



Clinical trial results:

LUME-Meso: Double blind, randomised, multicentre, phase II/III study of nintedanib in combination with pemetrexed / cisplatin followed by continuing nintedanib monotherapy versus placebo in combination with pemetrexed / cisplatin followed by continuing placebo monotherapy for the treatment of patients with unresectable malignant pleural mesothelioma

Summary

| | |
|--------------------------|---|
| EudraCT number | 2012-005201-48 |
| Trial protocol | DE IT GB FR DK ES BE NL SE PT CZ AT PL HR |
| Global end of trial date | 31 August 2018 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 21 September 2019 |
| First version publication date | 21 September 2019 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | 1199.93 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01907100 |
| 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, +001 8002430127, clintrriage.rdg@boehringer-ingelheim.com |
| Scientific contact | QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +001 8002430127, clintrriage.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 | Final |
| Date of interim/final analysis | 19 September 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 16 March 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 31 August 2018 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of nintedanib plus pemetrexed/cisplatin followed by nintedanib monotherapy vs. placebo plus pemetrexed/cisplatin followed by placebo monotherapy as first-line treatment for patients with unresectable malignant pleural mesothelioma (MPM).

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. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all patients as required.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 27 September 2013 |
| 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 | Egypt: 38 |
| Country: Number of subjects enrolled | South Africa: 6 |
| Country: Number of subjects enrolled | Japan: 31 |
| Country: Number of subjects enrolled | Australia: 56 |
| Country: Number of subjects enrolled | Austria: 5 |
| Country: Number of subjects enrolled | Belgium: 18 |
| Country: Number of subjects enrolled | Canada: 12 |
| Country: Number of subjects enrolled | Croatia: 14 |
| Country: Number of subjects enrolled | Czech Republic: 9 |
| Country: Number of subjects enrolled | Denmark: 18 |
| Country: Number of subjects enrolled | France: 49 |
| Country: Number of subjects enrolled | Germany: 22 |
| Country: Number of subjects enrolled | Israel: 11 |
| Country: Number of subjects enrolled | Italy: 84 |
| Country: Number of subjects enrolled | Netherlands: 20 |
| Country: Number of subjects enrolled | Norway: 11 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Poland: 19 |
| Country: Number of subjects enrolled | Portugal: 3 |
| Country: Number of subjects enrolled | Russian Federation: 18 |
| Country: Number of subjects enrolled | Spain: 39 |
| Country: Number of subjects enrolled | Sweden: 13 |
| Country: Number of subjects enrolled | Turkey: 12 |
| Country: Number of subjects enrolled | United Kingdom: 64 |
| Country: Number of subjects enrolled | United States: 17 |
| Country: Number of subjects enrolled | Argentina: 11 |
| Country: Number of subjects enrolled | Chile: 17 |
| Country: Number of subjects enrolled | Mexico: 28 |
| Worldwide total number of subjects | 645 |
| EEA total number of subjects | 388 |

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) | 270 |
| From 65 to 84 years | 373 |
| 85 years and over | 2 |

Subject disposition

Recruitment

Recruitment details:

Patients were initially treated with combination therapy consisting of nintedanib or placebo plus standard chemotherapy (pemetrexed/cisplatin), for a maximum of 6 cycles of 21 days duration. After completion of combination therapy, patients who had not progressed continued with nintedanib or placebo monotherapy.

Pre-assignment

Screening details:

All participants were screened for eligibility to participate in trial. Subjects attended specialist sites to ensure that they (the participants) met all implemented inclusion/exclusion criteria. Participants were not to be entered to trial if any of the specific entry criteria was violated. PD: Progressive Disease; approx.: approximately

Period 1

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

Blinding implementation details:

Double blind, randomised, multicentre, phase II/III study

Arms

| | |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo_Phase II |

Arm description:

Phase II part: Nintedanib matching placebo 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m² (100 mg or 500 mg vials) and Cisplatin 75 mg/m² (50 mL of 1 mg/mL solution) on Day 1 of each 21-day treatment course administered intravenously. 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 | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, soft |
| Routes of administration | Oral use |

Dosage and administration details:

Nintedanib matching placebo 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m² (100 mg or 500 mg vials) and Cisplatin 75 mg/m² (50 mL of 1 mg/mL solution) on Day 1 of each 21-day treatment course administered intravenously. 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_Phase II |
|------------------|---------------------|

Arm description:

Phase II part: Nintedanib 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m² (100 mg or 500 mg vials) and Cisplatin 75 mg/m² (50 mL of 1 mg/mL solution) on Day 1 of each 21-day treatment course administered intravenously. 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.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m² (100 mg or 500 mg vials) and Cisplatin 75 mg/m² (50 mL of 1 mg/ml solution) on Day 1 of each 21-day treatment course administered intravenously. 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 title | Placebo_Phase III |
|------------------|-------------------|

Arm description:

Phase III part: Nintedanib matching Placebo 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m² (100 mg or 500 mg vials) and Cisplatin 75 mg/m² (50 mL of 1 mg/ml solution) on Day 1 of each 21-day treatment course administered intravenously. 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 | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, soft |
| Routes of administration | Oral use |

Dosage and administration details:

Nintedanib matching placebo 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m² (100 mg or 500 mg vials) and Cisplatin 75 mg/m² (50 mL of 1 mg/ml solution) on Day 1 of each 21-day treatment course administered intravenously. 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_Phase III |
|------------------|----------------------|

Arm description:

Phase III part: Nintedanib 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m² (100 mg or 500 mg vials) and Cisplatin 75 mg/m² (50 mL of 1 mg/ml solution) on Day 1 of each 21-day treatment course administered intravenously. 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.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m² (100 mg or 500 mg vials) and Cisplatin 75 mg/m² (50 mL of 1 mg/ml solution) on Day 1 of each 21-day treatment course administered intravenously. 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_Phase II | Nintedanib_Phase II | Placebo_Phase III |
|---|------------------|---------------------|-------------------|
| Started | 43 | 44 | 229 |
| Treated Patients | 41 | 44 | 228 |
| Completed | 0 | 4 | 82 |
| Not completed | 43 | 40 | 147 |
| Adverse event, serious fatal | - | - | 4 |
| Consent withdrawn by subject | 2 | 5 | 10 |
| Adverse event, non-fatal | 7 | 3 | 26 |
| PD based on modified RECIST criteria | 31 | 32 | 95 |
| Other than reasons specified | 1 | - | 10 |
| Lost to follow-up | - | - | - |
| Not treated | 2 | - | 1 |
| Protocol deviation | - | - | 1 |

| Number of subjects in period 1^[1] | Nintedanib_Phase III |
|---|----------------------|
| Started | 229 |
| Treated Patients | 227 |
| Completed | 83 |
| Not completed | 146 |
| Adverse event, serious fatal | 4 |
| Consent withdrawn by subject | 13 |
| Adverse event, non-fatal | 27 |
| PD based on modified RECIST criteria | 92 |
| Other than reasons specified | 6 |
| Lost to follow-up | 1 |
| Not treated | 2 |
| Protocol deviation | 1 |

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_Phase II |
|-----------------------|------------------|

Reporting group description:

Phase II part: Nintedanib matching placebo 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m² (100 mg or 500 mg vials) and Cisplatin 75 mg/m² (50 mL of 1 mg/mL solution) on Day 1 of each 21-day treatment course administered intravenously. 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_Phase II |
|-----------------------|---------------------|

Reporting group description:

Phase II part: Nintedanib 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m² (100 mg or 500 mg vials) and Cisplatin 75 mg/m² (50 mL of 1 mg/mL solution) on Day 1 of each 21-day treatment course administered intravenously. 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 title | Placebo_Phase III |
|-----------------------|-------------------|

Reporting group description:

Phase III part: Nintedanib matching Placebo 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m² (100 mg or 500 mg vials) and Cisplatin 75 mg/m² (50 mL of 1 mg/mL solution) on Day 1 of each 21-day treatment course administered intravenously. 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_Phase III |
|-----------------------|----------------------|

Reporting group description:

Phase III part: Nintedanib 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m² (100 mg or 500 mg vials) and Cisplatin 75 mg/m² (50 mL of 1 mg/mL solution) on Day 1 of each 21-day treatment course administered intravenously. 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_Phase II | Nintedanib_Phase II | Placebo_Phase III |
|------------------------|------------------|---------------------|-------------------|
| Number of subjects | 43 | 44 | 229 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|--|-------|-------|-------|
| Age Continuous | | | |
| Randomised Set: This patient set included all randomized patients. | | | |
| Units: years | | | |
| arithmetic mean | 65.9 | 66.4 | 64.3 |
| standard deviation | ± 7.6 | ± 8.6 | ± 8.9 |
| Gender, Male/Female | | | |
| Randomised Set: This patient set included all randomized patients. | | | |
| Units: Subjects | | | |
| Female | 8 | 10 | 60 |
| Male | 35 | 34 | 169 |
| Race (NIH/OMB) | | | |
| Race was only collected where allowed by local law. Randomised Set: This patient set included all randomized patients. | | | |
| Units: Subjects | | | |

| | | | |
|---|----|----|-----|
| American Indian or Alaska Native | 0 | 0 | 14 |
| Asian | 0 | 0 | 16 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 0 |
| White | 38 | 38 | 180 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 5 | 6 | 19 |

| Reporting group values | Nintedanib_Phase III | Total | |
|------------------------------------|----------------------|-------|--|
| Number of subjects | 229 | 545 | |
| Age categorical Units: Subjects | | | |

| | | | |
|--|-------|-----|--|
| Age Continuous | | | |
| Randomised Set: This patient set included all randomized patients. | | | |
| Units: years | | | |
| arithmetic mean | 63.6 | | |
| standard deviation | ± 9.5 | - | |
| Gender, Male/Female | | | |
| Randomised Set: This patient set included all randomized patients. | | | |
| Units: Subjects | | | |
| Female | 64 | 142 | |
| Male | 165 | 403 | |
| Race (NIH/OMB) | | | |
| Race was only collected where allowed by local law. Randomised Set: This patient set included all randomized patients. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 12 | 26 | |
| Asian | 14 | 30 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 2 | 2 | |
| White | 185 | 441 | |
| More than one race | 0 | 0 | |
| Unknown or Not Reported | 16 | 46 | |

End points

End points reporting groups

| | |
|--|----------------------|
| Reporting group title | Placebo_Phase II |
| Reporting group description: Phase II part: Nintedanib matching placebo 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m ² (100 mg or 500 mg vials) and Cisplatin 75 mg/m ² (50 mL of 1 mg/mL solution) on Day 1 of each 21-day treatment course administered intravenously. 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_Phase II |
| Reporting group description: Phase II part: Nintedanib 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m ² (100 mg or 500 mg vials) and Cisplatin 75 mg/m ² (50 mL of 1 mg/mL solution) on Day 1 of each 21-day treatment course administered intravenously. 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 title | Placebo_Phase III |
| Reporting group description: Phase III part: Nintedanib matching Placebo 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m ² (100 mg or 500 mg vials) and Cisplatin 75 mg/m ² (50 mL of 1 mg/mL solution) on Day 1 of each 21-day treatment course administered intravenously. 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_Phase III |
| Reporting group description: Phase III part: Nintedanib 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m ² (100 mg or 500 mg vials) and Cisplatin 75 mg/m ² (50 mL of 1 mg/mL solution) on Day 1 of each 21-day treatment course administered intravenously. 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)

| | |
|---|---------------------------------|
| End point title | Progression-Free Survival (PFS) |
| End point description: This outcome measure presents progression-free survival. Disease progression was defined according to the modified Response Evaluation Criteria in Solid Tumours (RECIST) criteria. Progression-free survival time was calculated as the duration from the date of randomization to the date of disease progression or death, whichever occurred first. For patients with known date of progression (or death): PFS (days) = min (date of progression, date of death) - date of randomization + 1 day. For patients without progression or death, PFS was censored at the last imaging date that showed no disease progression: PFS (days, censored) = date of last imaging showing no progression - date randomization + 1 day. Randomised Set (RS) : This patient set included all randomized patients. | |
| End point type | Primary |
| End point timeframe: From (Fr.) randomization (randomiz.) until the earliest of disease progression, death or (Phase II: cut-off date of 4-March-2016; up to 889 days) (Phase III: cut-off date of 16-March-2018; up to 31 months (mth)) | |

| End point values | Placebo_Phase II | Nintedanib_Phase II | Placebo_Phase III | Nintedanib_Phase III |
|---------------------------------------|---------------------|----------------------|---------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 43 ^[1] | 44 ^[2] | 229 ^[3] | 229 ^[4] |
| Units: Months | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Phase II | 5.72 (5.19 to 8.18) | 9.36 (5.55 to 12.65) | 6.97 (5.42 to 9.00) | 6.77 (5.36 to 9.07) |

Notes:

[1] - RS

[2] - RS

[3] - RS

[4] - RS

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

Phase II Part:A Cox proportional hazards model was fitted to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for the comparison of treatment arms (Nintedanib vs Placebo). If the hazard ratio is below 1 then it favours nintedanib.

| | |
|---|--|
| Comparison groups | Placebo_Phase II v Nintedanib_Phase II |
| Number of subjects included in analysis | 87 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[5] |
| P-value | = 0.0174 |
| Method | Proportional hazards mode |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.555 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.34 |
| upper limit | 0.907 |

Notes:

[5] - Hazard ratio, confidence interval and p-value obtained from proportional hazards model stratified by tumour histology (epithelioid vs. biphasic).

| Statistical analysis title | Statistical analysis 2 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

Phase III part: A Cox proportional hazards model was fitted to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for the comparison of treatment arms (Nintedanib vs Placebo). If the hazard ratio is below 1 then it favours nintedanib.

| | |
|---|--|
| Comparison groups | Placebo_Phase III v Nintedanib_Phase III |
| Number of subjects included in analysis | 458 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.543 ^[6] |
| Method | Proportional hazards model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.01 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.79 |
| upper limit | 1.3 |

Notes:

[6] - one-sided p-value

Secondary: Overall Survival (OS)

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

End point description:

Overall survival was defined as the duration of time from randomization to time of death. This is the key secondary endpoint of the trial. 99999 is "Not applicable" as the 75th percentile was not reached because of insufficient number of patients with OS event thus not calculated.

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

End point timeframe:

From randomization until the earliest of disease progression, death or (Phase II: cut-off date of 4-March-2016; up to 889 days) (Phase III: cut-off date of 16-March-2018; up to 31 months)

| End point values | Placebo_Phase II | Nintedanib_Phase II | Placebo_Phase III | Nintedanib_Phase III |
|---------------------------------------|------------------------|------------------------|-----------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 43 ^[7] | 44 ^[8] | 229 ^[9] | 229 ^[10] |
| Units: Months | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Phase II | 14.46 (10.41 to 99999) | 18.30 (10.91 to 99999) | 16.07 (9.66 to 19.29) | 14.36 (9.13 to 18.69) |

Notes:

[7] - RS

[8] - RS

[9] - RS

[10] - RS

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Phase II: A Cox proportional hazards model was fitted to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for the comparison of treatment arms (Nintedanib vs Placebo). If the hazard ratio is below 1 then it favours nintedanib.

| | |
|---|--|
| Comparison groups | Placebo_Phase II v Nintedanib_Phase II |
| Number of subjects included in analysis | 87 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[11] |
| P-value | = 0.4132 |
| Method | Proportional hazards mode |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.782 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.433 |
| upper limit | 1.412 |

Notes:

[11] - Hazard ratio, confidence interval and p-value obtained from proportional hazards model stratified by tumour histology (epithelioid vs. biphasic).

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

Phase III: A Cox proportional hazards model was fitted to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for the comparison of treatment arms (Nintedanib vs Placebo). If the hazard ratio is below 1 then it favours nintedanib.

| | |
|---|--|
| Comparison groups | Placebo_Phase III v Nintedanib_Phase III |
| Number of subjects included in analysis | 458 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[12] |
| P-value | = 0.7306 ^[13] |
| Method | Proportional hazards model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.12 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.79 |
| upper limit | 1.58 |

Notes:

[12] - Hazard ratio, confidence interval and p-value obtained from a non-stratified proportional hazards model.

[13] - one-sided p-value

Secondary: Objective response according to modified RECIST– investigator assessment

| | |
|-----------------|--|
| End point title | Objective response according to modified RECIST– investigator assessment ^[14] |
|-----------------|--|

End point description:

Objective response (best overall tumour response of confirmed complete response [CR] or confirmed partial response [PR]). Complete Response: disappearance of all target lesions Partial Response: at least a 30 % decrease in the total tumour measurement of target lesions, taking as reference the baseline total tumour measurement. Percentage of Patients with confirmed objective response is presented. This endpoint was only evaluated for Phase III part.

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

End point timeframe:

Tumour imaging was to be performed every 6 weeks until disease progression, death or start of subsequent anti-cancer therapy, whichever occurred earlier; up to 54 months

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| End point values | Placebo_Phase III | Nintedanib_Phase III | | |
|-----------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 229 ^[15] | 229 ^[16] | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 42.8 (36.3 to 49.5) | 45.0 (38.4 to 51.7) | | |

Notes:

[15] - RS

[16] - RS

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|--|--|
| Statistical analysis description: | |
| Odds ratio and one-sided p-value are obtained from an un-adjusted logistic regression model (Nintedanib vs Placebo). | |
| Comparison groups | Placebo_Phase III v Nintedanib_Phase III |
| Number of subjects included in analysis | 458 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[17] |
| P-value | = 0.3189 ^[18] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.76 |
| upper limit | 1.58 |

Notes:

[17] - Odds ratio above 1 favours nintedanib.

[18] - one-sided p-value

Secondary: Disease control according to modified RECIST– investigator assessment

| End point title | Disease control according to modified RECIST– investigator assessment ^[19] |
|---|---|
| End point description: | |
| Disease control (best overall response of confirmed CR or PR, or Stable Disease (SD) that lasted ≥36 days) according to modified RECIST. Percentage of Patients with Disease control is presented. This endpoint was only evaluated for Phase III part. | |
| End point type | Secondary |

End point timeframe:

Tumour imaging was to be performed every 6 weeks until disease progression, death or start of subsequent anti-cancer therapy, whichever occurred earlier; up to 54 months

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| End point values | Placebo_Phase III | Nintedanib_Phase III | | |
|-----------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 229 ^[20] | 229 ^[21] | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 92.6 (88.4 to 95.6) | 90.8 (86.3 to 94.2) | | |

Notes:

[20] - RS

[21] - RS

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|--|--|
| Statistical analysis description: | |
| Odds ratio and one-sided p-value are obtained from an un-adjusted logistic regression model (Nintedanib vs Placebo). | |
| Comparison groups | Placebo_Phase III v Nintedanib_Phase III |
| Number of subjects included in analysis | 458 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[22] |
| P-value | = 0.7512 ^[23] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.4 |
| upper limit | 1.55 |

Notes:

[22] - Odds ratio above 1 favours nintedanib.

[23] - one-sided p-value

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAE & Non SAE: Fr. 1st dose until 28days(Phase II) or 30days(Phase III) after last dose, up to approx. 30mth(Phase II) & approx. 32mth(Phase III). All-cause mortality: Fr. randomiz until end of follow-up, up to approx. 30mth(Phase II) & approx. 32mth(Phase III)

Adverse event reporting additional description:

All-cause mortality numbers are based on randomized set whereas Serious Adverse Events (SAE) and non-SAE are based on treated set.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Placebo_Phase II |
|-----------------------|------------------|

Reporting group description:

Phase II part: Nintedanib matching placebo 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m² (100 mg or 500 mg vials) and Cisplatin 75 mg/m² (50 mL of 1 mg/mL solution) on Day 1 of each 21-day treatment course administered intravenously. 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_Phase II |
|-----------------------|---------------------|

Reporting group description:

Phase II part: Nintedanib 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m² (100 mg or 500 mg vials) and Cisplatin 75 mg/m² (50 mL of 1 mg/mL solution) on Day 1 of each 21-day treatment course administered intravenously. 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 title | Placebo_Phase III |
|-----------------------|-------------------|

Reporting group description:

Phase III part: Nintedanib matching Placebo 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m² (100 mg or 500 mg vials) and Cisplatin 75 mg/m² (50 mL of 1 mg/mL solution) on Day 1 of each 21-day treatment course administered intravenously. 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_Phase III |
|-----------------------|----------------------|

Reporting group description:

Phase III part: Nintedanib 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m² (100 mg or 500 mg vials) and Cisplatin 75 mg/m² (50 mL of 1 mg/mL solution) on Day 1 of each 21-day treatment course administered intravenously. 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_Phase II | Nintedanib_Phase II | Placebo_Phase III |
|---|------------------|---------------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 17 / 41 (41.46%) | 16 / 44 (36.36%) | 89 / 228 (39.04%) |
| number of deaths (all causes) | 25 | 22 | 63 |

| number of deaths resulting from adverse events | 0 | 1 | 4 |
|---|----------------|----------------|-----------------|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 2 / 44 (4.55%) | 2 / 228 (0.88%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 2 |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant pleural effusion | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural mesothelioma malignant | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour associated fever | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neuroendocrine tumour | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 44 (2.27%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 44 (2.27%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 44 (2.27%) | 2 / 228 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic aneurysm | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic thrombosis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Embolism | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jugular vein thrombosis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral ischaemia | | | |

| | | | |
|--|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subclavian artery thrombosis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subclavian vein thrombosis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vena cava thrombosis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Venous thrombosis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Venous thrombosis limb | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |

| | | | |
|---|----------------|----------------|------------------|
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 44 (0.00%) | 3 / 228 (1.32%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 44 (2.27%) | 2 / 228 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 2 / 44 (4.55%) | 10 / 228 (4.39%) |
| occurrences causally related to treatment / all | 2 / 5 | 0 / 2 | 4 / 13 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 5 / 228 (2.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Malaise | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 3 / 228 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Pain | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 2 / 228 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Performance status decreased | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chills | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Feeling of body temperature change | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Erosive balanitis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 2 / 44 (4.55%) | 6 / 228 (2.63%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 2 / 44 (4.55%) | 6 / 228 (2.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 1 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 4 / 44 (9.09%) | 7 / 228 (3.07%) |
| occurrences causally related to treatment / all | 0 / 1 | 3 / 4 | 3 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cough | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hiccups | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperventilation | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 4 / 228 (1.75%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 4 |
| Laryngeal oedema | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hallucination | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 44 (2.27%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 1 / 44 (2.27%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fibrin D dimer increased | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspartate aminotransferase | | | |

| | | | |
|---|----------------|----------------|-----------------|
| increased | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood potassium decreased | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Glomerular filtration rate decreased | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 44 (2.27%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Overdose | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 44 (2.27%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 44 (2.27%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toxicity to various agents | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |
| Aplasia | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular block second degree | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bundle branch block left | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac tamponade | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardio-respiratory arrest | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 2 / 228 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina unstable | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachyarrhythmia | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness postural | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal cord compression | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 2 / 44 (4.55%) | 8 / 228 (3.51%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 5 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Febrile bone marrow aplasia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 44 (0.00%) | 3 / 228 (1.32%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 44 (0.00%) | 3 / 228 (1.32%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 44 (0.00%) | 2 / 228 (0.88%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 4 / 41 (9.76%) | 1 / 44 (2.27%) | 7 / 228 (3.07%) |
| occurrences causally related to treatment / all | 4 / 4 | 2 / 2 | 7 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Thrombocytopenia | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 44 (0.00%) | 4 / 228 (1.75%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 3 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone marrow toxicity | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 2 / 228 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Splenic infarction | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone marrow failure | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphatic obstruction | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Deafness | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 44 (2.27%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoacusis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |

| | | | |
|---|----------------|----------------|-----------------|
| Visual acuity reduced | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 0 / 44 (0.00%) | 2 / 228 (0.88%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 0 / 44 (0.00%) | 7 / 228 (3.07%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 7 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine perforation | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 44 (2.27%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 1 / 44 (2.27%) | 4 / 228 (1.75%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | 4 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 44 (2.27%) | 8 / 228 (3.51%) |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 1 | 8 / 9 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 2 / 228 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Acute abdomen | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enteritis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 2 / 228 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal perforation | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumoperitoneum | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Stasis dermatitis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subcutaneous emphysema | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 44 (2.27%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 5 / 228 (2.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 4 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |

| | | | |
|---|----------------|----------------|-----------------|
| Calculus bladder | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 4 / 228 (1.75%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 3 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 44 (2.27%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Flank pain | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 2 / 44 (4.55%) | 2 / 228 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|-----------------|
| Sepsis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 44 (2.27%) | 2 / 228 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocarditis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia bacteraemia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis norovirus | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung infection | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophageal candidiasis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Onychomycosis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oral bacterial infection | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 4 / 228 (1.75%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| Tooth abscess | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia klebsiella | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 2 / 44 (4.55%) | 8 / 228 (3.51%) |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 2 | 2 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 44 (0.00%) | 2 / 228 (0.88%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 44 (0.00%) | 1 / 228 (0.44%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Decreased appetite | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 3 / 228 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 2 / 228 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lactic acidosis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 44 (0.00%) | 0 / 228 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Nintedanib_Phase III | | |
|---|----------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 99 / 227 (43.61%) | | |
| number of deaths (all causes) | 64 | | |
| number of deaths resulting from adverse events | 3 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cancer pain | | | |
| subjects affected / exposed | 2 / 227 (0.88%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malignant pleural effusion | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Pleural mesothelioma malignant subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tumour associated fever subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neuroendocrine tumour subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Squamous cell carcinoma subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Deep vein thrombosis subjects affected / exposed | 3 / 227 (1.32%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aortic aneurysm subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aortic thrombosis subjects affected / exposed | 2 / 227 (0.88%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Embolism subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypertension | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Jugular vein thrombosis | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Subclavian artery thrombosis | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subclavian vein thrombosis | | | |
| subjects affected / exposed | 2 / 227 (0.88%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vena cava thrombosis | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Venous thrombosis | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Venous thrombosis limb | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 227 (0.88%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 4 / 227 (1.76%) | | |
| occurrences causally related to treatment / all | 2 / 4 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 227 (1.76%) | | |
| occurrences causally related to treatment / all | 3 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chest pain | | | |
| subjects affected / exposed | 5 / 227 (2.20%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Death | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Malaise | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 2 / 227 (0.88%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Performance status decreased | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chills | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Feeling of body temperature change | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Erosive balanitis | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|------------------|--|--|
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 5 / 227 (2.20%) | | |
| occurrences causally related to treatment / all | 1 / 5 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 4 / 227 (1.76%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 13 / 227 (5.73%) | | |
| occurrences causally related to treatment / all | 10 / 13 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cough | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hiccups | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperventilation | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Pneumothorax | | | |
| subjects affected / exposed | 3 / 227 (1.32%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Laryngeal oedema | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hallucination | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 3 / 227 (1.32%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Fibrin D dimer increased | | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Alanine aminotransferase increased | | | | |
| subjects affected / exposed | 2 / 227 (0.88%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Aspartate aminotransferase increased | | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| C-reactive protein increased | | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ejection fraction decreased | | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hepatic enzyme increased | | | | |
| subjects affected / exposed | 2 / 227 (0.88%) | | | |
| occurrences causally related to treatment / all | 3 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neutrophil count decreased | | | | |
| subjects affected / exposed | 3 / 227 (1.32%) | | | |
| occurrences causally related to treatment / all | 2 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Platelet count decreased | | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Transaminases increased | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood potassium decreased | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Glomerular filtration rate decreased | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Overdose | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Toxicity to various agents | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Congenital, familial and genetic disorders | | | |
| Aplasia | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 227 (0.88%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrioventricular block second degree | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bundle branch block left | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Cardiac tamponade | | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardio-respiratory arrest | | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 1 / 1 | | | |
| Myocardial infarction | | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Pericardial effusion | | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pericarditis | | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sinus tachycardia | | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Supraventricular tachycardia | | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tachycardia | | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Angina unstable | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tachyarrhythmia | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dizziness postural | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Encephalopathy | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Headache | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Seizure | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal cord compression | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile bone marrow aplasia | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 4 / 227 (1.76%) | | |
| occurrences causally related to treatment / all | 3 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 6 / 227 (2.64%) | | |
| occurrences causally related to treatment / all | 3 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bone marrow toxicity | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancytopenia | | | |
| subjects affected / exposed | 2 / 227 (0.88%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Splenic infarction | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bone marrow failure | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lymphatic obstruction | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| Deafness | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoacusis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Visual acuity reduced | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 2 / 227 (0.88%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 8 / 227 (3.52%) | | |
| occurrences causally related to treatment / all | 8 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Large intestine perforation | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 4 / 227 (1.76%) | | |
| occurrences causally related to treatment / all | 4 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 6 / 227 (2.64%) | | |
| occurrences causally related to treatment / all | 4 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 227 (0.88%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute abdomen | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ascites | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enteritis | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal obstruction | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Intestinal perforation | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumoperitoneum | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Stasis dermatitis | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subcutaneous emphysema | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |

| | | | |
|---|-----------------|--|--|
| Acute kidney injury | | | |
| subjects affected / exposed | 9 / 227 (3.96%) | | |
| occurrences causally related to treatment / all | 5 / 9 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Calculus bladder | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Flank pain | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|--|--|--|
| <p>Infections and infestations</p> <p>Lower respiratory tract infection</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p> | <p>4 / 227 (1.76%)</p> <p>1 / 4</p> <p>0 / 0</p> | | |
| <p>Sepsis</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p> | <p>0 / 227 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p> | | |
| <p>Bronchitis</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p> | <p>0 / 227 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p> | | |
| <p>Cellulitis</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p> | <p>0 / 227 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p> | | |
| <p>Device related infection</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p> | <p>0 / 227 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p> | | |
| <p>Endocarditis</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p> | <p>1 / 227 (0.44%)</p> <p>0 / 1</p> <p>0 / 0</p> | | |
| <p>Escherichia bacteraemia</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p> | <p>1 / 227 (0.44%)</p> <p>0 / 1</p> <p>0 / 0</p> | | |
| <p>Gastroenteritis</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p> | <p>0 / 227 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p> | | |
| <p>Gastroenteritis norovirus</p> | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infection | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Influenza | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung infection | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 3 / 227 (1.32%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oesophageal candidiasis | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Onychomycosis | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oral bacterial infection | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peritonitis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 6 / 227 (2.64%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Tooth abscess | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia klebsiella | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 4 / 227 (1.76%) | | |
| occurrences causally related to treatment / all | 3 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypomagnesaemia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Decreased appetite | | | |
| subjects affected / exposed | 3 / 227 (1.32%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 2 / 227 (0.88%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lactic acidosis | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Placebo_Phase II | Nintedanib_Phase II | Placebo_Phase III |
|---|-------------------|---------------------|--------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 41 / 41 (100.00%) | 44 / 44 (100.00%) | 219 / 228 (96.05%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 6 / 41 (14.63%) | 6 / 44 (13.64%) | 21 / 228 (9.21%) |
| occurrences (all) | 6 | 6 | 26 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 12 / 41 (29.27%) | 14 / 44 (31.82%) | 46 / 228 (20.18%) |
| occurrences (all) | 26 | 25 | 62 |
| Chest pain | | | |
| subjects affected / exposed | 9 / 41 (21.95%) | 7 / 44 (15.91%) | 23 / 228 (10.09%) |
| occurrences (all) | 14 | 8 | 24 |
| Fatigue | | | |

| | | | |
|--|------------------------|------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 15 / 41 (36.59%) 34 | 18 / 44 (40.91%) 38 | 62 / 228 (27.19%) 85 |
| Mucosal inflammation subjects affected / exposed occurrences (all) | 4 / 41 (9.76%) 7 | 7 / 44 (15.91%) 9 | 22 / 228 (9.65%) 25 |
| Oedema peripheral subjects affected / exposed occurrences (all) | 5 / 41 (12.20%) 5 | 5 / 44 (11.36%) 8 | 16 / 228 (7.02%) 19 |
| Pyrexia subjects affected / exposed occurrences (all) | 4 / 41 (9.76%) 6 | 7 / 44 (15.91%) 13 | 22 / 228 (9.65%) 29 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 6 / 41 (14.63%) 6 | 15 / 44 (34.09%) 15 | 33 / 228 (14.47%) 40 |
| Dyspnoea subjects affected / exposed occurrences (all) | 7 / 41 (17.07%) 7 | 7 / 44 (15.91%) 7 | 26 / 228 (11.40%) 29 |
| Hiccups subjects affected / exposed occurrences (all) | 3 / 41 (7.32%) 3 | 1 / 44 (2.27%) 1 | 20 / 228 (8.77%) 27 |
| Epistaxis subjects affected / exposed occurrences (all) | 2 / 41 (4.88%) 2 | 1 / 44 (2.27%) 1 | 13 / 228 (5.70%) 15 |
| Dysphonia subjects affected / exposed occurrences (all) | 0 / 41 (0.00%) 0 | 3 / 44 (6.82%) 3 | 2 / 228 (0.88%) 2 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 6 / 41 (14.63%) 6 | 2 / 44 (4.55%) 2 | 4 / 228 (1.75%) 4 |
| Psychiatric disorders | | | |
| Insomnia subjects affected / exposed occurrences (all) | 4 / 41 (9.76%) 4 | 8 / 44 (18.18%) 8 | 12 / 228 (5.26%) 12 |
| Depression | | | |

| | | | |
|--|-----------------------|------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 3 / 41 (7.32%) 3 | 1 / 44 (2.27%) 1 | 2 / 228 (0.88%) 2 |
| Investigations | | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 1 / 41 (2.44%) 2 | 17 / 44 (38.64%) 39 | 10 / 228 (4.39%) 11 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 1 / 41 (2.44%) 1 | 13 / 44 (29.55%) 26 | 9 / 228 (3.95%) 14 |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 4 / 41 (9.76%) 13 | 6 / 44 (13.64%) 13 | 26 / 228 (11.40%) 39 |
| Blood magnesium decreased subjects affected / exposed occurrences (all) | 6 / 41 (14.63%) 14 | 10 / 44 (22.73%) 22 | 12 / 228 (5.26%) 14 |
| Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) | 1 / 41 (2.44%) 1 | 10 / 44 (22.73%) 41 | 13 / 228 (5.70%) 15 |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 3 / 41 (7.32%) 5 | 8 / 44 (18.18%) 20 | 26 / 228 (11.40%) 47 |
| Weight decreased subjects affected / exposed occurrences (all) | 9 / 41 (21.95%) 9 | 8 / 44 (18.18%) 11 | 23 / 228 (10.09%) 24 |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 1 / 41 (2.44%) 1 | 2 / 44 (4.55%) 2 | 15 / 228 (6.58%) 26 |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 1 / 41 (2.44%) 1 | 9 / 44 (20.45%) 9 | 6 / 228 (2.63%) 6 |
| Blood glucose increased subjects affected / exposed occurrences (all) | 1 / 41 (2.44%) 1 | 5 / 44 (11.36%) 5 | 1 / 228 (0.44%) 1 |
| Blood lactate dehydrogenase increased | | | |

| | | | |
|-----------------------------|------------------|------------------|-------------------|
| subjects affected / exposed | 0 / 41 (0.00%) | 3 / 44 (6.82%) | 1 / 228 (0.44%) |
| occurrences (all) | 0 | 3 | 1 |
| Blood potassium decreased | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 4 / 44 (9.09%) | 0 / 228 (0.00%) |
| occurrences (all) | 2 | 4 | 0 |
| Blood urea increased | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 8 / 44 (18.18%) | 10 / 228 (4.39%) |
| occurrences (all) | 3 | 8 | 10 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 4 / 44 (9.09%) | 2 / 228 (0.88%) |
| occurrences (all) | 2 | 4 | 2 |
| Platelet count decreased | | | |
| subjects affected / exposed | 4 / 41 (9.76%) | 8 / 44 (18.18%) | 7 / 228 (3.07%) |
| occurrences (all) | 8 | 22 | 12 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 5 / 41 (12.20%) | 3 / 44 (6.82%) | 18 / 228 (7.89%) |
| occurrences (all) | 5 | 3 | 22 |
| Dysgeusia | | | |
| subjects affected / exposed | 11 / 41 (26.83%) | 11 / 44 (25.00%) | 27 / 228 (11.84%) |
| occurrences (all) | 11 | 11 | 31 |
| Headache | | | |
| subjects affected / exposed | 4 / 41 (9.76%) | 5 / 44 (11.36%) | 23 / 228 (10.09%) |
| occurrences (all) | 4 | 5 | 23 |
| Lethargy | | | |
| subjects affected / exposed | 13 / 41 (31.71%) | 6 / 44 (13.64%) | 5 / 228 (2.19%) |
| occurrences (all) | 13 | 6 | 11 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 6 / 41 (14.63%) | 9 / 44 (20.45%) | 18 / 228 (7.89%) |
| occurrences (all) | 6 | 9 | 18 |
| Paraesthesia | | | |
| subjects affected / exposed | 4 / 41 (9.76%) | 4 / 44 (9.09%) | 19 / 228 (8.33%) |
| occurrences (all) | 4 | 4 | 21 |
| Neurotoxicity | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 1 / 44 (2.27%) | 4 / 228 (1.75%) |
| occurrences (all) | 3 | 1 | 4 |

| | | | |
|--------------------------------------|------------------|------------------|-------------------|
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 9 / 41 (21.95%) | 16 / 44 (36.36%) | 94 / 228 (41.23%) |
| occurrences (all) | 15 | 28 | 123 |
| Leukopenia | | | |
| subjects affected / exposed | 5 / 41 (12.20%) | 2 / 44 (4.55%) | 28 / 228 (12.28%) |
| occurrences (all) | 5 | 2 | 58 |
| Neutropenia | | | |
| subjects affected / exposed | 9 / 41 (21.95%) | 22 / 44 (50.00%) | 82 / 228 (35.96%) |
| occurrences (all) | 22 | 53 | 170 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 7 / 44 (15.91%) | 18 / 228 (7.89%) |
| occurrences (all) | 1 | 11 | 27 |
| Ear and labyrinth disorders | | | |
| Tinnitus | | | |
| subjects affected / exposed | 9 / 41 (21.95%) | 4 / 44 (9.09%) | 24 / 228 (10.53%) |
| occurrences (all) | 14 | 8 | 27 |
| Hypoacusis | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 4 / 44 (9.09%) | 4 / 228 (1.75%) |
| occurrences (all) | 1 | 4 | 4 |
| Eye disorders | | | |
| Dry eye | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 0 / 44 (0.00%) | 4 / 228 (1.75%) |
| occurrences (all) | 3 | 0 | 4 |
| Lacrimation increased | | | |
| subjects affected / exposed | 4 / 41 (9.76%) | 7 / 44 (15.91%) | 18 / 228 (7.89%) |
| occurrences (all) | 4 | 7 | 18 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 11 / 44 (25.00%) | 10 / 228 (4.39%) |
| occurrences (all) | 5 | 18 | 10 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 9 / 44 (20.45%) | 11 / 228 (4.82%) |
| occurrences (all) | 3 | 11 | 11 |
| Constipation | | | |
| subjects affected / exposed | 19 / 41 (46.34%) | 17 / 44 (38.64%) | 73 / 228 (32.02%) |
| occurrences (all) | 27 | 31 | 96 |

| | | | |
|--|------------------|------------------|--------------------|
| Diarrhoea | | | |
| subjects affected / exposed | 15 / 41 (36.59%) | 29 / 44 (65.91%) | 47 / 228 (20.61%) |
| occurrences (all) | 27 | 31 | 61 |
| Dyspepsia | | | |
| subjects affected / exposed | 11 / 41 (26.83%) | 3 / 44 (6.82%) | 20 / 228 (8.77%) |
| occurrences (all) | 12 | 3 | 20 |
| Nausea | | | |
| subjects affected / exposed | 34 / 41 (82.93%) | 37 / 44 (84.09%) | 134 / 228 (58.77%) |
| occurrences (all) | 101 | 114 | 234 |
| Stomatitis | | | |
| subjects affected / exposed | 5 / 41 (12.20%) | 3 / 44 (6.82%) | 16 / 228 (7.02%) |
| occurrences (all) | 5 | 3 | 18 |
| Vomiting | | | |
| subjects affected / exposed | 20 / 41 (48.78%) | 24 / 44 (54.55%) | 66 / 228 (28.95%) |
| occurrences (all) | 36 | 55 | 115 |
| Dry mouth | | | |
| subjects affected / exposed | 4 / 41 (9.76%) | 2 / 44 (4.55%) | 2 / 228 (0.88%) |
| occurrences (all) | 4 | 2 | 2 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 4 / 41 (9.76%) | 3 / 44 (6.82%) | 11 / 228 (4.82%) |
| occurrences (all) | 4 | 3 | 11 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 3 / 44 (6.82%) | 2 / 228 (0.88%) |
| occurrences (all) | 0 | 3 | 2 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 5 / 41 (12.20%) | 6 / 44 (13.64%) | 8 / 228 (3.51%) |
| occurrences (all) | 5 | 6 | 8 |
| Rash | | | |
| subjects affected / exposed | 7 / 41 (17.07%) | 11 / 44 (25.00%) | 23 / 228 (10.09%) |
| occurrences (all) | 7 | 11 | 28 |
| Dry skin | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 0 / 44 (0.00%) | 7 / 228 (3.07%) |
| occurrences (all) | 3 | 0 | 7 |
| Pruritus | | | |

| | | | |
|--|---------------------|---------------------|------------------------|
| subjects affected / exposed occurrences (all) | 1 / 41 (2.44%) 1 | 3 / 44 (6.82%) 3 | 10 / 228 (4.39%) 10 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 4 / 44 (9.09%) | 12 / 228 (5.26%) |
| occurrences (all) | 1 | 4 | 12 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 5 / 41 (12.20%) | 2 / 44 (4.55%) | 6 / 228 (2.63%) |
| occurrences (all) | 6 | 3 | 8 |
| Urinary tract infection | | | |
| subjects affected / exposed | 5 / 41 (12.20%) | 0 / 44 (0.00%) | 14 / 228 (6.14%) |
| occurrences (all) | 8 | 0 | 20 |
| Conjunctivitis | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 4 / 44 (9.09%) | 11 / 228 (4.82%) |
| occurrences (all) | 2 | 4 | 11 |
| Influenza | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 3 / 44 (6.82%) | 4 / 228 (1.75%) |
| occurrences (all) | 2 | 3 | 4 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 16 / 41 (39.02%) | 17 / 44 (38.64%) | 66 / 228 (28.95%) |
| occurrences (all) | 24 | 26 | 91 |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 4 / 44 (9.09%) | 13 / 228 (5.70%) |
| occurrences (all) | 2 | 6 | 18 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 8 / 41 (19.51%) | 13 / 44 (29.55%) | 20 / 228 (8.77%) |
| occurrences (all) | 8 | 13 | 28 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 2 / 44 (4.55%) | 15 / 228 (6.58%) |
| occurrences (all) | 1 | 2 | 22 |
| Hyponatraemia | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 1 / 44 (2.27%) | 14 / 228 (6.14%) |
| occurrences (all) | 2 | 1 | 15 |
| Dehydration | | | |

| | | | |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 3 / 41 (7.32%) | 4 / 44 (9.09%) | 8 / 228 (3.51%) |
| occurrences (all) | 3 | 4 | 8 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 0 / 44 (0.00%) | 2 / 228 (0.88%) |
| occurrences (all) | 3 | 0 | 2 |

| Non-serious adverse events | Nintedanib_Phase III | | |
|---|----------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 218 / 227 (96.04%) | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 26 / 227 (11.45%) | | |
| occurrences (all) | 30 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 53 / 227 (23.35%) | | |
| occurrences (all) | 79 | | |
| Chest pain | | | |
| subjects affected / exposed | 23 / 227 (10.13%) | | |
| occurrences (all) | 24 | | |
| Fatigue | | | |
| subjects affected / exposed | 60 / 227 (26.43%) | | |
| occurrences (all) | 81 | | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 16 / 227 (7.05%) | | |
| occurrences (all) | 21 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 16 / 227 (7.05%) | | |
| occurrences (all) | 18 | | |
| Pyrexia | | | |
| subjects affected / exposed | 17 / 227 (7.49%) | | |
| occurrences (all) | 19 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 29 / 227 (12.78%) | | |
| occurrences (all) | 33 | | |

| | | | |
|--------------------------------------|-------------------|--|--|
| Dyspnoea | | | |
| subjects affected / exposed | 34 / 227 (14.98%) | | |
| occurrences (all) | 35 | | |
| Hiccups | | | |
| subjects affected / exposed | 8 / 227 (3.52%) | | |
| occurrences (all) | 9 | | |
| Epistaxis | | | |
| subjects affected / exposed | 20 / 227 (8.81%) | | |
| occurrences (all) | 38 | | |
| Dysphonia | | | |
| subjects affected / exposed | 4 / 227 (1.76%) | | |
| occurrences (all) | 4 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 6 / 227 (2.64%) | | |
| occurrences (all) | 6 | | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 11 / 227 (4.85%) | | |
| occurrences (all) | 15 | | |
| Depression | | | |
| subjects affected / exposed | 6 / 227 (2.64%) | | |
| occurrences (all) | 6 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 35 / 227 (15.42%) | | |
| occurrences (all) | 50 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 32 / 227 (14.10%) | | |
| occurrences (all) | 49 | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 21 / 227 (9.25%) | | |
| occurrences (all) | 33 | | |
| Blood magnesium decreased | | | |
| subjects affected / exposed | 17 / 227 (7.49%) | | |
| occurrences (all) | 19 | | |
| Gamma-glutamyltransferase increased | | | |

| | | | |
|---------------------------------------|-------------------|--|--|
| subjects affected / exposed | 25 / 227 (11.01%) | | |
| occurrences (all) | 31 | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 28 / 227 (12.33%) | | |
| occurrences (all) | 45 | | |
| Weight decreased | | | |
| subjects affected / exposed | 20 / 227 (8.81%) | | |
| occurrences (all) | 20 | | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 18 / 227 (7.93%) | | |
| occurrences (all) | 29 | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 7 / 227 (3.08%) | | |
| occurrences (all) | 7 | | |
| Blood glucose increased | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences (all) | 1 | | |
| Blood potassium decreased | | | |
| subjects affected / exposed | 0 / 227 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood urea increased | | | |
| subjects affected / exposed | 9 / 227 (3.96%) | | |
| occurrences (all) | 9 | | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 1 / 227 (0.44%) | | |
| occurrences (all) | 1 | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 9 / 227 (3.96%) | | |
| occurrences (all) | 20 | | |
| Nervous system disorders | | | |
| Dizziness | | | |

| | | | |
|--------------------------------------|-------------------|--|--|
| subjects affected / exposed | 14 / 227 (6.17%) | | |
| occurrences (all) | 15 | | |
| Dysgeusia | | | |
| subjects affected / exposed | 27 / 227 (11.89%) | | |
| occurrences (all) | 32 | | |
| Headache | | | |
| subjects affected / exposed | 16 / 227 (7.05%) | | |
| occurrences (all) | 17 | | |
| Lethargy | | | |
| subjects affected / exposed | 13 / 227 (5.73%) | | |
| occurrences (all) | 21 | | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 13 / 227 (5.73%) | | |
| occurrences (all) | 13 | | |
| Paraesthesia | | | |
| subjects affected / exposed | 20 / 227 (8.81%) | | |
| occurrences (all) | 23 | | |
| Neurotoxicity | | | |
| subjects affected / exposed | 8 / 227 (3.52%) | | |
| occurrences (all) | 8 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 76 / 227 (33.48%) | | |
| occurrences (all) | 96 | | |
| Leukopenia | | | |
| subjects affected / exposed | 20 / 227 (8.81%) | | |
| occurrences (all) | 50 | | |
| Neutropenia | | | |
| subjects affected / exposed | 83 / 227 (36.56%) | | |
| occurrences (all) | 185 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 13 / 227 (5.73%) | | |
| occurrences (all) | 31 | | |
| Ear and labyrinth disorders | | | |
| Tinnitus | | | |

| | | | |
|-----------------------------|--------------------|--|--|
| subjects affected / exposed | 15 / 227 (6.61%) | | |
| occurrences (all) | 15 | | |
| Hypoacusis | | | |
| subjects affected / exposed | 7 / 227 (3.08%) | | |
| occurrences (all) | 7 | | |
| Eye disorders | | | |
| Dry eye | | | |
| subjects affected / exposed | 12 / 227 (5.29%) | | |
| occurrences (all) | 12 | | |
| Lacrimation increased | | | |
| subjects affected / exposed | 14 / 227 (6.17%) | | |
| occurrences (all) | 14 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 24 / 227 (10.57%) | | |
| occurrences (all) | 31 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 14 / 227 (6.17%) | | |
| occurrences (all) | 14 | | |
| Constipation | | | |
| subjects affected / exposed | 60 / 227 (26.43%) | | |
| occurrences (all) | 81 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 118 / 227 (51.98%) | | |
| occurrences (all) | 239 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 14 / 227 (6.17%) | | |
| occurrences (all) | 14 | | |
| Nausea | | | |
| subjects affected / exposed | 156 / 227 (68.72%) | | |
| occurrences (all) | 274 | | |
| Stomatitis | | | |
| subjects affected / exposed | 22 / 227 (9.69%) | | |
| occurrences (all) | 26 | | |
| Vomiting | | | |

| | | | |
|--|-------------------|--|--|
| subjects affected / exposed | 96 / 227 (42.29%) | | |
| occurrences (all) | 192 | | |
| Dry mouth | | | |
| subjects affected / exposed | 4 / 227 (1.76%) | | |
| occurrences (all) | 4 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 7 / 227 (3.08%) | | |
| occurrences (all) | 7 | | |
| Haemorrhoids | | | |
| subjects affected / exposed | 5 / 227 (2.20%) | | |
| occurrences (all) | 5 | | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 12 / 227 (5.29%) | | |
| occurrences (all) | 12 | | |
| Rash | | | |
| subjects affected / exposed | 22 / 227 (9.69%) | | |
| occurrences (all) | 26 | | |
| Dry skin | | | |
| subjects affected / exposed | 4 / 227 (1.76%) | | |
| occurrences (all) | 4 | | |
| Pruritus | | | |
| subjects affected / exposed | 3 / 227 (1.32%) | | |
| occurrences (all) | 3 | | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 9 / 227 (3.96%) | | |
| occurrences (all) | 10 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 16 / 227 (7.05%) | | |
| occurrences (all) | 18 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 12 / 227 (5.29%) | | |
| occurrences (all) | 16 | | |
| Conjunctivitis | | | |

| | | | |
|------------------------------------|-------------------|--|--|
| subjects affected / exposed | 11 / 227 (4.85%) | | |
| occurrences (all) | 11 | | |
| Influenza | | | |
| subjects affected / exposed | 5 / 227 (2.20%) | | |
| occurrences (all) | 5 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 66 / 227 (29.07%) | | |
| occurrences (all) | 97 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 12 / 227 (5.29%) | | |
| occurrences (all) | 12 | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 20 / 227 (8.81%) | | |
| occurrences (all) | 27 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 8 / 227 (3.52%) | | |
| occurrences (all) | 9 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 14 / 227 (6.17%) | | |
| occurrences (all) | 16 | | |
| Dehydration | | | |
| subjects affected / exposed | 4 / 227 (1.76%) | | |
| occurrences (all) | 4 | | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 4 / 227 (1.76%) | | |
| occurrences (all) | 4 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 21 September 2015 | - Changes in the procedures and timing of assessments in the combination therapy period and the monotherapy period (update of the flow chart, implementation of the changes listed below) - Addition of hydration as premedication regimen; clarification of study treatment interruption, stopping criteria (treatment beyond disease progression was allowed), and management of AEs; revision of timing of unblinding of patient data - Revision of efficacy endpoints (OS became key secondary endpoint; objective response and disease control secondary endpoints; and change in FVC, best overall response, time to objective response, duration of objective response, duration of disease control, and health-related quality of life [Phase III only] further endpoints); addition of healthcare resource use assessment and PK sampling; clarification of evaluation of lesions and assessment of AEs; revision of timing of laboratory and PGx sampling and required laboratory parameters; clarification of management of proteinuria; revision of collection of archived tissue and serum biomarkers (biomarker collection became optional) - Clarification of the timing of the run-in and screening period; permission of continuation of study treatment beyond disease progression; specification of procedures performed at Follow-up Visit 1 and at further follow-up visits; update of the definition of end-of-trial - Revision of the planned statistical analysis of all endpoints and of the sample size to allow for inclusion of 310 patients in the Phase III part |
| 22 June 2016 | Separation of flow charts for Phase 2 & 3; Changes in procedures and timing of assessments in combination therapy period & monotherapy period of Phase 3. Limitation of Phase 3 to patients with epithelioid tumour histology. Change of creatinine clearance limit for patients with mild to moderate renal insufficiency. Description of timing of: primary OS analysis for Phase 2, primary PFS & interim & primary OS analyses for Phase 3. Increase of sample size to 450 Phase 3 patients. Description of adaptive design with OS event number reassessment. Update of dose reduction and retreatment criteria, and of criteria for liver enzyme elevations; description of unblinding of Phase 2 & Phase 3 patients and of the sponsor's independent team with regard to primary PFS analysis/interim OS analysis of Phase 3. Update of observation period for primary & secondary endpoints; clarification of central assessment of tumour images and collection of bone scans; addition of criteria for treatment beyond disease progression; change of CTCAE version from 3.0 to 4.03 for Phase 3 patients; clarifications of procedures (AE reporting, ECG, PK [to be collected at 1 time point in the Phase 3] and biomarker sampling [to be collected at 2 time points in Phase 3 part and used for biobanking]); removal of FVC evaluation for Phase 3. Clarification of follow-up for PD & OS, separated by trial phase; update of definition for end-of-trial; clarification of reporting of different analyses (PFS, OS) for Phase 2 & Phase 3. Revised description of analyses for Phase 2 & Phase 3; change of hypotheses for Phase 3 to one-sided & alpha level to one-sided 0.025; description of analyses method for adaptive design with OS event number reassessment; description of pooled exploratory analyses for Phase 2 & Phase 3 (efficacy & safety); change of OS censoring rule if patient died with death date unknown; addition of sensitivity analysis for PFS based on EMA censoring rules; revision of sample size section for Phase 2 & Phase 3. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

In accordance with the specifications in the protocol, the trial was discontinued prematurely after the primary PFS analysis not because of any safety concerns but rather due to failure to meet the efficacy target.

Notes: