dsd-eu.com
Sponsor organisation name	ArQule, Inc.
Sponsor organisation address	One Wall Street, Burlington, Massachusetts, United States, 01803
Public contact	Clinical Trial Information, DAIICHI SANKYO DEVELOPMENT LIMITED, +44 1753482800, info@dsd-eu.com
Scientific contact	Clinical Trial Information, DAIICHI SANKYO DEVELOPMENT LIMITED, +44 1753482800, info@dsd-eu.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	Interim
Date of interim/final analysis	28 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 March 2017
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate overall survival (OS) among all subjects in the intent-to-treat (ITT) population compared to placebo.

Protection of trial subjects:

This trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 December 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	36 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Spain: 33
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	Austria: 19
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	France: 67
Country: Number of subjects enrolled	Germany: 36
Country: Number of subjects enrolled	Italy: 133
Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Brazil: 8
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	United States: 49

Worldwide total number of subjects	383
EEA total number of subjects	307

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)	164
From 65 to 84 years	215
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

A total of 383 patients were enrolled in 121 centers throughout Europe, the Americas, and Asia Pacific

Pre-assignment

Screening details:

A total of 826 patients were screened but not randomized.

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	Tivantinib 240 mg BID Cohort

Arm description:

Patients receive Tivantinib 240 mg, administered as oral tablets twice daily (BID), once in the morning and once in the evening, with food, for a total daily dose of 480 mg.

Arm type	Experimental
Investigational medicinal product name	Tivantinib
Investigational medicinal product code	
Other name	ARQ197
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tivantinib tablets for oral administration

Arm title	Placebo Matching 240 mg BID Cohort

Arm description:

Patients receive Placebo, administered as matching oral tablet(s) BID, once in the morning and once in the evening, with food.

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

Dosage and administration details:

Matching placebo tablets

Arm title	Tivantinib 120 mg BID Cohort

Arm description:

Patients receive Tivantinib 120 mg, administered as oral tablets twice daily (BID), once in the morning and once in the evening, with food, for a total daily dose of 240 mg.

Arm type	Experimental

Investigational medicinal product name	Tivantinib
Investigational medicinal product code	
Other name	ARQ197
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tivantinib tablets for oral administration

Arm title	Placebo Matching 120 mg BID Cohort

Arm description:

Patients receive Placebo, administered as matching oral tablet(s) BID, once in the morning and once in the evening, with food.

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

Dosage and administration details:

Matching placebo tablets

Number of subjects in period 1	Tivantinib 240 mg BID Cohort	Placebo Matching 240 mg BID Cohort	Tivantinib 120 mg BID Cohort
Started	28	15	226
Safety Analysis Set	28	15	225
Intention to Treat Analysis Set	28	15	226
Efficacy Analysis Set	0	0	226
Ongoing on the Study Treatment	0	0	5
Completed	0	0	0
Not completed	28	15	226
Radiographic Disease Progression	9	4	44
Patient Decision to Discontinue Treatment	-	-	10
Withdrawal of Consent from Treatment and Study	-	-	2
Adverse event, non-fatal	6	-	28
Death	1	2	15
Ongoing on the Study Treatment	-	-	5
Clinical Disease Progression	4	2	29
Progressive disease	8	7	91
Reason Not Provided	-	-	2

Number of subjects in period 1	Placebo Matching 120 mg BID Cohort
Started	114
Safety Analysis Set	114
Intention to Treat Analysis Set	114

Efficacy Analysis Set	114
Ongoing on the Study Treatment	2
Completed	0
Not completed	114
Radiographic Disease Progression	27
Patient Decision to Discontinue Treatment	3
Withdrawal of Consent from Treatment and Study	1
Adverse event, non-fatal	11
Death	4
Ongoing on the Study Treatment	2
Clinical Disease Progression	20
Progressive disease	43
Reason Not Provided	3

Baseline characteristics

Reporting groups	
Reporting group title	Tivantinib 240 mg BID Cohort
Reporting group description:	
Patients receive Tivantinib 240 mg, administered as oral tablets twice daily (BID), once in the morning and once in the evening, with food, for a total daily dose of 480 mg.	
Reporting group title	Placebo Matching 240 mg BID Cohort
Reporting group description:	
Patients receive Placebo, administered as matching oral tablet(s) BID, once in the morning and once in the evening, with food.	
Reporting group title	Tivantinib 120 mg BID Cohort
Reporting group description:	
Patients receive Tivantinib 120 mg, administered as oral tablets twice daily (BID), once in the morning and once in the evening, with food, for a total daily dose of 240 mg.	
Reporting group title	Placebo Matching 120 mg BID Cohort
Reporting group description:	
Patients receive Placebo, administered as matching oral tablet(s) BID, once in the morning and once in the evening, with food.	

Reporting group values	Tivantinib 240 mg BID Cohort	Placebo Matching 240 mg BID Cohort	Tivantinib 120 mg BID Cohort
Number of subjects	28	15	226
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 66.6 ± 9.34	 64.9 ± 7.38	 65.6 ± 10.13
Gender categorical Units: Subjects			
Female	4	0	27
Male	24	15	199

Reporting group values	Placebo Matching 120 mg BID Cohort	Total	
Number of subjects	114	383	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 64.7 ± 10.23	 -	
Gender categorical Units: Subjects			
Female	7	38	
Male	107	345	

End points

End points reporting groups

Reporting group title	Tivantinib 240 mg BID Cohort
Reporting group description:	
Patients receive Tivantinib 240 mg, administered as oral tablets twice daily (BID), once in the morning and once in the evening, with food, for a total daily dose of 480 mg.	
Reporting group title	Placebo Matching 240 mg BID Cohort
Reporting group description:	
Patients receive Placebo, administered as matching oral tablet(s) BID, once in the morning and once in the evening, with food.	
Reporting group title	Tivantinib 120 mg BID Cohort
Reporting group description:	
Patients receive Tivantinib 120 mg, administered as oral tablets twice daily (BID), once in the morning and once in the evening, with food, for a total daily dose of 240 mg.	
Reporting group title	Placebo Matching 120 mg BID Cohort
Reporting group description:	
Patients receive Placebo, administered as matching oral tablet(s) BID, once in the morning and once in the evening, with food.	

Primary: Rate of Overall Survival (OS) within 36 Months

End point title	Rate of Overall Survival (OS) within 36 Months[1]
End point description:	
OS is defined as the time from randomization to the date of death (i.e., the length of time from the start of treatment that patients are still alive). Rate of OS (Percentage of Patients Still Alive) is determined in the efficacy analysis set (Intent to Treat in the 120 mg BID Cohort) every 3 months for 36 months.	
End point type	Primary
End point timeframe:	
within 36 months	

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 efficacy population includes only patients in the intent to treat 120 mg BID Cohort

End point values	Tivantinib 120 mg BID Cohort	Placebo Matching 120 mg BID Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	114		
Units: Percentage of patients				
number (confidence interval 95%)				
at 3 Months	86.62 (81.43 to 90.45)	85.88 (77.99 to 91.10)		
at 6 Months	61.17 (54.46 to 67.20)	70.83 (61.51 to 78.29)		
at 9 Months	46.88 (40.23 to 53.25)	50.47 (40.93 to 59.24)		
at 12 Months	36.61 (30.34 to 42.90)	38.01 (29.11 to 46.86)		
at 15 Months	30.22 (24.25 to 36.38)	28.16 (20.04 to 36.82)		

at 18 Months	25.09 (19.40 to 31.16)	21.88 (14.29 to 30.51)		
at 21 Months	21.25 (15.80 to 27.24)	15.95 (9.11 to 24.51)		
at 24 Months	16.19 (11.01 to 22.25)	12.16 (5.91 to 20.79)		
at 27 Months	13.95 (8.88 to 20.13)	4.86 (1.05 to 13.44)		
at 30 Months	13.95 (8.88 to 20.13)	4.86 (1.05 to 13.44)		
at 33 Months	13.95 (8.88 to 20.13)	4.86 (1.05 to 13.44)		
at 36 Months	0.00 (0.00 to 0.00)	4.86 (1.05 to 13.44)		

Statistical analyses

Statistical analysis title	Unstratified COX Regression Analysis
Comparison groups	Tivantinib 120 mg BID Cohort v Placebo Matching 120 mg BID Cohort
Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7246 [2]
Method	Logrank
Parameter estimate	Unstratified COX Regression Analysis
Point estimate	0.9555
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.744
upper limit	1.2271

Notes:

[2] - Unstratified

Secondary: Rate of Progression Free Survival (PFS) within 10 months

End point title	Rate of Progression Free Survival (PFS) within 10 months[3]

End point description:

PFS is defined as the time from the date of randomization to the date of the first radiographic disease progression or death due to any cause.
Rate of PFS (Percentage of Patients Still Alive without Disease Progression) is determined in the efficacy analysis set (Intent to Treat in the 120 mg BID Cohort) every 2 months for 10 months.

End point type	Secondary

End point timeframe:

within 10 months

Notes:

[3] - 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 efficacy population includes only patients in the intent to treat 120 mg BID Cohort

End point values	Tivantinib 120 mg BID Cohort	Placebo Matching 120 mg BID Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	114		
Units: percentage of patients				
number (confidence interval 95%)				
at 2 Months	50.02 (43.20 to 56.45)	49.23 (39.51 to 58.22)		
at 4 Months	27.21 (21.41 to 33.32)	27.99 (19.78 to 36.77)		
at 6 Months	13.86 (9.56 to 18.95)	12.50 (6.92 to 19.80)		
at 8 Months	8.78 (5.39 to 13.18)	5.21 (1.95 to 10.88)		
at 10 Months	4.96 (2.50 to 8.67)	5.21 (1.95 to 10.88)		

Statistical analyses

Statistical analysis title	Unstratified COX Regression Analysis
Comparison groups	Tivantinib 120 mg BID Cohort v Placebo Matching 120 mg BID Cohort
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8044 [4]
Method	Logrank
Parameter estimate	Hazard Ratio Relative to Placebo
Point estimate	0.9675
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7634
upper limit	1.2263

Notes:

[4] - Unstratified

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent Adverse Events (TEAEs) are collected from the first day of treatment until the end of treatment plus a 30-day Safety Follow-up, for a total of 1519 days for Serious Adverse Events and 1489 days for non-serious adverse events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Tivantinib

Reporting group description:

Tivantinib administered by oral tablet

Reporting group title	Placebo

Reporting group description:

Matching placebo administered by oral tablet

Serious adverse events	Tivantinib	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	120 / 253 (47.43%)	61 / 129 (47.29%)	
number of deaths (all causes)	208	108	
number of deaths resulting from adverse events	51	12	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma pancreas			
subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver carcinoma ruptured			

subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to bone			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to spine			
subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour embolism			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	2 / 253 (0.79%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Hypovolaemic shock			

subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chest pain			
subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	3 / 253 (1.19%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Fatigue			
subjects affected / exposed	2 / 253 (0.79%)	2 / 129 (1.55%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			

subjects affected / exposed	11 / 253 (4.35%)	2 / 129 (1.55%)	
occurrences causally related to treatment / all	2 / 11	0 / 2	
deaths causally related to treatment / all	0 / 8	0 / 1	
Implant site haemorrhage			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 253 (0.40%)	2 / 129 (1.55%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchial obstruction			
subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cough			
subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	4 / 253 (1.58%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			

subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 253 (0.40%)	3 / 129 (2.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	4 / 253 (1.58%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Eastern Cooperative Oncology Group performance status worsened			

subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic enzyme increased			
subjects affected / exposed	3 / 253 (1.19%)	2 / 129 (1.55%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Liver function test abnormal			
subjects affected / exposed	6 / 253 (2.37%)	3 / 129 (2.33%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Adrenal gland injury			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprosthetic fracture			

subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	1 / 253 (0.40%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 253 (0.40%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			

subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 253 (0.79%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cardiac failure			
subjects affected / exposed	2 / 253 (0.79%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	4 / 253 (1.58%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 253 (0.40%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	2 / 253 (0.79%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			

subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	1 / 253 (0.40%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculitis			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord paralysis			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	4 / 253 (1.58%)	3 / 129 (2.33%)	
occurrences causally related to treatment / all	3 / 4	2 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 253 (1.19%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Leukopenia			
subjects affected / exposed	2 / 253 (0.79%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	9 / 253 (3.56%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	9 / 9	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	3 / 253 (1.19%)	4 / 129 (3.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			

subjects affected / exposed	7 / 253 (2.77%)	5 / 129 (3.88%)	
occurrences causally related to treatment / all	0 / 7	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Constipation			
subjects affected / exposed	1 / 253 (0.40%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 253 (0.79%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 253 (0.00%)	3 / 129 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	9 / 253 (3.56%)	2 / 129 (1.55%)	
occurrences causally related to treatment / all	1 / 13	1 / 2	
deaths causally related to treatment / all	0 / 4	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 253 (0.40%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic ascites			

subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemorrhage			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal haemorrhage			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	7 / 253 (2.77%)	5 / 129 (3.88%)	
occurrences causally related to treatment / all	0 / 12	0 / 6	
deaths causally related to treatment / all	0 / 3	0 / 0	
Peritoneal haemorrhage			
subjects affected / exposed	2 / 253 (0.79%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rectal haemorrhage			

subjects affected / exposed	2 / 253 (0.79%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	3 / 253 (1.19%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Varices oesophageal			
subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 253 (0.00%)	2 / 129 (1.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			

subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	2 / 253 (0.79%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic failure			
subjects affected / exposed	6 / 253 (2.37%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 7	0 / 1	
deaths causally related to treatment / all	0 / 5	0 / 1	
Hepatorenal failure			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatorenal syndrome			
subjects affected / exposed	1 / 253 (0.40%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hepatotoxicity			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	2 / 253 (0.79%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			

subjects affected / exposed	1 / 253 (0.40%)	2 / 129 (1.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Liver injury			
subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	2 / 253 (0.79%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal failure acute			
subjects affected / exposed	4 / 253 (1.58%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	2 / 5	0 / 1	
deaths causally related to treatment / all	1 / 3	0 / 1	
Renal impairment			
subjects affected / exposed	2 / 253 (0.79%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal injury			
subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral meatus stenosis			
subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 253 (0.40%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteolysis			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Cellulitis			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis orbital			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	2 / 253 (0.79%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			

subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	7 / 253 (2.77%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	3 / 7	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Septic shock			
subjects affected / exposed	1 / 253 (0.40%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 253 (0.79%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	2 / 253 (0.79%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 253 (0.79%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 253 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	2 / 253 (0.79%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 253 (0.40%)	2 / 129 (1.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolic acidosis			
subjects affected / exposed	1 / 253 (0.40%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Tivantinib	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	224 / 253 (88.54%)	111 / 129 (86.05%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	19 / 253 (7.51%)	6 / 129 (4.65%)	
occurrences (all)	22	7	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	55 / 253 (21.74%)	27 / 129 (20.93%)	
occurrences (all)	77	37	
Fatigue			
subjects affected / exposed	58 / 253 (22.92%)	34 / 129 (26.36%)	
occurrences (all)	74	46	
Oedema peripheral			
subjects affected / exposed	61 / 253 (24.11%)	20 / 129 (15.50%)	
occurrences (all)	85	23	
Pyrexia			
subjects affected / exposed	34 / 253 (13.44%)	14 / 129 (10.85%)	
occurrences (all)	47	28	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	37 / 253 (14.62%)	11 / 129 (8.53%)	
occurrences (all)	40	12	
Dyspnoea			
subjects affected / exposed	22 / 253 (8.70%)	7 / 129 (5.43%)	
occurrences (all)	27	8	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	10 / 253 (3.95%)	7 / 129 (5.43%)	
occurrences (all)	10	9	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	9 / 253 (3.56%)	9 / 129 (6.98%)	
occurrences (all)	12	11	
Aspartate aminotransferase increased			

subjects affected / exposed	15 / 253 (5.93%)	13 / 129 (10.08%)	
occurrences (all)	18	13	
Blood bilirubin increased			
subjects affected / exposed	13 / 253 (5.14%)	5 / 129 (3.88%)	
occurrences (all)	14	5	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	33 / 253 (13.04%)	0 / 129 (0.00%)	
occurrences (all)	34	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	16 / 253 (6.32%)	4 / 129 (3.10%)	
occurrences (all)	22	4	
Headache			
subjects affected / exposed	13 / 253 (5.14%)	3 / 129 (2.33%)	
occurrences (all)	14	4	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	50 / 253 (19.76%)	17 / 129 (13.18%)	
occurrences (all)	73	28	
Neutropenia			
subjects affected / exposed	42 / 253 (16.60%)	7 / 129 (5.43%)	
occurrences (all)	94	16	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	11 / 253 (4.35%)	8 / 129 (6.20%)	
occurrences (all)	13	9	
Abdominal pain			
subjects affected / exposed	47 / 253 (18.58%)	32 / 129 (24.81%)	
occurrences (all)	64	38	
Abdominal pain upper			
subjects affected / exposed	29 / 253 (11.46%)	16 / 129 (12.40%)	
occurrences (all)	39	17	
Ascites			
subjects affected / exposed	51 / 253 (20.16%)	29 / 129 (22.48%)	
occurrences (all)	66	39	
Constipation			

subjects affected / exposed	29 / 253 (11.46%)	15 / 129 (11.63%)	
occurrences (all)	38	17	
Diarrhoea			
subjects affected / exposed	53 / 253 (20.95%)	19 / 129 (14.73%)	
occurrences (all)	72	24	
Dyspepsia			
subjects affected / exposed	14 / 253 (5.53%)	9 / 129 (6.98%)	
occurrences (all)	16	11	
Nausea			
subjects affected / exposed	54 / 253 (21.34%)	14 / 129 (10.85%)	
occurrences (all)	73	16	
Vomiting			
subjects affected / exposed	28 / 253 (11.07%)	13 / 129 (10.08%)	
occurrences (all)	52	17	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	26 / 253 (10.28%)	23 / 129 (17.83%)	
occurrences (all)	34	30	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	19 / 253 (7.51%)	6 / 129 (4.65%)	
occurrences (all)	24	9	
Back pain			
subjects affected / exposed	20 / 253 (7.91%)	13 / 129 (10.08%)	
occurrences (all)	20	13	
Musculoskeletal pain			
subjects affected / exposed	9 / 253 (3.56%)	9 / 129 (6.98%)	
occurrences (all)	13	9	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 253 (3.56%)	7 / 129 (5.43%)	
occurrences (all)	9	7	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	38 / 253 (15.02%)	24 / 129 (18.60%)	
occurrences (all)	45	34	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 June 2013	Changed frequency of hematology testing and dose reduction requirements following recommendations from Data Monitoring Committee (DMC). Clarified in synopsis minimum requirement for regional lymph node to be considered involved (previously clarification was only in body of protocol). Corrected language that remained in error in the original protocol regarding stopping rules for subject treatment. Protocol now was consistent throughout with existing details in Section 4.2.1, Table 4.1. Updated to reflect the fact that the LabCorp IHC assay now has IDE approval for investigational use in this study and that assay has CE mark in EU. .Revised minimum number of tissue slides required per current lab manual. Revised language to account for the fact that some sites have a single consent form for the entire study while others had separate consent forms for various portions of the study. Corrected discrepancy in protocol regarding timing of PK on Cycle 1 Day 22. Protocol now was consistent throughout with existing details in Section 8.1. Following multiple queries, added clarification on use, storage and destruction of tissue samples for this study. Corrected typo (symbol for ≤ corrected to ≥) and added clarity on Hy's Law definition.
29 August 2013	Added exclusion criterion number 14 to exclude subjects with pleural effusion or clinically evident (visible or palpable) ascites following recommendations from Data Monitoring Committee (DMC). Such subjects may have been more susceptible to infections and more at risk if they were to develop neutropenia. Reduced starting dose from 240 mg BID to 120 mg BID following recommendations from DMC as higher than expected rate of severe neutropenia was seen at original starting dose of 240 mg BID and exposure was noted to be higherthan it was in the phase 2 HCC study. Updated clinical experience section and study rationale section to distinguish which prior studies used capsule formulation and which used tablet formulation and to clarify that in this study tablet formulation was used. Updated dose modifications section to allow one lower level dose reduction given that starting dose had been reduced following recommendations from DMC. Changed visit schedule to increase frequency of hematology testing during Cycle 1 following recommendations from DMC. Hematology must have now been performed every 2 days during cycle 1. This would help more closely monitor any changes in neutrophil values and take action more quickly if necessary. Updated contact information for CRO physician to generic contact as named physician was terminating employment. The updated contact information was valid even if the assigned CRO physician changed again in the future.
13 September 2013	Added description and rationale for the change of study design (eg, reduced dose) and subject grouping (2 cohorts: 120 mg cohort and 240 mg cohort) for statistical analyses. Updated study design due to reduced dose. Updated synopsis and statistical methods section to reflect that the efficacy analyses was to be performed only for the 120 mg cohort as 120 mg BID was the intended dose regimen for approval. Updated statistical methods section to reflect that the safety analyses and summary of disposition, demographic and baseline characteristics, and exposure were to be performed separately for the 120 mg and 240 mg cohorts. Updated the section of Risks and Benefits for Study Subjects to incorporate additional DMC review for the 120 mg cohort based on the DMC recommendation. An administrative update to make protocol PK and ECG schedule consistent with section 6.5.2. Editorial changes

17 December 2013	Updated to confirm enrollment could continue per new recommendations from the DMC after complete review of neutrophil count data on 15 November, 2013. For consistency, updated protocol so that retesting of hematology through resolution of AE was consistent regardless of whether neutropenia was grade 2, 3 or 4. Reduced frequency of hematology monitoring during the first cycle. Of the 29 subjects treated at 120 mg BID by 15 November 2013, 26 were treated from between 1 and 2½ months and 3 were treated for at least 3 weeks. After reviewing the Absolute Neutrophil Count (ANC) data provided on 15 November 2013, the DMC advised that the frequency of hematology monitoring during the first cycle could be reduced from every 2 days to every 4 days. Re-wrote sections regarding re-screening of subjects to more clearly distinguish between subjects requiring full re-screening and those who needed to send in fresh biopsy after MET low result initially received. Protocol section 4.2.3 and 6.1 were now consistent with footnote 6 in Appendix 17.1. Furthermore we clarified the timeframe between notification of MET-high status and initiation of screening procedures. Corrected typographical error in Section 5.1.2. Following suggestions from some regulatory agencies, modified the frequency of hematology testing post Cycle 1 to allow for a more gradual decrease in frequency of hematology testing between Cycle 1 and subsequent cycles. Instead of testing hematology twice a month in Cycle 2, it would be tested on weekly basis during Cycle 2 before reverting to twice a month testing in subsequent cycles.
17 March 2016	Updated current address of ArQule, Inc. co-sponsor of the study. Changed sponsor representative who signs the protocol approval page. In the event of a positive study showing significant difference favoring tivantinib over placebo, updated various sections in the protocol to allow for the possibility of subjects randomized to placebo to receive active treatment with tivantinib. This would occur after database lock and unblinding. The protocol was amended also to specify the safety eligibility criteria such patients would have to meet in order to receive active treatment. Added a definition of "end of trial" to the protocol. Added a sentence to clarify that after database lock, additional data will be reviewed via listings. Clarified that subjects unblinded before database lock would have to discontinue treatment immediately. Added updated standardized language to the protocol regarding drug accountability (which matches the process being followed to-date). Removed language requiring that MRI be used exclusively in certain countries. Listed safety procedures that are required at the time they start tivantinib for any subjects randomized to placebo who then receives tivantinib after database lock and unblinding (if the study is positive). Corrected typo to clarify that Alpha Fetoprotein (AFP) is collected at screening and not on Day 1. This is now consistent throughout all sections of the protocol. Added clarification language to one sentence in the statistical section. Updated wording in Child Pugh appendix to make consistent with wording in the body of the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported