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	v2 (current)
This version publication date	13 December 2021
First version publication date	14 October 2017
Version creation reason	

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	Czechia: 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	125

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: Out of 199 enrolled subjects only 198 were randomised.

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: Endpoint was analyzed only descriptively.

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)	-129.0 (± 29.47)	-137.5 (± 14.60)	-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 58.0)	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 (0.0 to 22.0)	3.5 (0.0 to 7.4)	12.2 (0.0 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	20.0	

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	100.0	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.

Adverse event reporting additional 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).

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 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 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.

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

subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	2 / 126 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	2 / 37 (5.41%)	0 / 35 (0.00%)	2 / 126 (1.59%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
Malignant neoplasm progression			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	1 / 37 (2.70%)	0 / 35 (0.00%)	2 / 126 (1.59%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	1 / 1
Metastases to lung			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to spine			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma			

subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Renal neoplasm			
subjects affected / exposed	0 / 37 (0.00%)	1 / 35 (2.86%)	0 / 126 (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 / 37 (0.00%)	0 / 35 (0.00%)	3 / 126 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid cancer			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 37 (0.00%)	1 / 35 (2.86%)	0 / 126 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 37 (0.00%)	1 / 35 (2.86%)	1 / 126 (0.79%)
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%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	1 / 37 (2.70%)	0 / 35 (0.00%)	0 / 126 (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%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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%)	1 / 35 (2.86%)	2 / 126 (1.59%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 37 (2.70%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Disease progression			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	2 / 126 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
General physical health deterioration			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Impaired healing			
subjects affected / exposed	0 / 37 (0.00%)	1 / 35 (2.86%)	0 / 126 (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
Multi-organ failure			

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

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

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

subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Pancreatic enzymes increased			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin I			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	1 / 37 (2.70%)	0 / 35 (0.00%)	2 / 126 (1.59%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
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 / 35 (0.00%)	0 / 126 (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%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	3 / 37 (8.11%)	1 / 35 (2.86%)	2 / 126 (1.59%)
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%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 37 (0.00%)	1 / 35 (2.86%)	0 / 126 (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
Meniscus injury			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 37 (0.00%)	1 / 35 (2.86%)	0 / 126 (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
Toxicity to various agents			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
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 disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 37 (0.00%)	1 / 35 (2.86%)	1 / 126 (0.79%)
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%)	0 / 35 (0.00%)	3 / 126 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			

subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	3 / 126 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	1 / 37 (2.70%)	0 / 35 (0.00%)	0 / 126 (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%)	0 / 35 (0.00%)	2 / 126 (1.59%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 35 (2.86%)	0 / 126 (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
Bundle branch block			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
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 arrest			
subjects affected / exposed	2 / 37 (5.41%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
Cardiac disorder			
subjects affected / exposed	0 / 37 (0.00%)	2 / 35 (5.71%)	0 / 126 (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
Cardiac failure			
subjects affected / exposed	0 / 37 (0.00%)	1 / 35 (2.86%)	5 / 126 (3.97%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Cardiac failure acute			

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

subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 37 (0.00%)	1 / 35 (2.86%)	0 / 126 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 37 (0.00%)	1 / 35 (2.86%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Coma			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Dizziness			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 37 (0.00%)	1 / 35 (2.86%)	0 / 126 (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
Hemiplegia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 35 (2.86%)	0 / 126 (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
Ischaemic stroke			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			

subjects affected / exposed	1 / 37 (2.70%)	0 / 35 (0.00%)	0 / 126 (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%)	0 / 35 (0.00%)	3 / 126 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 37 (0.00%)	1 / 35 (2.86%)	0 / 126 (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
Tremor			
subjects affected / exposed	1 / 37 (2.70%)	0 / 35 (0.00%)	0 / 126 (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 / 35 (0.00%)	0 / 126 (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%)	1 / 35 (2.86%)	2 / 126 (1.59%)
occurrences causally related to treatment / all	2 / 3	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal			
subjects affected / exposed	1 / 37 (2.70%)	0 / 35 (0.00%)	0 / 126 (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%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			

subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorder			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
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	2 / 37 (5.41%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 35 (2.86%)	1 / 126 (0.79%)
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%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 37 (0.00%)	1 / 35 (2.86%)	0 / 126 (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
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 37 (2.70%)	0 / 35 (0.00%)	0 / 126 (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%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	2 / 126 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Volvulus			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 37 (2.70%)	0 / 35 (0.00%)	0 / 126 (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%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Granuloma skin			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
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 and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	1 / 37 (2.70%)	0 / 35 (0.00%)	0 / 126 (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%)	0 / 35 (0.00%)	2 / 126 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary bladder polyp			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	0 / 37 (0.00%)	1 / 35 (2.86%)	0 / 126 (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
Musculoskeletal and connective tissue disorders			
Arthropathy			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exostosis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot deformity			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin pain			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

Bacterial infection			
subjects affected / exposed	0 / 37 (0.00%)	1 / 35 (2.86%)	0 / 126 (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
Bronchitis			
subjects affected / exposed	1 / 37 (2.70%)	1 / 35 (2.86%)	3 / 126 (2.38%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Bronchopneumonia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 35 (2.86%)	0 / 126 (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
Chlamydial infection			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fungal infection			
subjects affected / exposed	0 / 37 (0.00%)	1 / 35 (2.86%)	0 / 126 (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
Gastroenteritis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
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 clostridial			
subjects affected / exposed	1 / 37 (2.70%)	0 / 35 (0.00%)	0 / 126 (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%)	1 / 35 (2.86%)	0 / 126 (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
Influenza			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 37 (0.00%)	1 / 35 (2.86%)	4 / 126 (3.17%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 6
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 / 35 (2.86%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	1 / 37 (2.70%)	3 / 35 (8.57%)	5 / 126 (3.97%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Pneumonia			
subjects affected / exposed	3 / 37 (8.11%)	2 / 35 (5.71%)	6 / 126 (4.76%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 7
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 3
Pneumonia escherichia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
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 tract infection			
subjects affected / exposed	1 / 37 (2.70%)	1 / 35 (2.86%)	4 / 126 (3.17%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Urinary tract infection			
subjects affected / exposed	1 / 37 (2.70%)	0 / 35 (0.00%)	0 / 126 (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 / 35 (0.00%)	0 / 126 (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%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 37 (2.70%)	0 / 35 (0.00%)	0 / 126 (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%)	1 / 35 (2.86%)	0 / 126 (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

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

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

Idiopathic pulmonary fibrosis			
subjects affected / exposed	0 / 37 (0.00%)	3 / 35 (8.57%)	22 / 126 (17.46%)
occurrences (all)	0	3	28
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 37 (0.00%)	3 / 35 (8.57%)	4 / 126 (3.17%)
occurrences (all)	0	3	4
Depression			
subjects affected / exposed	2 / 37 (5.41%)	1 / 35 (2.86%)	4 / 126 (3.17%)
occurrences (all)	3	1	4
Insomnia			
subjects affected / exposed	0 / 37 (0.00%)	2 / 35 (5.71%)	2 / 126 (1.59%)
occurrences (all)	0	2	2
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 37 (5.41%)	0 / 35 (0.00%)	6 / 126 (4.76%)
occurrences (all)	2	0	8
Hepatic enzyme increased			
subjects affected / exposed	2 / 37 (5.41%)	0 / 35 (0.00%)	3 / 126 (2.38%)
occurrences (all)	2	0	3
Weight decreased			
subjects affected / exposed	10 / 37 (27.03%)	7 / 35 (20.00%)	29 / 126 (23.02%)
occurrences (all)	11	7	33
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 37 (0.00%)	2 / 35 (5.71%)	1 / 126 (0.79%)
occurrences (all)	0	2	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 37 (10.81%)	2 / 35 (5.71%)	11 / 126 (8.73%)
occurrences (all)	4	2	13
Paraesthesia			
subjects affected / exposed	0 / 37 (0.00%)	2 / 35 (5.71%)	1 / 126 (0.79%)
occurrences (all)	0	2	1
Sciatica			

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

subjects affected / exposed	9 / 37 (24.32%)	2 / 35 (5.71%)	22 / 126 (17.46%)
occurrences (all)	12	2	37
Vomiting			
subjects affected / exposed	7 / 37 (18.92%)	3 / 35 (8.57%)	17 / 126 (13.49%)
occurrences (all)	8	4	26
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	1 / 37 (2.70%)	2 / 35 (5.71%)	2 / 126 (1.59%)
occurrences (all)	1	2	2
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 37 (2.70%)	2 / 35 (5.71%)	7 / 126 (5.56%)
occurrences (all)	1	3	9
Rash			
subjects affected / exposed	2 / 37 (5.41%)	0 / 35 (0.00%)	3 / 126 (2.38%)
occurrences (all)	2	0	5
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 37 (0.00%)	2 / 35 (5.71%)	3 / 126 (2.38%)
occurrences (all)	0	2	4
Proteinuria			
subjects affected / exposed	1 / 37 (2.70%)	2 / 35 (5.71%)	2 / 126 (1.59%)
occurrences (all)	3	2	2
Urinary retention			
subjects affected / exposed	0 / 37 (0.00%)	2 / 35 (5.71%)	0 / 126 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 37 (5.41%)	1 / 35 (2.86%)	4 / 126 (3.17%)
occurrences (all)	2	1	6
Back pain			
subjects affected / exposed	2 / 37 (5.41%)	1 / 35 (2.86%)	10 / 126 (7.94%)
occurrences (all)	2	1	13
Muscle spasms			
subjects affected / exposed	2 / 37 (5.41%)	1 / 35 (2.86%)	2 / 126 (1.59%)
occurrences (all)	2	1	2

Osteoporosis			
subjects affected / exposed	0 / 37 (0.00%)	2 / 35 (5.71%)	1 / 126 (0.79%)
occurrences (all)	0	2	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	12 / 37 (32.43%)	6 / 35 (17.14%)	27 / 126 (21.43%)
occurrences (all)	24	11	53
Cystitis			
subjects affected / exposed	2 / 37 (5.41%)	1 / 35 (2.86%)	2 / 126 (1.59%)
occurrences (all)	2	2	2
Gastroenteritis			
subjects affected / exposed	0 / 37 (0.00%)	4 / 35 (11.43%)	8 / 126 (6.35%)
occurrences (all)	0	4	11
Influenza			
subjects affected / exposed	1 / 37 (2.70%)	6 / 35 (17.14%)	9 / 126 (7.14%)
occurrences (all)	1	6	10
Lower respiratory tract infection			
subjects affected / exposed	4 / 37 (10.81%)	1 / 35 (2.86%)	12 / 126 (9.52%)
occurrences (all)	18	1	28
Nasopharyngitis			
subjects affected / exposed	8 / 37 (21.62%)	6 / 35 (17.14%)	24 / 126 (19.05%)
occurrences (all)	14	6	41
Pneumonia			
subjects affected / exposed	2 / 37 (5.41%)	1 / 35 (2.86%)	3 / 126 (2.38%)
occurrences (all)	2	2	3
Respiratory tract infection			
subjects affected / exposed	3 / 37 (8.11%)	3 / 35 (8.57%)	8 / 126 (6.35%)
occurrences (all)	3	11	10
Sinusitis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 35 (0.00%)	9 / 126 (7.14%)
occurrences (all)	0	0	16
Tinea pedis			
subjects affected / exposed	0 / 37 (0.00%)	2 / 35 (5.71%)	0 / 126 (0.00%)
occurrences (all)	0	2	0
Tooth abscess			

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 September 2010	- 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	- 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	- 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