# 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

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

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

| | |
|---|---|
| Sponsor protocol code | ARQ197-A-U303 |

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

Notes:

| | |
|---|---|
| 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:

| | |
|---|---|
| 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:

| | |
|---|---|
| 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:

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:

| | |
|---|---|
| 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:

| | |
|---|---|
| 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 |

Recruitment details:

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

Screening details:

A total of 826 patients were screened but not randomized.

| | |
|---|---|
| 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 |

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| | 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

| | |
|---|---|
| | 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

| | |
|---|---|
| | 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

| | |
|---|---|
| | 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

| | 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 |

| | Placebo Matching 120 mg BID Cohort |
|---|---|
| Started | 114 |
| Safety Analysis Set | 114 |
| Intention to Treat Analysis Set | 114 |

| | |
|---|---|
| Efficacy Analysis Set | 114 |

| 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. | |

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

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

| 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. | |

| 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).<br>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.<br>Justification: The efficacy population includes only patients in the intent to treat 120 mg BID Cohort | |

| | 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) | | |

| | 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

| | |
|---|---|
| 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

| | 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) | | |

| | 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

| 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 name | MedDRA |
| Dictionary version | 15.1 |

| | |
|---|---|
| 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 | |

| | 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

| | | | |
|---|---|---|---|
| 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 %

| | 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 | | 13 / 129 (10.08%) | |

Were there any global substantial amendments to the protocol? Yes

| | |
|---|---|
| 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:

---

Were there any global interruptions to the trial? No

None reported