



Clinical trial results:

A double-blind, randomised, placebo controlled Phase III study of nintedanib plus Best Supportive Care (BSC) versus placebo plus BSC in patients with colorectal cancer refractory to standard therapies

Summary

| | |
|--------------------------|----------------------------------|
| EudraCT number | 2012-000095-42 |
| Trial protocol | LU IT SE AT DK BE DE PT NL PL FR |
| Global end of trial date | 15 September 2016 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 |
| This version publication date | 06 August 2017 |
| First version publication date | 06 August 2017 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | 1199.52 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02149108 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Boehringer Ingelheim |
| Sponsor organisation address | Binger Strasse 173, Ingelheim am Rhein, Germany, 55216 |
| Public contact | QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com |
| Scientific contact | QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Interim |
| Date of interim/final analysis | 14 June 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 13 May 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 September 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate efficacy and safety of Nintedanib plus BSC vs. placebo plus BSC in patients with metastatic colorectal cancer after failure of previous treatment with standard chemotherapy and biological agents.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. If a subject continued to take trial medication, close monitoring was adhered to and all adverse events recorded. Rules were implemented in all trials whereby doses would be reduced if required. There were 2 dose reductions planned in the protocol: From 200 mg bid to 150 mg bid; then from 150 mg bid to 100 mg bid. In case a patient had these 2 dose reductions and , thereafter had an adverse event that require further dose reduction, the patient should be withdrawn as no further dose reduction was allowed. Symptomatic treatment of tumour associated symptoms were allowed throughout.

Background therapy: -

Evidence for comparator:

Placebo soft gelatin capsule matching that of Nintedanib twice daily (b.i.d.) administered orally of 21-day treatment course was the active comparator.

| | |
|---|-----------------|
| Actual start date of recruitment | 14 October 2014 |
| 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 | Argentina: 23 |
| Country: Number of subjects enrolled | Australia: 37 |
| Country: Number of subjects enrolled | Austria: 27 |
| Country: Number of subjects enrolled | Belgium: 61 |
| Country: Number of subjects enrolled | Canada: 32 |
| Country: Number of subjects enrolled | Czech Republic: 33 |
| Country: Number of subjects enrolled | Denmark: 16 |
| Country: Number of subjects enrolled | France: 10 |
| Country: Number of subjects enrolled | Germany: 16 |
| Country: Number of subjects enrolled | Hong Kong: 15 |
| Country: Number of subjects enrolled | Israel: 12 |
| Country: Number of subjects enrolled | Italy: 104 |
| Country: Number of subjects enrolled | Japan: 112 |
| Country: Number of subjects enrolled | Korea, Democratic People's Republic of: 73 |
| Country: Number of subjects enrolled | Luxembourg: 3 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Mexico: 8 |
| Country: Number of subjects enrolled | Netherlands: 11 |
| Country: Number of subjects enrolled | Poland: 11 |
| Country: Number of subjects enrolled | Portugal: 30 |
| Country: Number of subjects enrolled | Russian Federation: 21 |
| Country: Number of subjects enrolled | Spain: 97 |
| Country: Number of subjects enrolled | Sweden: 11 |
| Country: Number of subjects enrolled | Taiwan: 29 |
| Country: Number of subjects enrolled | Turkey: 39 |
| Country: Number of subjects enrolled | United Kingdom: 64 |
| Country: Number of subjects enrolled | United States: 54 |
| Worldwide total number of subjects | 949 |
| EEA total number of subjects | 494 |

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) | 542 |
| From 65 to 84 years | 405 |
| 85 years and over | 2 |

Subject disposition

Recruitment

Recruitment details:

The "completed" patients were on treatment (2 patients on Placebo, 3 patients on Nintedanib) at the data cut-off date 14JUN2016. The "NOT Completed" patients were off-treatment (380 patients on Placebo, 383 patients on Nintedanib) at the data cut-off date 14JUN2016.
Enrolled=949 subjects were enrolled, randomised (entered) =768 and treated=765.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that they (the subjects) met all strictly implemented inclusion/exclusion criteria. Subjects were not to be randomised to trial treatment if any one of the specific entry criteria were not met.

Period 1

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

Blinding implementation details:

Patients, investigators, the sponsor's trial team, and everyone involved in the analysis or with an interest in this trial remained blinded with regard to the randomised treatment assignments until after database lock.

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

Placebo soft gelatin capsule matching that of Nintedanib twice daily (b.i.d.) administered orally of 21-day treatment course. If required the dose of placebo, could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, soft |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo soft gelatin capsule matching that of Nintedanib twice daily (b.i.d.) administered orally of 21-day treatment course. If required the dose of placebo, could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

| | |
|------------------|------------|
| Arm title | Nintedanib |
|------------------|------------|

Arm description:

Nintedanib 200 mg twice daily (b.i.d.) administered orally in the form of a soft gelatin capsule of 21-day treatment course. If required the dose of Nintedanib, could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|---------------|
| Investigational medicinal product name | Nintedanib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, soft |
| Routes of administration | Oral use |

Dosage and administration details:

Nintedanib 200 mg twice daily (b.i.d.) administered orally in the form of a soft gelatin capsule of 21-day treatment course. If required the dose of Nintedanib, could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

| Number of subjects in period 1^[1] | Placebo | Nintedanib |
|---|---------|------------|
| Started | 382 | 386 |
| Completed | 2 | 3 |
| Not completed | 380 | 383 |
| Adverse event, serious fatal | 11 | 12 |
| Other not defined above | - | 2 |
| Adverse event, non-fatal | 28 | 38 |
| Progressive Disease (PD) | 324 | 318 |
| Refusal to continue trial medication | 15 | 11 |
| Lost to follow-up | 1 | - |
| Not treated | 1 | 2 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one dose of the trial medication.

Baseline characteristics

Reporting groups

| | |
|---|------------|
| Reporting group title | Placebo |
| Reporting group description: Placebo soft gelatin capsule matching that of Nintedanib twice daily (b.i.d.) administered orally of 21-day treatment course. If required the dose of placebo, could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction. | |
| Reporting group title | Nintedanib |
| Reporting group description: Nintedanib 200 mg twice daily (b.i.d.) administered orally in the form of a soft gelatin capsule of 21-day treatment course. If required the dose of Nintedanib, could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction. | |

| Reporting group values | Placebo | Nintedanib | Total |
|---|----------------|--------------|-------|
| Number of subjects | 382 | 386 | 768 |
| Age categorical Units: Subjects | | | |
| Age Continuous | | | |
| Randomised Set (RS): This patient set included all patients who were randomised to receive treatment, whether treated or not. | | | |
| Units: years arithmetic mean standard deviation | 61.1 ± 10.8 | 61 ± 11.3 | - |
| Gender, Male/Female Units: Subjects | | | |
| Female | 164 | 150 | 314 |
| Male | 218 | 236 | 454 |

End points

End points reporting groups

| | |
|---|------------|
| Reporting group title | Placebo |
| Reporting group description: Placebo soft gelatin capsule matching that of Nintedanib twice daily (b.i.d.) administered orally of 21-day treatment course. If required the dose of placebo, could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction. | |
| Reporting group title | Nintedanib |
| Reporting group description: Nintedanib 200 mg twice daily (b.i.d.) administered orally in the form of a soft gelatin capsule of 21-day treatment course. If required the dose of Nintedanib, could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction. | |

Primary: Progression-Free Survival (PFS) by Central Review Assessment

| | |
|---|--|
| End point title | Progression-Free Survival (PFS) by Central Review Assessment |
| End point description: PFS by central review assessment was defined as the time from the date of randomisation to the date of disease progression according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 or death from any cause, whichever occurred first. Median, 95% Confidence Interval were calculated from an unadjusted Kaplan–Meier curve for each treatment arm. Randomised Set: This patient set included all patients who were randomised to receive treatment, whether treated or not. | |
| End point type | Primary |
| End point timeframe: From randomisation until cut-off date 14JUN2016. | |

| End point values | Placebo | Nintedanib | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 382 ^[1] | 386 ^[2] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 1.38 (1.38 to 1.41) | 1.51 (1.45 to 2.17) | | |

Notes:

[1] - RS

[2] - RS

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | Placebo v Nintedanib |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 768 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[3] |
| P-value | < 0.0001 ^[4] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.58 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.49 |
| upper limit | 0.69 |

Notes:

[3] - Hazard ratio <1 favors Nintedanib.

[4] - Hazard ratio, confidence interval and p-value obtained from log-rank test stratified by regorafenib pre-treatment (yes vs no), time from onset metastatic disease until randomisation (less than 24 months vs 24 months or more) and region.

Primary: Overall Survival (OS)

| | |
|---|-----------------------|
| End point title | Overall Survival (OS) |
| End point description: | |
| OS was defined as the time from randomisation to the time of death from any cause. Median, 95% Confidence Interval were calculated from an unadjusted Kaplan-Meier curve for each treatment arm. Randomised Set: This patient set included all patients who were randomised to receive treatment, whether treated or not. | |
| End point type | Primary |
| End point timeframe: | |
| From randomisation until cut-off date 14JUN2016. | |

| End point values | Placebo | Nintedanib | | |
|----------------------------------|---------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 382 ^[5] | 386 ^[6] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 6.05 (5.22 to 6.97) | 6.44 (5.98 to 7.1) | | |

Notes:

[5] - RS

[6] - RS

Statistical analyses

| | |
|---|-------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | Placebo v Nintedanib |
| Number of subjects included in analysis | 768 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[7] |
| P-value | = 0.8659 ^[8] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.01 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.86 |
| upper limit | 1.19 |

Notes:

[7] - Hazard ratio below 1 favors Nintedanib.

[8] - Hazard ratio, confidence interval and p-value obtained from log-rank test stratified by regorafenib pre-treatment (yes vs no), time from onset metastatic disease until randomisation (less than 24 months vs 24 months or more) and region.

Secondary: Objective Tumour Response (Complete Response (CR)) + Partial Response (PR) by Central Review Assessment

| | |
|-----------------|---|
| End point title | Objective Tumour Response (Complete Response (CR)) + Partial Response (PR) by Central Review Assessment |
|-----------------|---|

End point description:

Objective tumour response was defined as best overall response of CR or PR determined by central review assessment.

Randomised Set: This patient set included all patients who were randomised to receive treatment, whether treated or not.

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

End point timeframe:

From randomisation until cut-off date 14JUN2016.

| End point values | Placebo | Nintedanib | | |
|-----------------------------------|--------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 382 ^[9] | 386 ^[10] | | |
| Units: Percentage of participants | | | | |
| CR | 0 | 0 | | |
| PR | 0 | 0 | | |

Notes:

[9] - RS

[10] - RS

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control (Complete Response + Partial Response + Stable Disease) by Central Review Assessment

| | |
|-----------------|--|
| End point title | Disease Control (Complete Response + Partial Response + Stable Disease) by Central Review Assessment |
|-----------------|--|

End point description:

Disease control was defined as best overall response of CR, PR, or Stable Disease (SD).

Randomised Set: This patient set included all patients who were randomised to receive treatment, whether treated or not.

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

End point timeframe:

From randomisation until cut-off date 14JUN2016.

| End point values | Placebo | Nintedanib | | |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 382 ^[11] | 386 ^[12] | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 10.5 | 25.6 | | |

Notes:

[11] - RS

[12] - RS

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|--------------------------|
| Comparison groups | Placebo v Nintedanib |
| Number of subjects included in analysis | 768 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[13] |
| P-value | < 0.0001 ^[14] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.96 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2 |
| upper limit | 4.47 |

Notes:

[13] - An odds ratio >1 indicates benefit to Nintedanib.

[14] - Odds ratio and p-value are obtained from logistic regression model adjusted for regorafenib pre-treatment (yes vs no), time from onset metastatic disease until randomization in the trial (less than 24 months vs. 24 months or more) and region.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first drug administration until 28 days after last drug administration, up to 22.7 months.

Adverse event reporting additional description:

1 patient who was randomised to the Placebo was not treated. Consequently, number of subjects that started is 382 but only 381 reported that includes only treated patients.

2 patients were randomised to the Nintedanib were not treated. Consequently, number of subjects that started is 386 but only 384 reported that includes only treated patients.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 19.0 |

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo soft gelatin capsule matching that of Nintedanib twice daily (b.i.d.) administered orally of 21-day treatment course. If required the dose of placebo, could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

| | |
|-----------------------|------------|
| Reporting group title | Nintedanib |
|-----------------------|------------|

Reporting group description:

Nintedanib 200 mg twice daily (b.i.d.) administered orally in the form of a soft gelatin capsule of 21-day treatment course. If required the dose of Nintedanib, could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

| Serious adverse events | Placebo | Nintedanib | |
|---|--------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 133 / 381 (34.91%) | 149 / 384 (38.80%) | |
| number of deaths (all causes) | 51 | 55 | |
| number of deaths resulting from adverse events | 2 | 1 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bowen's disease | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cancer pain | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intracranial tumour haemorrhage | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Malignant ascites | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 24 / 381 (6.30%) | 27 / 384 (7.03%) | |
| occurrences causally related to treatment / all | 0 / 24 | 0 / 27 | |
| deaths causally related to treatment / all | 0 / 24 | 0 / 27 | |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to liver | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to spine | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour associated fever | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour haemorrhage | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour pain | | | |
| subjects affected / exposed | 5 / 381 (1.31%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour perforation | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 2 / 381 (0.52%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphoedema | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vena cava thrombosis | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (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 / 381 (0.79%) | 4 / 384 (1.04%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |

| | | | |
|---|-----------------|-----------------|--|
| Chest pain | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chills | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Condition aggravated | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 4 / 381 (1.05%) | 2 / 384 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 2 | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 2 / 384 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gait disturbance | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 3 / 381 (0.79%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | |
| Generalised oedema | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malaise | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 3 / 384 (0.78%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Performance status decreased | | | |
| subjects affected / exposed | 3 / 381 (0.79%) | 5 / 384 (1.30%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 5 | |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 381 (1.05%) | 3 / 384 (0.78%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic inflammatory response syndrome | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis in device | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Contrast media allergy | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |

| | | | |
|---|------------------|------------------|--|
| Pelvic pain | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acquired diaphragmatic eventration | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Aspiration | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Dyspnoea | | | |
| subjects affected / exposed | 12 / 381 (3.15%) | 12 / 384 (3.13%) | |
| occurrences causally related to treatment / all | 0 / 12 | 1 / 12 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 5 | |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 6 / 381 (1.57%) | 3 / 384 (0.78%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 381 (0.52%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Respiratory distress | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vocal cord polyp | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Completed suicide | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Delirium | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 3 / 381 (0.79%) | 7 / 384 (1.82%) | |
| occurrences causally related to treatment / all | 1 / 3 | 7 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 5 / 381 (1.31%) | 6 / 384 (1.56%) | |
| occurrences causally related to treatment / all | 1 / 5 | 6 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 6 / 381 (1.57%) | 2 / 384 (0.52%) | |
| occurrences causally related to treatment / all | 1 / 6 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 2 / 381 (0.52%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 2 / 384 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Liver function test increased | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 2 / 384 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-----------------|-----------------|--|
| Spinal compression fracture subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stoma site haemorrhage subjects affected / exposed | 0 / 381 (0.00%) | 2 / 384 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial fibrillation subjects affected / exposed | 2 / 381 (0.52%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block complete subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradycardia subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac failure subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Altered state of consciousness subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Ataxia | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain oedema | | | |
| subjects affected / exposed | 3 / 381 (0.79%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral infarction | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cognitive disorder | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depressed level of consciousness | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysarthria | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage intracranial | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 2 / 381 (0.52%) | 2 / 384 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hemiparesis | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intracranial pressure increased | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolic encephalopathy | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorder | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (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 | 2 / 381 (0.52%) | 2 / 384 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraparesis | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peroneal nerve palsy | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sensory loss | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord compression | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 2 / 384 (0.52%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 4 / 381 (1.05%) | 2 / 384 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Abdominal hernia | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| 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 | 4 / 381 (1.05%) | 6 / 384 (1.56%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 4 / 381 (1.05%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 2 / 384 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 381 (0.52%) | 2 / 384 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 2 / 384 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocutaneous fistula | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Fistula of small intestine | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (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 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal hypomotility | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| 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 / 381 (0.52%) | 5 / 384 (1.30%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Incarcerated inguinal hernia | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 2 / 384 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 6 / 381 (1.57%) | 6 / 384 (1.56%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal prolapse | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestinal obstruction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestinal stenosis | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine perforation | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 2 / 384 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 381 (0.52%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mallory-Weiss syndrome | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (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 | 4 / 381 (1.05%) | 3 / 384 (0.78%) | |
| occurrences causally related to treatment / all | 1 / 4 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Proctalgia | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal obstruction | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal tenesmus | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Subileus | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 381 (0.52%) | 5 / 384 (1.30%) | |
| occurrences causally related to treatment / all | 1 / 2 | 3 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Bile duct obstruction | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bile duct stenosis | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 4 / 384 (1.04%) | |
| occurrences causally related to treatment / all | 1 / 1 | 6 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic failure | | | |
| subjects affected / exposed | 4 / 381 (1.05%) | 2 / 384 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 3 | 1 / 1 | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 2 / 384 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Jaundice | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaundice cholestatic | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver disorder | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 381 (0.79%) | 7 / 384 (1.82%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 5 | |
| Focal segmental glomerulosclerosis | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydronephrosis | | | |
| subjects affected / exposed | 5 / 381 (1.31%) | 4 / 384 (1.04%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Micturition disorder | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| 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 | 1 / 381 (0.26%) | 3 / 384 (0.78%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 5 / 381 (1.31%) | 4 / 384 (1.04%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fistula | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Flank pain | | | |
| subjects affected / exposed | 2 / 381 (0.52%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 3 / 381 (0.79%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal column stenosis | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis infectious | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia sepsis | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver abscess | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 3 / 384 (0.78%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Oral candidiasis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 2 / 384 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 5 / 381 (1.31%) | 3 / 384 (0.78%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (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 | 0 / 381 (0.00%) | 4 / 384 (1.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Small intestine gangrene | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Streptococcal sepsis | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 6 / 384 (1.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection pseudomonal | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 5 / 381 (1.31%) | 6 / 384 (1.56%) | |
| occurrences causally related to treatment / all | 2 / 5 | 1 / 6 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 381 (0.26%) | 4 / 384 (1.04%) | |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 381 (0.79%) | 0 / 384 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 0 / 381 (0.00%) | 1 / 384 (0.26%) | |
| 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 | Placebo | Nintedanib | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 309 / 381 (81.10%) | 351 / 384 (91.41%) | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 23 / 381 (6.04%) | 90 / 384 (23.44%) | |
| occurrences (all) | 25 | 111 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 44 / 381 (11.55%) | 90 / 384 (23.44%) | |
| occurrences (all) | 47 | 108 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 22 / 381 (5.77%) | 28 / 384 (7.29%) | |
| occurrences (all) | 22 | 33 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 15 / 381 (3.94%) | 26 / 384 (6.77%) | |
| occurrences (all) | 18 | 27 | |

| | | | |
|--|---|---|--|
| Weight decreased subjects affected / exposed occurrences (all) | 13 / 381 (3.41%) 13 | 35 / 384 (9.11%) 35 | |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 15 / 381 (3.94%) 16 | 42 / 384 (10.94%) 43 | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 19 / 381 (4.99%) 24 | 25 / 384 (6.51%) 30 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 22 / 381 (5.77%) 23 | 23 / 384 (5.99%) 26 | |
| General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) | 46 / 381 (12.07%) 50 89 / 381 (23.36%) 95 28 / 381 (7.35%) 28 21 / 381 (5.51%) 21 45 / 381 (11.81%) 58 | 54 / 384 (14.06%) 60 113 / 384 (29.43%) 127 22 / 384 (5.73%) 25 9 / 384 (2.34%) 9 53 / 384 (13.80%) 61 | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper | 59 / 381 (15.49%) 60 | 65 / 384 (16.93%) 69 | |

| | | | |
|---|--------------------|--------------------|--|
| subjects affected / exposed | 21 / 381 (5.51%) | 25 / 384 (6.51%) | |
| occurrences (all) | 22 | 28 | |
| Constipation | | | |
| subjects affected / exposed | 57 / 381 (14.96%) | 65 / 384 (16.93%) | |
| occurrences (all) | 60 | 73 | |
| Diarrhoea | | | |
| subjects affected / exposed | 57 / 381 (14.96%) | 175 / 384 (45.57%) | |
| occurrences (all) | 76 | 301 | |
| Nausea | | | |
| subjects affected / exposed | 103 / 381 (27.03%) | 163 / 384 (42.45%) | |
| occurrences (all) | 129 | 202 | |
| Vomiting | | | |
| subjects affected / exposed | 71 / 381 (18.64%) | 149 / 384 (38.80%) | |
| occurrences (all) | 93 | 229 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 48 / 381 (12.60%) | 42 / 384 (10.94%) | |
| occurrences (all) | 48 | 47 | |
| Dyspnoea | | | |
| subjects affected / exposed | 40 / 381 (10.50%) | 35 / 384 (9.11%) | |
| occurrences (all) | 43 | 37 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 14 / 381 (3.67%) | 20 / 384 (5.21%) | |
| occurrences (all) | 14 | 21 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 22 / 381 (5.77%) | 30 / 384 (7.81%) | |
| occurrences (all) | 22 | 33 | |
| Renal and urinary disorders | | | |
| Proteinuria | | | |
| subjects affected / exposed | 12 / 381 (3.15%) | 34 / 384 (8.85%) | |
| occurrences (all) | 14 | 38 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |

| | | | |
|--|--------------------------|---------------------------|--|
| subjects affected / exposed occurrences (all) | 6 / 381 (1.57%) 6 | 21 / 384 (5.47%) 22 | |
| Back pain subjects affected / exposed occurrences (all) | 30 / 381 (7.87%) 32 | 33 / 384 (8.59%) 37 | |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 96 / 381 (25.20%) 100 | 128 / 384 (33.33%) 143 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|---|
| 28 July 2014 | <p>In the amendment 1 primary endpoint PFS and key secondary endpoint OS were changed to coprimary endpoints to reflect the clinical benefit for patients in this trial. As the trial was already powered for OS, no other changes in the trial design or patient number were needed. All relevant sections of the Clinical Trial Protocol (CTP) were adapted accordingly. The subgroup analysis 'previous treatment with TAS-102 (yes vs. no)' was added for both coprimary endpoints.</p> <p>The amendment 1 also clarified that analyses to describe the pattern of time to death would be described, while accounting for the extent and influence of postprogression anticancer treatments.</p> <p>The amendment 1 added the analysis on exposure-response relationship to the CTP.</p> |
| 13 March 2015 | <p>The amendment 2 clarified that previous treatment for Colo Rectal Cancer (CRC) with TAS-102, if available to the patient according to local standards, was allowed in this trial. Further clarifications regarding dose reduction in the case of diarrhoea, treatment interruption in case of haematological AEs, and the threshold for liver enzymes not being dependent on CTCAE were provided. The information about history of CRC that should be obtained and recorded in the electronic Case Report Form (eCRF) was extended by 'reasons for not administering regorafenib'.</p> <p>For the HRQoL analysis, it was clarified that the main HRQoL endpoints in this trial are the changes in mean scores over the duration of the median follow-up period for the physical functioning scale and global health status (QoL scale measured on the EORTC QCL-C30 questionnaire using longitudinal models). These are mixed-effects growth curve models with the average profile over time for each HRQoL endpoint described using a piecewise linear model. A mean score per patient for each HRQoL endpoint will be calculated from the area under the estimated growth curve up to the median follow-up time. An additional responder analysis will compare the proportions of patients in each treatment group that achieved an average 10-point increase from the baseline score over the follow-up time for each HRQoL endpoint of interest.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported