



Clinical trial results:

An open-label, randomized, multi-center, Phase III study to compare the safety and efficacy of TKI258 versus sorafenib in patients with metastatic renal cell carcinoma after failure of anti-angiogenic (VEGF-targeted and mTOR inhibitor) therapies

Summary

| | |
|--------------------------|----------------------------------------|
| EudraCT number | 2009-015459-25 |
| Trial protocol | CZ NL BE ES HU SK IT DE SE AT GR GB NO |
| Global end of trial date | 30 June 2014 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 13 July 2016 |
| First version publication date | 07 August 2015 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CTKI258A2302 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01223027 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|-----------------------------------------------------------------------------------------|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Study Director, Novartis Pharma AG, 41 613241111, |
| Scientific contact | Study Director, Novartis Pharma AG, 41 613241111, trialandresults.registry@novartis.com |

Notes:

Paediatric regulatory details

| | |
|----------------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|------------------------------------------------------|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 30 June 2014 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 June 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare dovitinib vs. sorafenib with respect to progression free survival (PFS) determined by central radiology assessment in patients with mRCC after failure of anti-angiogenic (VEGF-targeted and mTOR inhibitor) therapies.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

| | |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment | 01 March 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------------------------------|
| Country: Number of subjects enrolled | Germany: 35 |
| Country: Number of subjects enrolled | Spain: 45 |
| Country: Number of subjects enrolled | Argentina: 4 |
| Country: Number of subjects enrolled | Australia: 29 |
| Country: Number of subjects enrolled | Austria: 2 |
| Country: Number of subjects enrolled | Belgium: 12 |
| Country: Number of subjects enrolled | Brazil: 3 |
| Country: Number of subjects enrolled | Canada: 60 |
| Country: Number of subjects enrolled | Colombia: 1 |
| Country: Number of subjects enrolled | Czech Republic: 15 |
| Country: Number of subjects enrolled | France: 57 |
| Country: Number of subjects enrolled | Greece: 12 |
| Country: Number of subjects enrolled | Hungary: 17 |
| Country: Number of subjects enrolled | Israel: 9 |
| Country: Number of subjects enrolled | Italy: 54 |
| Country: Number of subjects enrolled | Japan: 40 |
| Country: Number of subjects enrolled | Korea, Democratic People's Republic of: 24 |
| Country: Number of subjects enrolled | Netherlands: 11 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Norway: 4 |
| Country: Number of subjects enrolled | Poland: 31 |
| Country: Number of subjects enrolled | Saudi Arabia: 1 |
| Country: Number of subjects enrolled | Slovakia: 4 |
| Country: Number of subjects enrolled | Sweden: 5 |
| Country: Number of subjects enrolled | Switzerland: 3 |
| Country: Number of subjects enrolled | Thailand: 3 |
| Country: Number of subjects enrolled | United Kingdom: 24 |
| Country: Number of subjects enrolled | United States: 65 |
| Worldwide total number of subjects | 570 |
| EEA total number of subjects | 328 |

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) | 352 |
| From 65 to 84 years | 217 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening/Baseline assessments were performed within 28 days prior to the first dose of study treatment. Certain specified assessments were to be performed \leq 14 days prior to the start of the study treatment.

Period 1

| | |
|------------------------------|-----------------------------------------------------------|
| Period 1 title | End of Treatment phase before F/u visits (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|----------------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Dovitinib + best supportive care (BSC) |

Arm description:

Patients randomized to the dovitinib treatment arm received 500 mg of dovitinib taken orally on 5 days on/2 days off dosing schedule.

| | |
|----------------------------------------|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Dovitinib |
| Investigational medicinal product code | TKI258 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

100 mg capsule to deliver 500 mg 5 days on 2 days off regimen

| | |
|------------------|-----------------|
| Arm title | Sorafenib + BSC |
|------------------|-----------------|

Arm description:

Patients in the sorafenib control arm received 400 mg of sorafenib (2 x 200 mg tablets) taken orally twice daily.

| | |
|----------------------------------------|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | tosylate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Patients in the sorafenib control arm received 400 mg of sorafenib (2 x 200 mg tablets) taken orally twice daily.

| Number of subjects in period 1 | Dovitinib + best supportive care (BSC) | Sorafenib + BSC |
|--------------------------------|----------------------------------------|-----------------|
| | | |
| Started | 284 | 286 |
| Completed | 35 | 40 |
| Not completed | 249 | 246 |
| Adverse event, serious fatal | 18 | 20 |
| Physician decision | 7 | 9 |
| Adverse event, non-fatal | 42 | 28 |
| Progressive Disease | 160 | 173 |
| Lost to follow-up | 1 | 1 |
| Protocol deviation | 2 | - |
| Subject/guardian decision | 19 | 15 |

Baseline characteristics

Reporting groups

| | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| Reporting group title | Dovitinib + best supportive care (BSC) |
| Reporting group description: Patients randomized to the dovitinib treatment arm received 500 mg of dovitinib taken orally on 5 days on/2 days off dosing schedule. | |
| Reporting group title | Sorafenib + BSC |
| Reporting group description: Patients in the sorafenib control arm received 400 mg of sorafenib (2 x 200 mg tablets) taken orally twice daily. | |

| Reporting group values | Dovitinib + best supportive care (BSC) | Sorafenib + BSC | Total |
|----------------------------------------------------|----------------------------------------|-----------------|-------|
| Number of subjects | 284 | 286 | 570 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 187 | 165 | 352 |
| From 65-84 years | 96 | 121 | 217 |
| 85 years and over | 1 | 0 | 1 |
| Age continuous Units: years | | | |
| arithmetic mean | 60.6 | 61.1 | |
| standard deviation | ± 10.39 | ± 10.09 | - |
| Gender, Male/Female Units: Participants | | | |
| Female | 71 | 67 | 138 |
| Male | 213 | 219 | 432 |
| Age, Customized Units: Subjects | | | |
| < 65 | 187 | 165 | 352 |
| ≥ 65 | 97 | 121 | 218 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Caucasian | 233 | 232 | 465 |
| Asian | 42 | 40 | 82 |
| Black | 3 | 5 | 8 |
| Unknown | 1 | 6 | 7 |
| Other | 5 | 3 | 8 |
| Study Specific Characteristic Units: Subjects | | | |

| | | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|-------------|-----|
| 100 - Normal no complaints; no evidence of disease | 83 | 73 | 156 |
| 90 - Able to carry on normal activity | 93 | 101 | 194 |
| 80 - Normal activity with efforts | 73 | 83 | 156 |
| 70 - Cares for self | 35 | 29 | 64 |
| Study Specific Characteristic | | | |
| Pts were place into 3 distinct risk groups based on the number of risk factors that the patient had at baseline: Low Karnofsky Performance Status: <80%, Low serum hemoglobin: males (≤ 13 g/dL); females (≤ 11.5 g/dL), High corrected serum calcium: ≥ 10 mg/dL. Pts in the favorable group are expected to live longer while patients in the poor risk group are expected to die sooner than the patients in the other groups. Favorable = Pt. had none of the risks; Intermediate = Patient had 1 risk factor; Poor = Pt. had 2 or 3 risk factors Missing = not enough information at baseline to categorize | | | |
| Units: Subjects | | | |
| Favorable | 70 | 65 | 135 |
| Intermediate | 156 | 155 | 311 |
| Poor | 54 | 61 | 115 |
| Missing | 4 | 5 | 9 |
| Study Specific Characteristic | | | |
| Units: years | | | |
| arithmetic mean | 74.9 | 75.5 | |
| standard deviation | ± 15.39 | ± 15.96 | - |

End points

End points reporting groups

| | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| Reporting group title | Dovitinib + best supportive care (BSC) |
| Reporting group description: Patients randomized to the dovitinib treatment arm received 500 mg of dovitinib taken orally on 5 days on/2 days off dosing schedule. | |
| Reporting group title | Sorafenib + BSC |
| Reporting group description: Patients in the sorafenib control arm received 400 mg of sorafenib (2 x 200 mg tablets) taken orally twice daily. | |

Primary: Progression Free Survival (PFS) per independent central radiology review

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| End point title | Progression Free Survival (PFS) per independent central radiology review |
| End point description: Assessed according to RECIST 1.1. PFS was defined as the time from the date of randomization to the date of the first documented disease progression or death due to any cause. If a patient had not progressed or died, on the date of the analysis cut-off or when he/she received any further anti-neoplastic therapy, PFS was censored on the date of last tumor assessment before the cutoff date or the anti-neoplastic therapy date. The distribution of PFS was estimated using the Kaplan-Meier method. The median PFS along with 95% confidence intervals was presented by treatment group. | |
| End point type | Primary |
| End point timeframe: Until disease progression or discontinuation of treatment due to unacceptable toxicity | |

| End point values | Dovitinib + best supportive care (BSC) | Sorafenib + BSC | | |
|----------------------------------|----------------------------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 284 | 286 | | |
| Units: Participants | | | | |
| median (confidence interval 95%) | 3.7 (3.5 to 3.9) | 3.6 (3.5 to 3.7) | | |

Statistical analyses

| | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|
| Statistical analysis title | PFS per independent central radiological review |
| Statistical analysis description: The primary statistical analysis to compare PFS between the two treatment arms was performed using a log-rank test stratified by MSKCC group. | |
| Comparison groups | Dovitinib + best supportive care (BSC) v Sorafenib + BSC |

| | |
|-----------------------------------------|------------------------|
| Number of subjects included in analysis | 570 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.063 ^[1] |
| Method | Logrank |

Notes:

[1] - P-value is one tailed and is based on the stratified log rank test.

Secondary: Overall Survival (OS)

| | |
|-----------------|-----------------------|
| End point title | Overall Survival (OS) |
|-----------------|-----------------------|

End point description:

Overall survival (OS) was the key secondary endpoint and was defined as the time from date of randomization to the date of death due to any cause. If a patient was not known to have died, survival was censored on the date of last contact.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

until at least 386 deaths are documented in the clinical database.

| End point values | Dovitinib + best supportive care (BSC) | Sorafenib + BSC | | |
|------------------------------|----------------------------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 284 | 286 | | |
| Units: Participants | | | | |
| median (confidence interval) | 11.1 (9.5 to 13.4) | 11 (8.6 to 13.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) per Investigator's radiology review

| | |
|-----------------|---------------------------------------------------------------------|
| End point title | Progression Free Survival (PFS) per Investigator's radiology review |
|-----------------|---------------------------------------------------------------------|

End point description:

PFS was defined as the time from the date of randomization to the date of the first documented disease progression or death due to any cause. The primary analysis for PFS (based on central review) was also to be repeated on FAS considering the Investigator assessments and using the same analytical conventions as the primary analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Until disease progression or discontinuation of treatment due to unacceptable toxicity

| End point values | Dovitinib + best supportive care (BSC) | Sorafenib + BSC | | |
|----------------------------------|----------------------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 284 | 286 | | |
| Units: Participants | | | | |
| median (confidence interval 95%) | 3.9 (3.7 to 5.1) | 3.9 (3.7 to 5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR) by central radiology review

| | |
|-----------------|---------------------------------------------------------|
| End point title | Overall response rate (ORR) by central radiology review |
|-----------------|---------------------------------------------------------|

End point description:

Overall response rate (ORR) was defined as the proportion of patients with best overall response of complete response (CR) or partial response (PR). Best overall response (BOR) for each patient was determined from the sequence of overall (lesion) responses according to the following rules: CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required. CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required. SD = at least one SD assessment (or better) > 6 weeks after randomization (and not qualifying for CR or PR). PD = progression ≤ 17 weeks after randomization (and not qualifying for CR, PR or SD).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Until disease progression or discontinuation of treatment due to unacceptable toxicity

| End point values | Dovitinib + best supportive care (BSC) | Sorafenib + BSC | | |
|-----------------------------|----------------------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 284 | 286 | | |
| Units: Participants | 11 | 11 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to definitive worsening of Karnofsky performance status (KPS)

| | |
|-----------------|--------------------------------------------------------------------|
| End point title | Time to definitive worsening of Karnofsky performance status (KPS) |
|-----------------|--------------------------------------------------------------------|

End point description:

Time to definitive worsening of Karnofsky performance status (KPS) was defined as the time from date of randomization to the date of definitive worsening of KPS or to the date of death whichever occurred earlier. Definitive worsening was defined as a definitive decrease in performance status by at least one Karnofsky category (i.e. at least 10 points less) compared to Baseline. Worsening was considered definitive if no later increase above the defined threshold was observed within the course of the study. A single measure reporting a decrease in Karnofsky performance status was sufficient to consider it as

definitive only if it was the last one available for this patient. Time to definitive worsening of KPS was analyzed at the time of the final analysis for PFS.

| | |
|--------------------------------------------------------------------------------------------------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| from date of randomization to the date of definitive worsening of KPS or to the date of death whichever occurred earlier | |

| End point values | Dovitinib + best supportive care (BSC) | Sorafenib + BSC | | |
|----------------------------------|----------------------------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 284 | 286 | | |
| Units: Participants | | | | |
| median (confidence interval 95%) | 5.1 (3.8 to 6.5) | 5.7 (4.6 to 7.4) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Patient-reported outcomes (PROs): Time to deterioration of FKSI-DRS by at least 2 scores

| | |
|-----------------|------------------------------------------------------------------------------------------|
| End point title | Patient-reported outcomes (PROs): Time to deterioration of FKSI-DRS by at least 2 scores |
|-----------------|------------------------------------------------------------------------------------------|

End point description:

The primary analyses of patient-reported outcomes was the Disease- Related Symptoms of the FKSI (FKSI-DRS). The compliance to the schedule of administration of both questionnaires, FKSI-DRS and EORTC QoLQ-C30, were summarized by treatment arm for each visit, as well as the number of patients who completed or not the QoL data. The statistical analysis was comprised of the estimation of the treatment difference in terms of the time to definitive deterioration of the FKSI-DRS from Baseline by at least 2 score units in patients with a maximum score at Baseline of 34. Time to definitive worsening was calculated from the date of randomization.

| | |
|----------------------------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| from date of randomization, at least 2 score units | |

| End point values | Dovitinib + best supportive care (BSC) | Sorafenib + BSC | | |
|----------------------------------|----------------------------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 284 | 286 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 4.9 (4.5 to 6.6) | 6.4 (5.5 to 7.7) | | |

Statistical analyses

Secondary: Patient-reported outcomes (PROs): Time to definitive deterioration of the Physical Functioning (PF) scale of EORTC QLQ-C30 by at least 10%

| | |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Patient-reported outcomes (PROs): Time to definitive deterioration of the Physical Functioning (PF) scale of EORTC QLQ-C30 by at least 10% |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The key secondary endpoints of patient reported outcomes were the physical functioning (PF, 5 items) and the global health status/QoL scale (QoL) scores of the EORTC QoLQ-C30. The compliance to the schedule of administration of both questionnaires, FKSI-DRS and EORTC QoLQ-C30, were summarized by treatment arm for each visit, as well as the number of patients who completed or not the QoL data. The statistical analysis was comprised of the estimation of the treatment difference in terms of the time to definitive deterioration by 10% of the PF scale of the EORTC QoLQ-C30. Time to definitive worsening was calculated from the date of randomization.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

from date of randomization

| End point values | Dovitinib + best supportive care (BSC) | Sorafenib + BSC | | |
|----------------------------------|----------------------------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 284 | 286 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 3.8 (3.2 to 4.6) | 5.6 (4.5 to 6.4) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Patient-reported outcomes (PROs): Time to definitive deterioration of the quality of life (QoL) scale of EORTC QLQ-C30 by at least 10%

| | |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Patient-reported outcomes (PROs): Time to definitive deterioration of the quality of life (QoL) scale of EORTC QLQ-C30 by at least 10% |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The key secondary endpoints of patient reported outcomes were the physical functioning (PF, 5 items) and the global health status/QoL scale (QoL) scores of the EORTC QoLQ-C30. The compliance to the schedule of administration of both questionnaires, FKSI-DRS and EORTC QoLQ-C30, were summarized by treatment arm for each visit, as well as the number of patients who completed or not the QoL data. The statistical analysis was comprised of the estimation of the treatment difference in terms of the time to definitive deterioration by 10% of the QoL scale of the EORTC QoLQ-C30. Time to definitive worsening was calculated from the date of randomization.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

from date of randomization

| End point values | Dovitinib + best supportive care (BSC) | Sorafenib + BSC | | |
|----------------------------------|----------------------------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 284 | 286 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 3.7 (2.8 to 4.6) | 4.5 (3.7 to 5.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose concentration in plasma in Dovitinib

| | |
|-----------------|--------------------------------------------------------------|
| End point title | Pre-dose concentration in plasma in Dovitinib ^[2] |
|-----------------|--------------------------------------------------------------|

End point description:

Predose concentrations of dovitinib were summarized by visit using PAS. All concentration data was listed by patient and time point using FAS. Mean pre-dose concentrations along with standard deviation (SD) was plotted over time if appropriate.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 2 Day 5, Week 4 Day 5, Week 6 Day 5

Notes:

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

| End point values | Dovitinib + best supportive care (BSC) | | | |
|-----------------------------|----------------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 284 | | | |
| Units: ng/ml | | | | |
| median (standard error) | | | | |
| Week 2 Day 5 (n: 205) | 128.06 (± 92.571) | | | |
| Week 4 Day 5 (n: 202) | 114.08 (± 77.884) | | | |
| Week 6 Day 5 (n: 170) | 118.27 (± 84.246) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Dovitinib |
|-----------------------|-----------|

Reporting group description:

Dovitinib

| | |
|-----------------------|-----------|
| Reporting group title | Sorafenib |
|-----------------------|-----------|

Reporting group description:

Sorafenib

| Serious adverse events | Dovitinib | Sorafenib | |
|---------------------------------------------------------------------|--------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 140 / 280 (50.00%) | 123 / 284 (43.31%) | |
| number of deaths (all causes) | 42 | 47 | |
| number of deaths resulting from adverse events | 7 | 5 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| CANCER PAIN | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INFECTED NEOPLASM | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MALIGNANT PLEURAL EFFUSION | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 284 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| METASTASES TO BLADDER | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| METASTASES TO CENTRAL NERVOUS SYSTEM | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| METASTATIC PAIN | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEOPLASM PROGRESSION | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| OESOPHAGEAL CARCINOMA | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PERICARDIAL EFFUSION MALIGNANT | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| TUMOUR PAIN | | | |
| subjects affected / exposed | 3 / 280 (1.07%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| EMBOLISM | | | |

| | | | |
|------------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 280 (0.71%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPERTENSION | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOTENSION | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 284 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PHLEBITIS | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SHOCK | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| THROMBOSIS | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VASCULAR FRAGILITY | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| ASTHENIA | | | |
| subjects affected / exposed | 3 / 280 (1.07%) | 6 / 284 (2.11%) | |
| occurrences causally related to treatment / all | 2 / 4 | 4 / 6 | |
| deaths causally related to treatment / all | 0 / 1 | 1 / 1 | |
| DEATH | | | |

| | | | |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed | 2 / 280 (0.71%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | |
| DISEASE PROGRESSION | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 3 / 284 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 3 | |
| FATIGUE | | | |
| subjects affected / exposed | 5 / 280 (1.79%) | 5 / 284 (1.76%) | |
| occurrences causally related to treatment / all | 6 / 6 | 3 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| GENERAL PHYSICAL HEALTH DETERIORATION | | | |
| subjects affected / exposed | 11 / 280 (3.93%) | 17 / 284 (5.99%) | |
| occurrences causally related to treatment / all | 1 / 12 | 0 / 17 | |
| deaths causally related to treatment / all | 0 / 10 | 0 / 15 | |
| GENERALISED OEDEMA | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| MALAISE | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| MULTI-ORGAN FAILURE | | | |
| subjects affected / exposed | 3 / 280 (1.07%) | 3 / 284 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 3 | |
| NON-CARDIAC CHEST PAIN | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OEDEMA PERIPHERAL | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PAIN | | | |
| subjects affected / exposed | 3 / 280 (1.07%) | 3 / 284 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| PERFORMANCE STATUS DECREASED | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 3 / 284 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| PYREXIA | | | |
| subjects affected / exposed | 8 / 280 (2.86%) | 5 / 284 (1.76%) | |
| occurrences causally related to treatment / all | 4 / 9 | 2 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SUDDEN DEATH | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Immune system disorders | | | |
| SERUM SICKNESS | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| GENITAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| ACUTE PULMONARY OEDEMA | | | |

| | | | |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| ACUTE RESPIRATORY FAILURE | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| ALVEOLITIS | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| ATELECTASIS | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BRONCHIAL OBSTRUCTION | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COUGH | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DYSPNOEA | | | |
| subjects affected / exposed | 15 / 280 (5.36%) | 16 / 284 (5.63%) | |
| occurrences causally related to treatment / all | 4 / 16 | 1 / 16 | |
| deaths causally related to treatment / all | 1 / 4 | 0 / 7 | |
| EPISTAXIS | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HAEMOPTYSIS | | | |

| | | | |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed | 0 / 280 (0.00%) | 3 / 284 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYDROTHORAX | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (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 | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PLEURAL EFFUSION | | | |
| subjects affected / exposed | 10 / 280 (3.57%) | 11 / 284 (3.87%) | |
| occurrences causally related to treatment / all | 0 / 12 | 2 / 11 | |
| deaths causally related to treatment / all | 0 / 3 | 1 / 1 | |
| PNEUMONIA ASPIRATION | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| PNEUMONITIS | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 2 / 284 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMOTHORAX | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PRODUCTIVE COUGH | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PULMONARY EMBOLISM | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 7 / 280 (2.50%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 4 / 7 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| RESPIRATORY ARREST | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| RESPIRATORY DISTRESS | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| RESPIRATORY FAILURE | | | |
| subjects affected / exposed | 4 / 280 (1.43%) | 3 / 284 (1.06%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 3 | |
| Psychiatric disorders | | | |
| APATHY | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| COMPLETED SUICIDE | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| CONFUSIONAL STATE | | | |
| subjects affected / exposed | 4 / 280 (1.43%) | 2 / 284 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| DELIRIUM | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| ALANINE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 2 / 284 (0.70%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| AMYLASE INCREASED | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (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 | 0 / 280 (0.00%) | 2 / 284 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BLOOD ALKALINE PHOSPHATASE INCREASED | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BLOOD CREATININE INCREASED | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HAEMATOCRIT DECREASED | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LIPASE INCREASED | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LIVER FUNCTION TEST ABNORMAL | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| OXYGEN SATURATION DECREASED | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PLATELET COUNT DECREASED | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TROPONIN INCREASED | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| WEIGHT DECREASED | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| CONTRAST MEDIA REACTION | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FEMORAL NECK FRACTURE | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FEMUR FRACTURE | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| HUMERUS FRACTURE | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| OVERDOSE | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SPINAL COMPRESSION FRACTURE | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SUBDURAL HAEMATOMA | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TOXICITY TO VARIOUS AGENTS | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| UPPER LIMB FRACTURE | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| WRIST FRACTURE | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (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 / 280 (0.36%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ACUTE MYOCARDIAL INFARCTION | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| ATRIAL FIBRILLATION | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ATRIOVENTRICULAR BLOCK COMPLETE | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CARDIAC FAILURE | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CARDIAC FAILURE CONGESTIVE | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CARDIAC TAMPONADE | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CARDIOPULMONARY FAILURE | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| CORONARY ARTERY DISEASE | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CORONARY ARTERY OCCLUSION | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LEFT VENTRICULAR DYSFUNCTION | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MYOCARDIAL INFARCTION | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MYOCARDIAL ISCHAEMIA | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MYOCARDIAL NECROSIS | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SUPRAVENTRICULAR TACHYCARDIA | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 284 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| TACHYCARDIA | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| APHASIA | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CEREBROVASCULAR ACCIDENT | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CONVULSION | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 280 (0.71%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DEPRESSED LEVEL OF CONSCIOUSNESS | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DIZZINESS | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| EPILEPSY | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HEMIPARESIS | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOGLYCAEMIC UNCONSCIOUSNESS | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LOSS OF CONSCIOUSNESS | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| NEURALGIA | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEUROLOGICAL DECOMPENSATION | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PARAESTHESIA | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PRESYNCOPE | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SCIATICA | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (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 | 2 / 280 (0.71%) | 2 / 284 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| SYNCOPE | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TRANSIENT ISCHAEMIC ATTACK | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| ANAEMIA | | | |
| subjects affected / exposed | 7 / 280 (2.50%) | 8 / 284 (2.82%) | |
| occurrences causally related to treatment / all | 2 / 7 | 7 / 10 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 1 | |
| LEUKOPENIA | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 280 (0.71%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LYMPHOPENIA | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEUTROPENIA | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| THROMBOCYTOPENIA | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| DIPLOPIA | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| ABDOMINAL HERNIA | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ABDOMINAL PAIN | | | |
| subjects affected / exposed | 7 / 280 (2.50%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 3 / 9 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ABDOMINAL PAIN UPPER | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 2 / 284 (0.70%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ABDOMINAL TENDERNESS | | | |

| | | | |
|-------------------------------------------------|------------------|-----------------|--|
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ANAL FISSURE | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ASCITES | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 284 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COLONIC FISTULA | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CONSTIPATION | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 3 / 284 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DIARRHOEA | | | |
| subjects affected / exposed | 10 / 280 (3.57%) | 4 / 284 (1.41%) | |
| occurrences causally related to treatment / all | 9 / 11 | 4 / 4 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| DYSPEPSIA | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DYSPHAGIA | | | |
| subjects affected / exposed | 3 / 280 (1.07%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FAECAL INCONTINENCE | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTRIC PERFORATION | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTRITIS | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTROINTESTINAL HAEMORRHAGE | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTROINTESTINAL MOTILITY DISORDER | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ILEUS | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 2 / 284 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| ILEUS PARALYTIC | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INTESTINAL OBSTRUCTION | | | |
| subjects affected / exposed | 3 / 280 (1.07%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LARGE INTESTINAL HAEMORRHAGE | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| LARGE INTESTINE PERFORATION | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| LOWER GASTROINTESTINAL HAEMORRHAGE | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NAUSEA | | | |
| subjects affected / exposed | 6 / 280 (2.14%) | 3 / 284 (1.06%) | |
| occurrences causally related to treatment / all | 5 / 6 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OBSTRUCTION GASTRIC | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 3 / 284 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ODYNOPHAGIA | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ORAL PAIN | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PANCREATITIS | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMOPERITONEUM | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RECTAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| RETROPERITONEAL HAEMATOMA | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RETROPERITONEAL HAEMORRHAGE | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| STOMATITIS | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 3 / 284 (1.06%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| VOMITING | | | |
| subjects affected / exposed | 8 / 280 (2.86%) | 3 / 284 (1.06%) | |
| occurrences causally related to treatment / all | 7 / 9 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| CHOLECYSTITIS | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HEPATIC FAILURE | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 2 / 284 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| JAUNDICE CHOLESTATIC | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| ANGIOEDEMA | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DIABETIC FOOT | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| PRURITUS GENERALISED | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RASH | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RASH ERYTHEMATOUS | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RASH GENERALISED | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SKIN LESION | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TOXIC EPIDERMAL NECROLYSIS | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| TOXIC SKIN ERUPTION | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| AZOTAEMIA | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HAEMATURIA | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 3 / 284 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| POLAKIURIA | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RENAL FAILURE | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 3 / 284 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| RENAL FAILURE ACUTE | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RENAL FAILURE CHRONIC | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| URINARY BLADDER HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| URINARY INCONTINENCE | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| URINARY RETENTION | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| HYPERCALCAEMIA OF MALIGNANCY | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| AMYOTROPHY | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| ARTHRALGIA | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 3 / 284 (1.06%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BACK PAIN | | | |
| subjects affected / exposed | 5 / 280 (1.79%) | 7 / 284 (2.46%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| BONE PAIN | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 2 / 284 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| FLANK PAIN | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INTERVERTEBRAL DISC DISORDER | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MUSCULAR WEAKNESS | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MUSCULOSKELETAL CHEST PAIN | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MUSCULOSKELETAL PAIN | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| 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 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MYOPATHY | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NECK PAIN | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OSTEONECROSIS OF JAW | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (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 | 3 / 280 (1.07%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PATHOLOGICAL FRACTURE | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 284 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SPINAL COLUMN STENOSIS | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SPINAL OSTEOARTHRITIS | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| ANAL ABSCESS | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CONJUNCTIVITIS | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CYSTITIS | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| EMPHYSEMATOUS CYSTITIS | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (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 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INFECTIVE GLOSSITIS | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LOBAR PNEUMONIA | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LUNG INFECTION | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| MENINGITIS CRYPTOCOCCAL | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| PNEUMONIA | | | |
| subjects affected / exposed | 8 / 280 (2.86%) | 8 / 284 (2.82%) | |
| occurrences causally related to treatment / all | 1 / 9 | 0 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 4 | |
| PYELONEPHRITIS ACUTE | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SEPSIS | | | |
| subjects affected / exposed | 7 / 280 (2.50%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 7 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 3 | 0 / 0 | |
| SEPTIC SHOCK | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| SPINAL CORD INFECTION | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (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 | 1 / 280 (0.36%) | 2 / 284 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| CACHEXIA | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| DECREASED APPETITE | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 4 / 284 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 2 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 1 / 1 | |
| DEHYDRATION | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 6 / 280 (2.14%) | 4 / 284 (1.41%) | |
| occurrences causally related to treatment / all | 3 / 6 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPERCALCAEMIA | | | |
| subjects affected / exposed | 3 / 280 (1.07%) | 2 / 284 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPERKALAEMIA | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 3 / 284 (1.06%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPERTRIGLYCERIDAEMIA | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOCALCAEMIA | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOKALAEMIA | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOMAGNESAEMIA | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPONATRAEMIA | | | |
| subjects affected / exposed | 3 / 280 (1.07%) | 4 / 284 (1.41%) | |
| occurrences causally related to treatment / all | 1 / 3 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOPHAGIA | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 280 (0.71%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| HYPOPROTEINAEMIA | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LACTIC ACIDOSIS | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 284 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TUMOUR LYSIS SYNDROME | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Dovitinib | Sorafenib | |
|-------------------------------------------------------------|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 268 / 280 (95.71%) | 272 / 284 (95.77%) | |
| Vascular disorders | | | |
| HYPERTENSION | | | |
| subjects affected / exposed | 55 / 280 (19.64%) | 78 / 284 (27.46%) | |
| occurrences (all) | 63 | 93 | |
| General disorders and administration site conditions | | | |
| ASTHENIA | | | |
| subjects affected / exposed | 64 / 280 (22.86%) | 45 / 284 (15.85%) | |
| occurrences (all) | 74 | 47 | |
| FATIGUE | | | |
| subjects affected / exposed | 113 / 280 (40.36%) | 97 / 284 (34.15%) | |
| occurrences (all) | 126 | 118 | |
| NON-CARDIAC CHEST PAIN | | | |

| | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>OEDEMA PERIPHERAL</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>PAIN</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>PYREXIA</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>22 / 280 (7.86%)</p> <p>25</p> <p>26 / 280 (9.29%)</p> <p>28</p> <p>8 / 280 (2.86%)</p> <p>9</p> <p>40 / 280 (14.29%)</p> <p>47</p> | <p>21 / 284 (7.39%)</p> <p>23</p> <p>20 / 284 (7.04%)</p> <p>21</p> <p>16 / 284 (5.63%)</p> <p>18</p> <p>39 / 284 (13.73%)</p> <p>54</p> | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>COUGH</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>DYSPHONIA</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>DYSPNOEA</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>52 / 280 (18.57%)</p> <p>61</p> <p>22 / 280 (7.86%)</p> <p>23</p> <p>54 / 280 (19.29%)</p> <p>61</p> | <p>52 / 284 (18.31%)</p> <p>60</p> <p>26 / 284 (9.15%)</p> <p>26</p> <p>49 / 284 (17.25%)</p> <p>57</p> | |
| <p>Psychiatric disorders</p> <p>INSOMNIA</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>15 / 280 (5.36%)</p> <p>15</p> | <p>21 / 284 (7.39%)</p> <p>25</p> | |
| <p>Investigations</p> <p>BLOOD ALKALINE PHOSPHATASE INCREASED</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>GAMMA-GLUTAMYLTRANSFERASE INCREASED</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>LIPASE INCREASED</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>25 / 280 (8.93%)</p> <p>27</p> <p>27 / 280 (9.64%)</p> <p>30</p> <p>17 / 280 (6.07%)</p> <p>20</p> | <p>5 / 284 (1.76%)</p> <p>5</p> <p>8 / 284 (2.82%)</p> <p>8</p> <p>11 / 284 (3.87%)</p> <p>13</p> | |

| | | | |
|-----------------------------------------------------------------------------------------------------|---------------------------|---------------------------|--|
| WEIGHT DECREASED subjects affected / exposed occurrences (all) | 63 / 280 (22.50%) 73 | 89 / 284 (31.34%) 92 | |
| Nervous system disorders DIZZINESS subjects affected / exposed occurrences (all) | 27 / 280 (9.64%) 33 | 8 / 284 (2.82%) 8 | |
| DYSGEUSIA subjects affected / exposed occurrences (all) | 31 / 280 (11.07%) 31 | 9 / 284 (3.17%) 10 | |
| HEADACHE subjects affected / exposed occurrences (all) | 26 / 280 (9.29%) 32 | 25 / 284 (8.80%) 32 | |
| Blood and lymphatic system disorders ANAEMIA subjects affected / exposed occurrences (all) | 29 / 280 (10.36%) 33 | 30 / 284 (10.56%) 36 | |
| Eye disorders LACRIMATION INCREASED subjects affected / exposed occurrences (all) | 19 / 280 (6.79%) 19 | 3 / 284 (1.06%) 4 | |
| Gastrointestinal disorders ABDOMINAL PAIN subjects affected / exposed occurrences (all) | 34 / 280 (12.14%) 40 | 41 / 284 (14.44%) 47 | |
| ABDOMINAL PAIN UPPER subjects affected / exposed occurrences (all) | 28 / 280 (10.00%) 32 | 23 / 284 (8.10%) 24 | |
| CONSTIPATION subjects affected / exposed occurrences (all) | 50 / 280 (17.86%) 66 | 70 / 284 (24.65%) 77 | |
| DIARRHOEA subjects affected / exposed occurrences (all) | 185 / 280 (66.07%) 305 | 132 / 284 (46.48%) 200 | |
| DRY MOUTH subjects affected / exposed occurrences (all) | 23 / 280 (8.21%) 26 | 13 / 284 (4.58%) 16 | |

| | | | |
|------------------------------------------------|--------------------|--------------------|--|
| DYSPEPSIA | | | |
| subjects affected / exposed | 32 / 280 (11.43%) | 14 / 284 (4.93%) | |
| occurrences (all) | 34 | 15 | |
| NAUSEA | | | |
| subjects affected / exposed | 146 / 280 (52.14%) | 82 / 284 (28.87%) | |
| occurrences (all) | 207 | 96 | |
| STOMATITIS | | | |
| subjects affected / exposed | 30 / 280 (10.71%) | 55 / 284 (19.37%) | |
| occurrences (all) | 35 | 60 | |
| VOMITING | | | |
| subjects affected / exposed | 122 / 280 (43.57%) | 47 / 284 (16.55%) | |
| occurrences (all) | 227 | 60 | |
| Skin and subcutaneous tissue disorders | | | |
| ALOPECIA | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 61 / 284 (21.48%) | |
| occurrences (all) | 2 | 62 | |
| DERMATITIS ACNEIFORM | | | |
| subjects affected / exposed | 23 / 280 (8.21%) | 6 / 284 (2.11%) | |
| occurrences (all) | 28 | 6 | |
| DRY SKIN | | | |
| subjects affected / exposed | 22 / 280 (7.86%) | 26 / 284 (9.15%) | |
| occurrences (all) | 25 | 27 | |
| ERYTHEMA | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 15 / 284 (5.28%) | |
| occurrences (all) | 1 | 22 | |
| PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME | | | |
| subjects affected / exposed | 32 / 280 (11.43%) | 117 / 284 (41.20%) | |
| occurrences (all) | 36 | 142 | |
| PRURITUS | | | |
| subjects affected / exposed | 15 / 280 (5.36%) | 30 / 284 (10.56%) | |
| occurrences (all) | 18 | 33 | |
| RASH | | | |
| subjects affected / exposed | 54 / 280 (19.29%) | 48 / 284 (16.90%) | |
| occurrences (all) | 65 | 62 | |
| Endocrine disorders | | | |

| | | | |
|-------------------------------------------------|-------------------|-------------------|--|
| HYPOTHYROIDISM | | | |
| subjects affected / exposed | 14 / 280 (5.00%) | 10 / 284 (3.52%) | |
| occurrences (all) | 14 | 10 | |
| Musculoskeletal and connective tissue disorders | | | |
| ARTHRALGIA | | | |
| subjects affected / exposed | 27 / 280 (9.64%) | 30 / 284 (10.56%) | |
| occurrences (all) | 29 | 38 | |
| BACK PAIN | | | |
| subjects affected / exposed | 38 / 280 (13.57%) | 33 / 284 (11.62%) | |
| occurrences (all) | 43 | 37 | |
| MUSCLE SPASMS | | | |
| subjects affected / exposed | 19 / 280 (6.79%) | 25 / 284 (8.80%) | |
| occurrences (all) | 21 | 26 | |
| MUSCULAR WEAKNESS | | | |
| subjects affected / exposed | 14 / 280 (5.00%) | 6 / 284 (2.11%) | |
| occurrences (all) | 15 | 6 | |
| MUSCULOSKELETAL CHEST PAIN | | | |
| subjects affected / exposed | 16 / 280 (5.71%) | 14 / 284 (4.93%) | |
| occurrences (all) | 16 | 14 | |
| MYALGIA | | | |
| subjects affected / exposed | 27 / 280 (9.64%) | 17 / 284 (5.99%) | |
| occurrences (all) | 33 | 17 | |
| PAIN IN EXTREMITY | | | |
| subjects affected / exposed | 36 / 280 (12.86%) | 33 / 284 (11.62%) | |
| occurrences (all) | 43 | 48 | |
| Infections and infestations | | | |
| CONJUNCTIVITIS | | | |
| subjects affected / exposed | 16 / 280 (5.71%) | 2 / 284 (0.70%) | |
| occurrences (all) | 18 | 2 | |
| Metabolism and nutrition disorders | | | |
| DECREASED APPETITE | | | |
| subjects affected / exposed | 91 / 280 (32.50%) | 98 / 284 (34.51%) | |
| occurrences (all) | 111 | 109 | |
| HYPERTRIGLYCERIDAEMIA | | | |
| subjects affected / exposed | 55 / 280 (19.64%) | 2 / 284 (0.70%) | |
| occurrences (all) | 64 | 2 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 10 December 2010 | Following an Investigator notification dated 16-Jul-2010 about a serious, unexpected, possibly study drug related adverse event of hepatotoxicity (cholestatic liver injury) in a patient and subsequent death of that patient enrolled into the CTKI258A2202 study, the protocol was amended to monitor liver function more closely and to allow early detection of study drug induced liver injury, if any. Gamma-glutamyl transferase (GGT) was added in order to have a complete liver function test. |
| 09 February 2011 | Change of inclusion criteria to require Baseline ALT, AST and total bilirubin grade 1 or less regardless of whether hepatic metastases are present at Baseline. Change of exclusion criteria to employ two forms of highly effective contraception for patients participating in the study, and for patients with partners who are biologically able to conceive based on an oral embryo-fetal development study in rats, showing that dovitinib is teratogenic. Addition of precautionary advice to avoid concomitant medication known to cause liver toxicity, as well as addition of list of hepatotoxic agents not permitted as concomitant medication in order to further reduce hepatotoxic events. Collection of a trough concentration at Day 5 Week 6 to obtain at least one dovitinib trough concentration at time points beyond Cycle 1 in order to have steady state PK to evaluate the potential relationship of safety and efficacy in regards to steady state. |
| 01 September 2011 | Novartis Oncology implemented a new radiology data review procedure in Phase III trials involving tumor assessments performed by the Investigator at the time of declaration of disease progression to decrease the rates of discordance between local and central interpretation of radiological data. At this precise time, an expedited tumor response evaluation by the central radiologist is required. The time to definitive worsening of KPS was added as a secondary objective. Patient stratification by 4 pre-determined geographic regions (Japan, Asia Pacific, Europe/Middle East and Americas) was added to document plans for an anticipated exploratory subgroup analysis of PFS based on geographic region. |
| 25 January 2012 | Based on the results of the food effect test (CTKI258A2112 Arm 2; FMI capsule formulation), dovitinib could be taken, as previously, without food, or with an amount of food up to the level tested, i.e. low-fat meal of ≤ 500 calories with ≤ 20 grams fat. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported