



Clinical trial results:

A Phase II open-label, roll-over study of the long-term tolerability, safety and efficacy of oral BIBF 1120 in patients with idiopathic pulmonary fibrosis

Summary

| | |
|--------------------------|-------------------------------------|
| EudraCT number | 2009-013788-21 |
| Trial protocol | ES BE FR PT IT DE IE HU CZ BG GB GR |
| Global end of trial date | 26 September 2016 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 |
| This version publication date | 14 October 2017 |
| First version publication date | 14 October 2017 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | 1199.35 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01170065 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 08 November 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 26 September 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 26 September 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to establish the long-term tolerability and safety profile of nintedanib in patients with idiopathic pulmonary fibrosis (IPF) who had completed parent trial 1199.30 (NCT00514683).

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.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 25 June 2010 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Ethical reason |
| Long term follow-up duration | 6 Years |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Argentina: 3 |
| Country: Number of subjects enrolled | Australia: 9 |
| Country: Number of subjects enrolled | Belgium: 10 |
| Country: Number of subjects enrolled | Brazil: 7 |
| Country: Number of subjects enrolled | Bulgaria: 1 |
| Country: Number of subjects enrolled | Canada: 11 |
| Country: Number of subjects enrolled | Chile: 6 |
| Country: Number of subjects enrolled | China: 16 |
| Country: Number of subjects enrolled | Czech Republic: 5 |
| Country: Number of subjects enrolled | France: 32 |
| Country: Number of subjects enrolled | Germany: 24 |
| Country: Number of subjects enrolled | Greece: 6 |
| Country: Number of subjects enrolled | Hungary: 4 |
| Country: Number of subjects enrolled | Ireland: 1 |
| Country: Number of subjects enrolled | Italy: 25 |
| Country: Number of subjects enrolled | Mexico: 5 |
| Country: Number of subjects enrolled | Netherlands: 6 |

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Portugal: 6 |
| Country: Number of subjects enrolled | Russian Federation: 4 |
| Country: Number of subjects enrolled | Spain: 5 |
| Country: Number of subjects enrolled | United Kingdom: 13 |
| Worldwide total number of subjects | 199 |
| EEA total number of subjects | 138 |

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) | 69 |
| From 65 to 84 years | 127 |
| 85 years and over | 3 |

Subject disposition

Recruitment

Recruitment details:

Treatment groups are displayed according to dose at randomisation in 1199.30 (NCT00514683).

Pre-assignment

Screening details:

Patients were not randomised to study medication in trial 1199.35 but were to receive open-label nintedanib, either at the dose received in period 2 of parent trial 1199.30 (NCT00514683) or they could increase their dose to nintedanib 150 mg twice daily (bid) after implementation of protocol amendment 1.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

Trial was open-label. The treatment allocation of patients in parent trial 1199.30 was unblinded prior to the start of trial 1199.35.

Arms

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

Arm description:

Patients were treated with oral administration of placebo in period 1 of the parent trial and with soft gelatine capsules of Nintedanib 50 mg once daily (qd) in the second period of the 1199.30 (parent trial). In the 1199.35 trial they could remain on this last dose or increase to Nintedanib 150 mg twice daily (bid)

| | |
|--|--|
| Arm type | Placebo in 1199.30 and Experimental in 1199.35 |
| Investigational medicinal product name | Nintedanib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Patients were treated with oral administration of placebo in period 1 of the parent trial and with soft gelatine capsules of Nintedanib 50 mg once daily (qd) in the second period of the 1199.30 (parent trial). In the 1199.35 trial they could remain on this last dose or increase to Nintedanib 150 mg twice daily (bid). Continuous daily dosing until the patient met one of the withdrawal criteria.

| | |
|------------------|--------------------------|
| Arm title | Nintedanib 50 mg- 100 mg |
|------------------|--------------------------|

Arm description:

Patients were treated with oral administration of soft gelatine capsules of Nintedanib 50 mg qd, 50 mg bid or 100 mg bid in the parent trial. In the 1199.35 trial they could remain on their last dose in the parent trial or increase to Nintedanib 150 mg bid.

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

Dosage and administration details:

Patients were treated with oral administration of soft gelatine capsules of Nintedanib 50 mg qd, 50 mg bid or 100 mg bid in the parent trial. In the 1199.35 trial they could remain on their last dose in the

parent trial or increase to Nintedanib 150 mg bid. Continuous daily dosing until the patient met one of the withdrawal criteria

| | |
|---|-------------------|
| Arm title | Nintedanib 150 mg |
| Arm description: Patients were treated with oral administration of soft gelatine capsules of Nintedanib 150 mg bid and could step down to 100 mg bid. In the 1199.35 trial they could remain on their last dose in the parent trial. | |
| Arm type | Experimental |
| Investigational medicinal product name | Nintedanib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Patients were treated with oral administration of soft gelatine capsules of Nintedanib 150 mg bid and could step down to 100 mg bid. In the 1199.35 trial they could remain on their last dose in the parent trial. Continuous daily dosing until the patient met one of the withdrawal criteria.

| Number of subjects in period 1^[1] | Placebo | Nintedanib 50 mg-100 mg | Nintedanib 150 mg |
|---|---------|-------------------------|-------------------|
| Started | 37 | 126 | 35 |
| Completed | 9 | 34 | 9 |
| Not completed | 28 | 92 | 26 |
| Adverse event, serious fatal | 14 | 42 | 7 |
| Adverse event, non-fatal | 3 | 8 | 3 |
| Consent withdrawn, not due to AE | 2 | 4 | 2 |
| Reason other than specified | 3 | 8 | 3 |
| Lost to follow-up | 1 | 4 | 1 |
| Ongoing after planned observation time | 5 | 26 | 10 |

Notes:

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

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

Baseline characteristics

Reporting groups

| | |
|---|--------------------------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Patients were treated with oral administration of placebo in period 1 of the parent trial and with soft gelatine capsules of Nintedanib 50 mg once daily (qd) in the second period of the 1199.30 (parent trial). In the 1199.35 trial they could remain on this last dose or increase to Nintedanib 150 mg twice daily (bid) | |
| Reporting group title | Nintedanib 50 mg- 100 mg |
| Reporting group description: | |
| Patients were treated with oral administration of soft gelatine capsules of Nintedanib 50 mg qd, 50 mg bid or 100 mg bid in the parent trial. In the 1199.35 trial they could remain on their last dose in the parent trial or increase to Nintedanib 150 mg bid. | |
| Reporting group title | Nintedanib 150 mg |
| Reporting group description: | |
| Patients were treated with oral administration of soft gelatine capsules of Nintedanib 150 mg bid and could step down to 100 mg bid. In the 1199.35 trial they could remain on their last dose in the parent trial. | |

| Reporting group values | Placebo | Nintedanib 50 mg- 100 mg | Nintedanib 150 mg |
|------------------------|---------|-----------------------------|-------------------|
| Number of subjects | 37 | 126 | 35 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|--|-------|-------|-------|
| Age Continuous | | | |
| Treated set (TS): The treated set which included all patients who received at least 1 dose of open-label study medication in trial 1199.35 | | | |
| Units: years | | | |
| arithmetic mean | 64.2 | 65.4 | 65.2 |
| standard deviation | ± 7.3 | ± 8.6 | ± 7.2 |
| Gender, Male/Female | | | |
| Treated set (TS): The treated set which included all patients who received at least 1 dose of open-label study medication in trial 1199.35 | | | |
| Units: Subjects | | | |
| Female | 14 | 36 | 7 |
| Male | 23 | 90 | 28 |

| Reporting group values | Total | | |
|------------------------|-------|--|--|
| Number of subjects | 198 | | |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|--|---|--|--|
| Age Continuous | | | |
| Treated set (TS): The treated set which included all patients who received at least 1 dose of open-label study medication in trial 1199.35 | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |

| | | | |
|--|-----|--|--|
| Gender, Male/Female | | | |
| Treated set (TS): The treated set which included all patients who received at least 1 dose of open-label study medication in trial 1199.35 | | | |
| Units: Subjects | | | |
| Female | 57 | | |
| Male | 141 | | |

End points

End points reporting groups

| | |
|---|--------------------------|
| Reporting group title | Placebo |
| Reporting group description: Patients were treated with oral administration of placebo in period 1 of the parent trial and with soft gelatine capsules of Nintedanib 50 mg once daily (qd) in the second period of the 1199.30 (parent trial). In the 1199.35 trial they could remain on this last dose or increase to Nintedanib 150 mg twice daily (bid) | |
| Reporting group title | Nintedanib 50 mg- 100 mg |
| Reporting group description: Patients were treated with oral administration of soft gelatine capsules of Nintedanib 50 mg qd, 50 mg bid or 100 mg bid in the parent trial. In the 1199.35 trial they could remain on their last dose in the parent trial or increase to Nintedanib 150 mg bid. | |
| Reporting group title | Nintedanib 150 mg |
| Reporting group description: Patients were treated with oral administration of soft gelatine capsules of Nintedanib 150 mg bid and could step down to 100 mg bid. In the 1199.35 trial they could remain on their last dose in the parent trial. | |

Primary: Annual rate of decline in forced vital capacity (FVC)

| | |
|--|--|
| End point title | Annual rate of decline in forced vital capacity (FVC) ^[1] |
| End point description: Forced vital capacity (FVC) is the total amount of air exhaled during the lung function test. For this endpoint reported means represent the adjusted rate. The full analysis set (FAS) which included all patients in the treated set who provided baseline data (for the first trial visit) for at least 1 endpoint in trial 1199.35 is the population set used for this endpoint | |
| End point type | Primary |
| End point timeframe: From first drug administration in 1199.35 until database lock 15Oct2015, up to 61.8 Months | |
| Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested. | |

| End point values | Placebo | Nintedanib 50 mg- 100 mg | Nintedanib 150 mg | |
|--------------------------------------|-------------------|--------------------------|-------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 37 ^[2] | 126 ^[3] | 35 ^[4] | |
| Units: milliliters per year (mL/ yr) | | | | |
| arithmetic mean (standard error) | -129 (± 29.47) | -137.5 (± 14.6) | -132.9 (± 28.22) | |

Notes:

[2] - FAS

[3] - FAS

[4] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

| | |
|--|------------------|
| End point title | Overall survival |
| End point description: | |
| Overall survival is defined as the time from the first intake of nintedanib in trial 1199.35 to death. For presentation of overall survival results, Kaplan-Meier estimates and confidence intervals (using Greenwood variance formula) for the overall on-treatment survival is calculated within each treatment arm. | |
| End point type | Secondary |
| End point timeframe: | |
| From first drug administration in 1199.35 until database lock 15Oct2015, up to 61.8 Months | |

| End point values | Placebo | Nintedanib 50 mg- 100 mg | Nintedanib 150 mg | |
|---|-------------------|--------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 37 ^[5] | 126 ^[6] | 35 ^[7] | |
| Units: percentage | | | | |
| arithmetic mean (confidence interval 95%) | 37.4 (16.8 to 58) | 46.8 (35.3 to 58.4) | 66.2 (46.9 to 85.5) | |

Notes:

[5] - FAS

[6] - FAS

[7] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

| | |
|---|---------------------------|
| End point title | Progression-free survival |
| End point description: | |
| Progression-free survival was defined as the time from the first nintedanib intake in trial 1199.35 to disease progression. For presentation of progression-free survival results, Kaplan-Meier estimates and confidence intervals (using Greenwood variance formula) for the overall on-treatment progression-free survival is calculated within each treatment arm. | |
| End point type | Secondary |
| End point timeframe: | |
| From first trial drug intake in 1199.35 to disease progression; up to 61.8 months | |

| End point values | Placebo | Nintedanib 50 mg- 100 mg | Nintedanib 150 mg | |
|---|-------------------|--------------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 37 ^[8] | 126 ^[9] | 35 ^[10] | |
| Units: percentage | | | | |
| arithmetic mean (confidence interval 95%) | 9.6 (0 to 22) | 3.5 (0 to 7.4) | 12.2 (0 to 24.9) | |

Notes:

[8] - FAS

[9] - FAS

[10] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Annual rate of decline in haemoglobin corrected diffusing capacity of the lung for carbon monoxide (DLCO) decrease

| | |
|-----------------|--|
| End point title | Annual rate of decline in haemoglobin corrected diffusing capacity of the lung for carbon monoxide (DLCO) decrease |
|-----------------|--|

End point description:

Haemoglobin corrected DLCO decrease was a secondary endpoint for the trial. It was considered important that all investigators used the same method of testing and recording data at each visit for each patient. Haemoglobin corrected DLCO was calculated for each patient using the following formulae: Males: Hb corrected DLCO = measured DLCO x (10.22 + Hb concentration) / (1.7 x Hb concentration) Females: Hb corrected DLCO = measured DLCO x (9.38 + Hb concentration) / (1.7 x Hb concentration). Annual rate of decline in haemoglobin corrected diffusing capacity of the lung for carbon monoxide (DLCO) decrease is presented.

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

End point timeframe:

From first drug administration in 1199.35 until database lock 15Oct2015, up to 61.8 Months

| End point values | Placebo | Nintedanib 50 mg- 100 mg | Nintedanib 150 mg | |
|----------------------------------|--------------------|--------------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 37 ^[11] | 126 ^[12] | 35 ^[13] | |
| Units: mmol/min/kPa/yr | | | | |
| arithmetic mean (standard error) | -0.4 (± 0.08) | -0.3 (± 0.04) | -0.2 (± 0.07) | |

Notes:

[11] - FAS

[12] - FAS

[13] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with at least one acute idiopathic pulmonary fibrosis (IPF) exacerbation

| | |
|-----------------|---|
| End point title | Percentage of patients with at least one acute idiopathic pulmonary fibrosis (IPF) exacerbation |
|-----------------|---|

End point description:

Percentage of patients with at least one acute idiopathic pulmonary fibrosis (IPF) exacerbation are presented. An exacerbation was defined as otherwise unexplained clinical features occurring within 1 month including all of the following: -Progression of dyspnoea over several days to 4 weeks -New diffuse pulmonary infiltrates on chest X-ray and/or high-resolution computerised tomography (HRCT) Parenchymal abnormalities with no pneumothorax or pleural effusion (new ground-glass opacities) since the last visit -A decrease in arterial oxygen partial pressure (PaO₂) of ≥10 mmHg or PaO₂/fraction of inspired oxygen (FiO₂) of <225 mmHg since the last visit -Exclusion of infection based on routine clinical practice and microbiological studies -Absence of other contributory causes such as congestive heart failure, pulmonary embolism, etc.

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

End point timeframe:

From first drug administration in 1199.35 until database lock 15Oct2015, up to 61.8 Months

| End point values | Placebo | Nintedanib 50 mg- 100 mg | Nintedanib 150 mg | |
|-----------------------------------|--------------------|--------------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 37 ^[14] | 126 ^[15] | 35 ^[16] | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 13.5 | 19.8 | 20 | |

Notes:

[14] - FAS

[15] - FAS

[16] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of patients with at least one acute IPF exacerbation over time

| | |
|-----------------|--|
| End point title | Incidence of patients with at least one acute IPF exacerbation over time |
|-----------------|--|

End point description:

Incidence rate = (Patients with at least one acute IPF exacerbation / Total number of years at risk) x 100

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

End point timeframe:

From first drug administration in 1199.35 until database lock 15Oct2015, up to 61.8 Months

| End point values | Placebo | Nintedanib 50 mg- 100 mg | Nintedanib 150 mg | |
|-------------------------------|--------------------|--------------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 37 ^[17] | 126 ^[18] | 35 ^[19] | |
| Units: Exacerbations Per Year | | | | |
| number (not applicable) | 6.1 | 7.6 | 7.8 | |

Notes:

[17] - FAS

[18] - FAS

[19] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first acute IPF exacerbation

| | |
|-----------------|--------------------------------------|
| End point title | Time to first acute IPF exacerbation |
|-----------------|--------------------------------------|

End point description:

Time to acute IPF as 'time from the first nintedanib intake in trial 1199.35 to the first occurrence of an acute IPF exacerbation. For presentation of Time to first acute IPF exacerbation results, Kaplan-Meier estimates and confidence intervals (using Greenwood variance formula) for the overall time-to-event rate is calculated within each treatment arm.

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

End point timeframe:

From first drug administration in 1199.35 until database lock 15Oct2015, up to 61.8 Months

| End point values | Placebo | Nintedanib 50 mg- 100 mg | Nintedanib 150 mg | |
|---|---------------------|--------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 37 ^[20] | 126 ^[21] | 35 ^[22] | |
| Units: percentage | | | | |
| arithmetic mean (confidence interval 95%) | 67.7 (39.4 to 95.9) | 68.6 (56.8 to 80.4) | 73.5 (55.9 to 91.1) | |

Notes:

[20] - FAS

[21] - FAS

[22] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with at least one Adverse events (AEs), with investigator defined drug-related AEs, AEs leading to discontinuation of trial drug, serious AEs

| | |
|-----------------|--|
| End point title | Percentage of patients with at least one Adverse events (AEs), with investigator defined drug-related AEs, AEs leading to discontinuation of trial drug, serious AEs |
|-----------------|--|

End point description:

Percentage of patients with at least one Adverse events (AEs), with investigator defined drug-related AEs, AEs leading to discontinuation of trial drug, serious AEs are presented

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

End point timeframe:

From the first nintedanib intake in trial 1199.35 to the last nintedanib intake + 28 days; up to 61.8 months + 28 days

| End point values | Placebo | Nintedanib 50 mg- 100 mg | Nintedanib 150 mg | |
|--|--------------------|--------------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 37 ^[23] | 126 ^[24] | 35 ^[25] | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| AEs | 100 | 99.2 | 97.1 | |
| Investigator defined drug-related AEs | 70.3 | 65.9 | 54.3 | |
| AEs leading to discontinuation of trial drug | 48.6 | 41.3 | 34.3 | |
| Serious AE | 67.6 | 74.6 | 62.9 | |

Notes:

[23] - TS

[24] - TS

[25] - TS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first nintedanib intake in trial 1199.35 to the last nintedanib intake + 28 days; up to 61.8 months + 28 days

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

Reporting groups

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

Reporting group description:

Patients were treated with oral administration of placebo in period 1 of the parent trial and with soft gelatine capsules of Nintedanib 50 mg once daily (qd) in the second period of the 1199.30 (parent trial). In the 1199.35 trial they could remain on this last dose or increase to Nintedanib 150 mg twice daily (bid)

| | |
|-----------------------|--------------------------|
| Reporting group title | Nintedanib 50 mg -100 mg |
|-----------------------|--------------------------|

Reporting group description:

Patients were treated with oral administration of soft gelatine capsules of Nintedanib 50 mg qd, 50 mg bid or 100 mg bid in the parent trial. In the 1199.35 trial they could remain on their last dose in the parent trial or increase to Nintedanib 150 mg bid.

| | |
|-----------------------|-------------------|
| Reporting group title | Nintedanib 150 mg |
|-----------------------|-------------------|

Reporting group description:

Patients were treated with oral administration of soft gelatine capsules of Nintedanib 150 mg bid and could step down to 100 mg bid. In the 1199.35 trial they could remain on their last dose in the parent trial.

| Serious adverse events | Placebo | Nintedanib 50 mg - 100 mg | Nintedanib 150 mg |
|---|------------------|---------------------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 25 / 37 (67.57%) | 94 / 126 (74.60%) | 22 / 35 (62.86%) |
| number of deaths (all causes) | 15 | 41 | 8 |
| number of deaths resulting from adverse events | 0 | 1 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 2 / 126 (1.59%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colon cancer | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 2 / 126 (1.59%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Metastases to liver | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 2 / 126 (1.59%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| Metastases to lung | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Metastases to spine | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Non-small cell lung cancer | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Renal neoplasm | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 126 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 3 / 126 (2.38%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Thyroid cancer | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 | | | |
| Aortic aneurysm | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 126 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Orthostatic hypotension | | | |

| | | | |
|--|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 126 (0.00%) | 0 / 35 (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 |
| Peripheral artery aneurysm | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 2 / 126 (1.59%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 1 / 126 (0.79%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Disease progression | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 2 / 126 (1.59%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Impaired healing | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 126 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multi-organ failure | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Pyrexia | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 37 (2.70%) | 1 / 126 (0.79%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden death | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 2 / 126 (1.59%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 2 / 126 (1.59%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Bronchial hyperreactivity | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Bronchiectasis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Bronchostenosis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Bullous lung disease | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Dyspnoea | | | |

| | | | |
|---|------------------|-------------------|------------------|
| subjects affected / exposed | 2 / 37 (5.41%) | 11 / 126 (8.73%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 14 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Hypoventilation | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Idiopathic pulmonary fibrosis | | | |
| subjects affected / exposed | 11 / 37 (29.73%) | 41 / 126 (32.54%) | 10 / 35 (28.57%) |
| occurrences causally related to treatment / all | 0 / 12 | 0 / 50 | 0 / 12 |
| deaths causally related to treatment / all | 0 / 5 | 0 / 20 | 0 / 7 |
| Lung consolidation | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Lung disorder | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumomediastinum | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 126 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax spontaneous | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Pulmonary arterial hypertension | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 126 (0.00%) | 1 / 35 (2.86%) |
| 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 congestion | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 6 / 126 (4.76%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 6 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| Pulmonary fibrosis | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 126 (0.00%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 5 / 126 (3.97%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory disorder | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 126 (0.00%) | 0 / 35 (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 |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 7 / 126 (5.56%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 9 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 1 |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Suicide attempt | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 | | | |
| Pancreatic enzymes increased | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Troponin I | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 2 / 126 (1.59%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Cervical vertebral fracture | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 126 (0.00%) | 0 / 35 (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 |
| Contusion | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Fall | | | |
| subjects affected / exposed | 3 / 37 (8.11%) | 2 / 126 (1.59%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal stoma complication | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |

| | | | |
|---|----------------|-----------------|----------------|
| Hip fracture | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 126 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meniscus injury | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Overdose | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 126 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toxicity to various agents | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 3 / 126 (2.38%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 3 / 126 (2.38%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arrhythmia | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 126 (0.00%) | 0 / 35 (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 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 2 / 126 (1.59%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 126 (0.00%) | 1 / 35 (2.86%) |
| 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 | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Cardiac arrest | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 1 / 126 (0.79%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| Cardiac disorder | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 126 (0.00%) | 2 / 35 (5.71%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 5 / 126 (3.97%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| Cardiac failure acute | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Cardio-respiratory arrest | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 126 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 1 / 126 (0.79%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 2 / 126 (1.59%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Right ventricular failure | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 2 / 126 (1.59%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebral infarction | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 126 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Coma | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 126 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemiplegia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 126 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Loss of consciousness | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 126 (0.00%) | 0 / 35 (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 |
| Syncope | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 37 (0.00%) | 3 / 126 (2.38%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 126 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tremor | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 126 (0.00%) | 0 / 35 (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 |
| Gastrointestinal disorders | | | |
| Anal haemorrhage | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 126 (0.00%) | 0 / 35 (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 |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 37 (8.11%) | 2 / 126 (1.59%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 2 / 3 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulum intestinal | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 126 (0.00%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Gastrointestinal disorder | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Haemorrhoids | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 1 / 126 (0.79%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 126 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Nausea | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 126 (0.00%) | 0 / 35 (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 |
| Oesophageal ulcer | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Umbilical hernia | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 37 (0.00%) | 2 / 126 (1.59%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Volvulus | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 126 (0.00%) | 0 / 35 (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 |
| Skin and subcutaneous tissue disorders | | | |
| Erythema multiforme | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Granuloma skin | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Haematuria | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 126 (0.00%) | 0 / 35 (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 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 2 / 126 (1.59%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary bladder polyp | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 126 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthropathy | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Back pain | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Exostosis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Foot deformity | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Groin pain | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Infections and infestations | | | |
| Bacterial infection | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 126 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |

| | | | |
|---|----------------|-----------------|----------------|
| Bronchitis | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 3 / 126 (2.38%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 126 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chlamydial infection | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Fungal infection | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 126 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Gastroenteritis clostridial | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 126 (0.00%) | 0 / 35 (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 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 126 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 4 / 126 (3.17%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 6 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection bacterial | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung infection | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 5 / 126 (3.97%) | 3 / 35 (8.57%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 9 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 37 (8.11%) | 6 / 126 (4.76%) | 2 / 35 (5.71%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 7 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 0 |
| Pneumonia escherichia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 4 / 126 (3.17%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Septic shock | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 126 (0.00%) | 0 / 35 (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 |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 126 (0.00%) | 0 / 35 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 0 / 35 (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 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 126 (0.00%) | 0 / 35 (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 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 126 (0.00%) | 1 / 35 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Placebo | Nintedanib 50 mg - 100 mg | Nintedanib 150 mg |
|---|------------------|------------------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 34 / 37 (91.89%) | 111 / 126 (88.10%) | 32 / 35 (91.43%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 7 / 126 (5.56%) | 3 / 35 (8.57%) |
| occurrences (all) | 0 | 7 | 3 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 3 / 126 (2.38%) | 2 / 35 (5.71%) |
| occurrences (all) | 0 | 3 | 2 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 10 / 126 (7.94%) | 1 / 35 (2.86%) |
| occurrences (all) | 2 | 10 | 1 |
| Condition aggravated | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 0 / 126 (0.00%) | 1 / 35 (2.86%) |
| occurrences (all) | 2 | 0 | 1 |
| Fatigue | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 9 / 126 (7.14%) | 4 / 35 (11.43%) |
| occurrences (all) | 2 | 10 | 5 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 126 (0.00%) | 2 / 35 (5.71%) |
| occurrences (all) | 0 | 0 | 2 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 3 / 37 (8.11%) | 27 / 126 (21.43%) | 4 / 35 (11.43%) |
| occurrences (all) | 3 | 38 | 7 |
| Dyspnoea | | | |
| subjects affected / exposed | 5 / 37 (13.51%) | 19 / 126 (15.08%) | 3 / 35 (8.57%) |
| occurrences (all) | 6 | 24 | 3 |
| Epistaxis | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 8 / 126 (6.35%) | 1 / 35 (2.86%) |
| occurrences (all) | 3 | 8 | 2 |
| Idiopathic pulmonary fibrosis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 22 / 126 (17.46%) | 3 / 35 (8.57%) |
| occurrences (all) | 0 | 28 | 3 |

| | | | |
|--------------------------------------|------------------|-------------------|-----------------|
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 4 / 126 (3.17%) | 3 / 35 (8.57%) |
| occurrences (all) | 0 | 4 | 3 |
| Depression | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 4 / 126 (3.17%) | 1 / 35 (2.86%) |
| occurrences (all) | 3 | 4 | 1 |
| Insomnia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 2 / 126 (1.59%) | 2 / 35 (5.71%) |
| occurrences (all) | 0 | 2 | 2 |
| Investigations | | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 6 / 126 (4.76%) | 0 / 35 (0.00%) |
| occurrences (all) | 2 | 8 | 0 |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 3 / 126 (2.38%) | 0 / 35 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| Weight decreased | | | |
| subjects affected / exposed | 10 / 37 (27.03%) | 29 / 126 (23.02%) | 7 / 35 (20.00%) |
| occurrences (all) | 11 | 33 | 7 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 2 / 35 (5.71%) |
| occurrences (all) | 0 | 1 | 2 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 4 / 37 (10.81%) | 11 / 126 (8.73%) | 2 / 35 (5.71%) |
| occurrences (all) | 4 | 13 | 2 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 2 / 35 (5.71%) |
| occurrences (all) | 0 | 1 | 2 |
| Sciatica | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 126 (0.79%) | 3 / 35 (8.57%) |
| occurrences (all) | 0 | 1 | 5 |
| Blood and lymphatic system disorders | | | |

| | | | |
|---|--|---|---|
| Anaemia subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 2 | 1 / 126 (0.79%) 2 | 2 / 35 (5.71%) 2 |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 2 | 1 / 126 (0.79%) 1 | 0 / 35 (0.00%) 0 |
| Eye disorders Cataract subjects affected / exposed occurrences (all) Glaucoma subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 2 0 / 37 (0.00%) 0 | 9 / 126 (7.14%) 13 1 / 126 (0.79%) 1 | 3 / 35 (8.57%) 4 2 / 35 (5.71%) 3 |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Frequent bowel movements subjects affected / exposed occurrences (all) Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting | 2 / 37 (5.41%) 2 2 / 37 (5.41%) 2 2 / 37 (5.41%) 4 19 / 37 (51.35%) 30 1 / 37 (2.70%) 1 3 / 37 (8.11%) 3 9 / 37 (24.32%) 12 | 9 / 126 (7.14%) 9 4 / 126 (3.17%) 4 11 / 126 (8.73%) 12 68 / 126 (53.97%) 111 0 / 126 (0.00%) 0 4 / 126 (3.17%) 4 22 / 126 (17.46%) 37 | 4 / 35 (11.43%) 5 0 / 35 (0.00%) 0 1 / 35 (2.86%) 1 22 / 35 (62.86%) 33 2 / 35 (5.71%) 2 2 / 35 (5.71%) 2 2 / 35 (5.71%) 2 |

| | | | |
|---|--|--|--|
| subjects affected / exposed occurrences (all) | 7 / 37 (18.92%) 8 | 17 / 126 (13.49%) 26 | 3 / 35 (8.57%) 4 |
| Hepatobiliary disorders Hepatic function abnormal subjects affected / exposed occurrences (all) | 1 / 37 (2.70%) 1 | 2 / 126 (1.59%) 2 | 2 / 35 (5.71%) 2 |
| Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) | 1 / 37 (2.70%) 1 2 / 37 (5.41%) 2 | 7 / 126 (5.56%) 9 3 / 126 (2.38%) 5 | 2 / 35 (5.71%) 3 0 / 35 (0.00%) 0 |
| Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all) Proteinuria subjects affected / exposed occurrences (all) Urinary retention subjects affected / exposed occurrences (all) | 0 / 37 (0.00%) 0 1 / 37 (2.70%) 3 0 / 37 (0.00%) 0 | 3 / 126 (2.38%) 4 2 / 126 (1.59%) 2 0 / 126 (0.00%) 0 | 2 / 35 (5.71%) 2 2 / 35 (5.71%) 2 2 / 35 (5.71%) 2 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Osteoporosis subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 2 2 / 37 (5.41%) 2 2 / 37 (5.41%) 2 0 / 37 (0.00%) 0 | 4 / 126 (3.17%) 6 10 / 126 (7.94%) 13 2 / 126 (1.59%) 2 1 / 126 (0.79%) 1 | 1 / 35 (2.86%) 1 1 / 35 (2.86%) 1 1 / 35 (2.86%) 1 2 / 35 (5.71%) 2 |

| | | | |
|-----------------------------------|------------------|-------------------|-----------------|
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 12 / 37 (32.43%) | 27 / 126 (21.43%) | 6 / 35 (17.14%) |
| occurrences (all) | 24 | 53 | 11 |
| Cystitis | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 2 / 126 (1.59%) | 1 / 35 (2.86%) |
| occurrences (all) | 2 | 2 | 2 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 8 / 126 (6.35%) | 4 / 35 (11.43%) |
| occurrences (all) | 0 | 11 | 4 |
| Influenza | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 9 / 126 (7.14%) | 6 / 35 (17.14%) |
| occurrences (all) | 1 | 10 | 6 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 4 / 37 (10.81%) | 12 / 126 (9.52%) | 1 / 35 (2.86%) |
| occurrences (all) | 18 | 28 | 1 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 8 / 37 (21.62%) | 24 / 126 (19.05%) | 6 / 35 (17.14%) |
| occurrences (all) | 14 | 41 | 6 |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 3 / 126 (2.38%) | 1 / 35 (2.86%) |
| occurrences (all) | 2 | 3 | 2 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 3 / 37 (8.11%) | 8 / 126 (6.35%) | 3 / 35 (8.57%) |
| occurrences (all) | 3 | 10 | 11 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 9 / 126 (7.14%) | 0 / 35 (0.00%) |
| occurrences (all) | 0 | 16 | 0 |
| Tinea pedis | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 126 (0.00%) | 2 / 35 (5.71%) |
| occurrences (all) | 0 | 0 | 2 |
| Tooth abscess | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 2 / 126 (1.59%) | 0 / 35 (0.00%) |
| occurrences (all) | 3 | 2 | 0 |
| Tracheobronchitis | | | |

| | | | |
|---|----------------------|-------------------------|---------------------|
| subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 2 | 2 / 126 (1.59%) 2 | 2 / 35 (5.71%) 3 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 37 (2.70%) 1 | 10 / 126 (7.94%) 11 | 1 / 35 (2.86%) 1 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 3 | 11 / 126 (8.73%) 14 | 1 / 35 (2.86%) 1 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 6 / 37 (16.22%) 6 | 17 / 126 (13.49%) 21 | 2 / 35 (5.71%) 2 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 1 / 37 (2.70%) 1 | 3 / 126 (2.38%) 3 | 2 / 35 (5.71%) 2 |
| Hyponatraemia subjects affected / exposed occurrences (all) | 0 / 37 (0.00%) 0 | 0 / 126 (0.00%) 0 | 2 / 35 (5.71%) 3 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 02 September 2010 | <ul style="list-style-type: none">- Described findings derived from analysis of the data from parent trial 1199.30 that showed a clinically-relevant, beneficial effect for patients receiving the nintedanib 150 mg bid dose.- In the light of the new efficacy findings, the amendment recommended that patients in trial 1199.35 be offered the option to switch dose (if applicable) to nintedanib 150 mg bid; the amendment also specified procedures to be followed for patients undergoing the newly-permitted dose increase (including additional monitoring in the 17 weeks after dose increase).- Described procedures to be followed for patients who underwent dose increase to nintedanib 150 mg bid and experienced severe gastrointestinal AEs or liver enzyme elevations |
| 29 November 2012 | <ul style="list-style-type: none">- Specified interim analysis of data from trial 1199.35, to support the regulatory submission for use of nintedanib as a treatment for patients with IPF.- Introduced a range of changes to harmonise the management of AEs with Phase III nintedanib studies, in particular: procedures for the identification and management of indicators of drug-induced liver injury were clarified, in line with nintedanib project specific procedures; procedures for managing severe gastrointestinal events were specified for patients receiving the different nintedanib doses.- Specified procedures for clinical evaluation of liver injury.- Specified procedures to be conducted in association with dose modification.- Revised the processes for reporting worsening underlying disease and other pre-existing conditions- Specified liver function impairment, severe gastrointestinal events, and pregnancy as necessitating discontinuation of nintedanib treatment- Clarified the reporting of pregnancy and clinically-relevant laboratory test results, and characterised some AEs as always serious.- Defined protocol-specified significant AEs and expected AEs.- The time required for use of highly-effective contraceptive measures after participation in trial 1199.35 was increased from 10 weeks to 3 months, to ensure standardised safety procedures across nintedanib IPF and oncology projects |
| 01 June 2015 | <ul style="list-style-type: none">- Protocol amendment 3 was implemented following the awarding of market authorisation for nintedanib (Ofev®) for the treatment of IPF in the US in October 2014 and approval from the European Medicinal Agency in January 2015. While worldwide submissions were in progress, nintedanib had been made available by BI in the named-patient use and compassionate-use programmes and had become commercially available in some countries. As a result, it was anticipated that patients and physicians may want to discontinue participation in the study. The amendment allowed the final complete analysis to be conducted before the number of patients became too low to derive meaningful data summaries.- After completion of the final analysis, patients still participating in the trial were to be followed up with a limited assessment schedule, focussing on AEs, laboratory tests and physical examination. Patients receiving lower nintedanib doses could still undergo dose increase to nintedanib 150 mg and, in this case, would follow the flow-chart assessment schedule until the next complete visit and then start the limited-assessment schedule |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported