Clinical trial results:
Multicenter, randomized, double-blind, Phase III trial to investigate the efficacy and safety of oral BIBF 1120 plus standard pemetrexed therapy compared to placebo plus standard pemetrexed therapy in patients with stage IIIB/IV or recurrent non small cell lung cancer after failure of first line chemotherapy.

Summary

EudraCT number	2008-002072-10
Trial protocol	HU LV NL IE SE RO PL DE BG DK
Global end of trial date	30 December 2015

Results information

Result version number	v1 (current)
This version publication date	23 December 2016
First version publication date	23 December 2016

Trial information

Trial identification

Sponsor protocol code	1199.14

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00806819
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	173 Binger Strasse, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim , 001 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 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	15 February 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 July 2012
Global end of trial reached?	Yes
Global end of trial date	30 December 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy and safety of nintedanib as compared to matching placebo in patients with stage IIIB/IV or recurrent non-small cell lung cancer (NSCLC) treated with standard therapy of pemetrexed after failure of first-line chemotherapy

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all patients as required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 December 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Hong Kong: 9
Country: Number of subjects enrolled	Malaysia: 44
Country: Number of subjects enrolled	Taiwan: 43
Country: Number of subjects enrolled	Korea, Republic of: 114
Country: Number of subjects enrolled	Philippines: 38
Country: Number of subjects enrolled	Thailand: 73
Country: Number of subjects enrolled	Australia: 23
Country: Number of subjects enrolled	New Zealand: 33
Country: Number of subjects enrolled	Bosnia and Herzegovina: 16
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Hungary: 12
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Latvia: 28
Country: Number of subjects enrolled	Moldova, Republic of: 8
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 10
Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Romania: 25

Country: Number of subjects enrolled	Sweden: 9
Country: Number of subjects enrolled	Turkey: 42
Country: Number of subjects enrolled	Ukraine: 26
Country: Number of subjects enrolled	Serbia: 90
Country: Number of subjects enrolled	Canada: 53
Country: Number of subjects enrolled	United States: 133
Country: Number of subjects enrolled	Brazil: 128
Country: Number of subjects enrolled	Colombia: 4
Country: Number of subjects enrolled	Ecuador: 3
Country: Number of subjects enrolled	Mexico: 10
Country: Number of subjects enrolled	Panama: 6
Country: Number of subjects enrolled	Peru: 49
Country: Number of subjects enrolled	Argentina: 22
Country: Number of subjects enrolled	Chile: 37
Worldwide total number of subjects	1116
EEA total number of subjects	102

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)	766
From 65 to 84 years	344
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

5 patients at one investigator site were excluded from the enrollment count because of site non-compliance. In the subject disposition , started are actually the randomised patients and completed patients were On-treatment at analysis DBL date (15 February 2013).

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in trial. Subjects attended specialist sites to ensure that they (the subjects) met all implemented inclusion/exclusion criteria. Subjects were not to be randomised to trial drug if an specific entry criteria was violated.

Period 1

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

Blinding implementation details:

This was a randomised, double-blind and placebo-controlled study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Nintedanib plus pemetrexed

Arm description:

Nintedanib 200 mg twice daily administered orally in a form of a soft gelatin capsule on day2 to 21 of each 21-day treatment course administered plus pemetrexed 500 mg/m2 on Day1 of each 21-day treatment course administered via intravenous infusion. If required the dose of nitedanib could be reduced to 150 mg twice daily (b.i.d.) or 100 mg b.i.d. and two dose reductions for pemetrexed were allowed (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

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

Dosage and administration details:

Nintedanib 200 mg twice daily administered orally in a form of a soft gelatin capsule on day2 to 21 of each 21-day treatment course. If required the dose of nitedanib could be reduced to 150 mg twice daily (b.i.d.) or 100 mg b.i.d. No dose increase was allowed after a dose reduction.

Investigational medicinal product name	pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

pemetrexed 500 mg/m2 on Day1 of each 21-day treatment course administered via intravenous infusion. If required the two dose reductions for pemetrexed were allowed (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

Arm title	Placebo plus pemetrexed

Arm description:

Placebo soft gelatin capsule matching that of nintedanib twice daily on day 2 to 21 of each 21-day treatment course administered orally plus pemetrexed 500 mg/m2 on Day 1 of each 21-day treatment

course administered via intravenous infusion. If required the dose of placebo could be reduced to 150 mg twice daily (b.i.d.) or 100 mg b.i.d. and two dose reductions for pemetrexed were allowed (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

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

Dosage and administration details:

Placebo soft gelatin capsule matching that of nintedanib 2 times daily on day 2 to 21 of each 21-day treatment course administered orally. If required the dose of placebo could be reduced to 150 mg twice daily (b.i.d.) or 100 mg b.i.d.

Investigational medicinal product name	pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

pemetrexed 500 mg/m2 on Day 1 of each 21-day treatment course administered via intravenous infusion. If required two dose reductions for pemetrexed were allowed (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

Number of subjects in period 1[1]	Nintedanib plus pemetrexed	Placebo plus pemetrexed
Started	353	360
Completed	7	2
Not completed	346	358
Adverse event, serious fatal	8	9
Adverse event, non-fatal	30	31
Worsening or AE of underlying disease	18	25
Refused to continue taking trial medication	32	29
progressive disease (modified RECIST)	217	216
Lost to follow-up	1	-
Protocol deviation	9	4
Not treated	6	3
Reasons other than stated above	25	41

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 the patients who were randomised after successfully completing the screening period and received at least one of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	Nintedanib plus pemetrexed

Reporting group description:

Nintedanib 200 mg twice daily administered orally in a form of a soft gelatin capsule on day2 to 21 of each 21-day treatment course administered plus pemetrexed 500 mg/m2 on Day1 of each 21-day treatment course administered via intravenous infusion. If required the dose of nitedanib could be reduced to 150 mg twice daily (b.i.d.) or 100 mg b.i.d. and two dose reductions for pemetrexed were allowed (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

Reporting group title	Placebo plus pemetrexed

Reporting group description:

Placebo soft gelatin capsule matching that of nintedanib twice daily on day 2 to 21 of each 21-day treatment course administered orally plus pemetrexed 500 mg/m2 on Day 1 of each 21-day treatment course administered via intravenous infusion. If required the dose of placebo could be reduced to 150 mg twice daily (b.i.d.) or 100 mg b.i.d. and two dose reductions for pemetrexed were allowed (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

Reporting group values	Nintedanib plus pemetrexed	Placebo plus pemetrexed	Total
Number of subjects	353	360	713
Age categorical Units: Subjects			

Age Continuous			
Randomised set uncut (RS): all patients who were randomised whether patients had received study treatment or not. Patients were allocated to the treatment groups as randomised, regardless of the actual medication taken.			
Units: years			
arithmetic mean	59.2	58.7	
standard deviation	± 10.3	± 10.9	-
Gender, Male/Female Units: participants			
Female	158	152	310
Male	195	208	403

End points

End points reporting groups

Reporting group title	Nintedanib plus pemetrexed

Reporting group description:

Nintedanib 200 mg twice daily administered orally in a form of a soft gelatin capsule on day2 to 21 of each 21-day treatment course administered plus pemetrexed 500 mg/m2 on Day1 of each 21-day treatment course administered via intravenous infusion. If required the dose of nitedanib could be reduced to 150 mg twice daily (b.i.d.) or 100 mg b.i.d. and two dose reductions for pemetrexed were allowed (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

Reporting group title	Placebo plus pemetrexed

Reporting group description:

Placebo soft gelatin capsule matching that of nintedanib twice daily on day 2 to 21 of each 21-day treatment course administered orally plus pemetrexed 500 mg/m2 on Day 1 of each 21-day treatment course administered via intravenous infusion. If required the dose of placebo could be reduced to 150 mg twice daily (b.i.d.) or 100 mg b.i.d. and two dose reductions for pemetrexed were allowed (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

Subject analysis set title	Nintedanib 200 mg bid plus pemetrexed
Subject analysis set type	Full analysis

Subject analysis set description:

Nintedanib 200 mg twice daily administered orally in a form of a soft gelatin capsule plus pemetrexed 500 mg/m2 on Day 1 of each 21-day treatment course administered via intravenous infusion.

Subject analysis set title	Nintedanib 150 mg bid Plus pemetrexed
Subject analysis set type	Full analysis

Subject analysis set description:

Nintedanib 150 mg twice daily administered orally in a form of a
soft gelatin capsule plus pemetrexed 500 mg/m2 on Day 1 of each 21-day treatment course administered via intravenous infusion.

Primary: Progression Free Survival (PFS) as Assessed by Central Independent Review

End point title	Progression Free Survival (PFS) as Assessed by Central Independent Review

End point description:

Progression Free Survival (PFS) as assessed by central independent review according to the modified RECIST (version 1.0) criteria. Progression free survival (PFS) is defined as the duration of time from date of randomisation to date of progression or death (whatever occurs earlier).
Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve.
Randomised set uncut (RS): all patients who were randomised whether patients had received study treatment or not. Patients were allocated to the treatment groups as randomised, regardless of the actual medication taken.

End point type	Primary

End point timeframe:

From randomisation until cut-off date 9 July 2012

End point values	Nintedanib plus pemetrexed	Placebo plus pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	353[1]	360[2]		
Units: months				
median (inter-quartile range (Q1-Q3))	4.4 (2.3 to 9.5)	3.6 (1.4 to 7.5)		

Notes:
[1] - RS
[2] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Proportional hazards model stratified by baseline ECOG PS (0 vs 1), tumour histology (adenocarcinoma vs. non-adenocarcinoma), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no) was used to obtain the HR, CI and p-value. HR below 1 favors nintedanib.

Comparison groups	Nintedanib plus pemetrexed v Placebo plus pemetrexed
Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0435
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	0.99

Secondary: Overall Survival (Key Secondary Endpoint)

End point title	Overall Survival (Key Secondary Endpoint)

End point description:

Overall Survival (OS) defined as the duration from randomisation to death (irrespective of the reason of death). Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve.

End point type	Secondary

End point timeframe:

From randomisation until data cut-off (15 February 2013), Up to 30 months

End point values	Nintedanib plus pemetrexed	Placebo plus pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	353[3]	360[4]		
Units: months				
median (inter-quartile range (Q1-Q3))	12 (7 to 24.2)	12.7 (5.4 to 24)		

Notes:
[3] - RS
[4] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Proportional hazards model stratified by baseline ECOG PS (0 vs 1), tumour histology (adenocarcinoma vs non-adenocarcinoma), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no) was used to obtain HR, CI and p-value. HR below 1 favors nintedanib.

Comparison groups	Nintedanib plus pemetrexed v Placebo plus pemetrexed
Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.894
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.21

Secondary: Follow-up Analysis of Progression Free Survival (PFS) as Assessed by Central Independent Review

End point title	Follow-up Analysis of Progression Free Survival (PFS) as Assessed by Central Independent Review

End point description:

Follow-up analysis was conducted at the time of overall survival analysis. Progression Free Survival (PFS) as assessed by central independent review according to the modified RECIST (version 1.0) criteria. Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve.

End point type	Secondary

End point timeframe:

From randomisation until data cut-off (15 February 2013), Up to 30 months

End point values	Nintedanib plus pemetrexed	Placebo plus pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	353[5]	360[6]		
Units: Months				
median (inter-quartile range (Q1-Q3))	4.4 (2.3 to 9.5)	3.4 (1.4 to 7.5)		

Notes:

[5] - RS

[6] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Proportional hazards model stratified by baseline ECOG PS (0 vs 1), tumour histology (adenocarcinoma vs. non-adenocarcinoma), brain metastases at baseline (yes vs no) and prior treatment with

bevacizumab (yes vs no) to obtain HR, CI and p-value. HR below 1 favors nintedanib

Comparison groups	Nintedanib plus pemetrexed v Placebo plus pemetrexed
Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0506
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1

Secondary: Follow-up Analysis of Progression Free Survival (PFS) as Assessed by Investigator

End point title	Follow-up Analysis of Progression Free Survival (PFS) as Assessed by Investigator

End point description:

Follow-up analysis was conducted at the time of overall survival analysis. Progression Free Survival (PFS) as assessed by investigator according to the modified RECIST (version 1.0) criteria. Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve.

End point type	Secondary

End point timeframe:

From randomisation until data cut-off (15 February 2013), Up to 30 months

End point values	Nintedanib plus pemetrexed	Placebo plus pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	353[7]	360[8]		
Units: Months				
median (inter-quartile range (Q1-Q3))	5.3 (2.6 to 9.4)	4.3 (1.9 to 8.3)		

Notes:

[7] - RS

[8] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Proportional hazards model stratified by baseline ECOG PS (0 vs 1), tumour histology (adenocarcinoma vs. non-adenocarcinoma), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no) to obtain HR, CI and p-value. HR below 1 favors nintedanib.

Comparison groups	Nintedanib plus pemetrexed v Placebo plus pemetrexed

Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0865 [9]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.02

Notes:

[9] - HR, CI and p-value obtained from the proportional hazards model stratified by baseline ECOG PS (0 vs 1), tumour histology (adenocarcinoma vs. non-adenocarcinoma), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (y vs no)

Secondary: Objective tumor response

End point title	Objective tumor response

End point description:

Confirmed objective response is defined as confirmed Complete Response (CR) and Partial Response (PR) and evaluated according to the modified RECIST criteria version 1.0. This endpoint was analysed based on the central independent reviewer as well as the investigator

End point type	Secondary

End point timeframe:

From randomisation until data cut-off (15 February 2013), Up to 30 months

End point values	Nintedanib plus pemetrexed	Placebo plus pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	353[10]	360[11]		
Units: % of participants				
number (not applicable)				
Central independent reviewer	9.1	8.3		
Investigator assessment	15	13.3		

Notes:

[10] - RS

[11] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis based on the central independent review

Comparison groups	Nintedanib plus pemetrexed v Placebo plus pemetrexed

Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7279 [12]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.85

Notes:

[12] - Odds ratio and p-value are obtained from logistic regression model adjusted for baseline ECOG PS (0 vs 1). An odds ratio >1 indicates a benefit to nintedanib.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Analysis based on the investigator's assessment

Comparison groups	Nintedanib plus pemetrexed v Placebo plus pemetrexed
Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.518 [13]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.76

Notes:

[13] - Odds ratio and p-value are obtained from logistic regression model adjusted for baseline ECOG PS (0 vs 1). An odds ratio >1 indicates a benefit to nintedanib.

Secondary: Duration of Confirmed Objective Tumour Response

End point title	Duration of Confirmed Objective Tumour Response

End point description:

The duration of objective response is the time from first documented (CR) or (PR) to the time of progression or death and evaluated according to the modified RECIST criteria version 1.0. Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve.
This endpoint was analysed based on the central independent reviewer as well as the investigator.

End point type	Secondary

End point timeframe:

From randomisation until data cut-off (15 February 2013), Up to 30 months

End point values	Nintedanib plus pemetrexed	Placebo plus pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	353[14]	360[15]		
Units: Months				
median (inter-quartile range (Q1-Q3))				
central independent reviewer (N=32, 30)	6.9 (5.1 to 11.3)	4.4 (3.3 to 8.9)		
Investigator assessment (N=53, 48)	6.5 (4.4 to 12.7)	7.2 (4.2 to 16.2)		

Notes:

[14] - RS

[15] - RS

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Confirmed Objective Tumour Response

End point title	Time to Confirmed Objective Tumour Response

End point description:

Time to confirmed objective response is defined as time from randomisation to the date of first documented (CR) or (PR) and evaluated according to the modified RECIST criteria version 1.0. Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve.
This endpoint was analysed based on the central independent reviewer as well as the investigator.

End point type	Secondary

End point timeframe:

From randomisation until data cut-off (15 February 2013), Up to 30 months

End point values	Nintedanib plus pemetrexed	Placebo plus pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	353[16]	360[17]		
Units: Months				
median (inter-quartile range (Q1-Q3))				
Central independent review (N=32, 30)	2.6 (1.4 to 4)	2.7 (1.4 to 4.2)		
Investigator assessment (N=53, 48)	2.6 (1.4 to 3)	2.8 (1.4 to 3.1)		

Notes:

[16] - RS

[17] - RS

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control

End point title	Disease control

End point description:

Disease control was defined as a best overall response of Complete Response (CR), Partial Response (PR), or Stable Disease (SD) and evaluated according to the modified RECIST criteria version 1.0.
This endpoint was analysed based on the central independent reviewer as well as the investigator.

End point type	Secondary

End point timeframe:

From randomisation until data cut-off (15 February 2013), Up to 30 months

End point values	Nintedanib plus pemetrexed	Placebo plus pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	353[18]	360[19]		
Units: % of participants				
number (not applicable)				
Central independent review (N=215, 192)	60.9	53.3		
Investigator assessment (N=233, 217)	66	60.3		

Notes:

[18] - RS

[19] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis based on the central independent review

Comparison groups	Nintedanib plus pemetrexed v Placebo plus pemetrexed
Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0387 [20]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	1.85

Notes:

[20] - Odds ratio and p-value are obtained from logistic regression model adjusted for baseline ECOG PS (0 vs 1). An odds ratio >1 indicates a benefit to nintedanib.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Analysis based on investigator's assessment

Comparison groups	Nintedanib plus pemetrexed v Placebo plus pemetrexed
Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1071 [21]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.29

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.75

Notes:

[21] - Odds ratio and p-value are obtained from logistic regression model adjusted for baseline ECOG PS (0 vs 1). An odds ratio >1 indicates a benefit to nintedanib.

Secondary: Duration of Disease Control

End point title	Duration of Disease Control

End point description:

The duration of disease control was defined as the time from randomisation to the date of disease progression or death (which ever occurs first) for patients with disease control. Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve.
This endpoint was analysed based on the central independent reviewer as well as the investigator.

End point type	Secondary

End point timeframe:

From randomisation until data cut-off (15 February 2013), Up to 30 months

End point values	Nintedanib plus pemetrexed	Placebo plus pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	353[22]	360[23]		
Units: Months				
median (inter-quartile range (Q1-Q3))				
Central independent review (N=215, 192)	7.4 (4.3 to 11.2)	6.8 (4.2 to 12.5)		
Investigator assessment (N=233, 217)	6.9 (4.4 to 12.5)	6.8 (4.4 to 11.1)		

Notes:

[22] - RS

[23] - RS

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Tumour Size

End point title	Change From Baseline in Tumour Size

End point description:

Percentage change from baseline in tumour size is defined as decrease in the sum of the longest diameter of the target lesion. Presented means are in fact adjusted best means percentage changes generated from ANOVA model adjusted for baseline ECOG PS (0 vs. 1), tumour histology (adenocarcinoma vs. non-adenocarcinoma), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no)
This endpoint was analysed based on the central independent reviewer as well as the investigator.

End point type	Secondary

End point timeframe:

From randomisation until data cut-off (15 February 2013), Up to 30 months

End point values	Nintedanib plus pemetrexed	Placebo plus pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	353[24]	360[25]		
Units: percentage of change in tumor size in mm				
arithmetic mean (confidence interval 95%)				
Central independent review (N=298, 305)	-10.1 (-12.63 to -7.58)	-7.53 (-10.03 to -5.04)		
Investigator assessment (N=322, 325)	-15.6 (-18.75 to -12.46)	-11.28 (-14.42 to -8.15)		

Notes:

[24] - RS

[25] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis based on the central independent review

Comparison groups	Nintedanib plus pemetrexed v Placebo plus pemetrexed
Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1558 [26]
Method	ANOVA

Notes:

[26] - P-value generated from ANOVA model adjusted for baseline ECOG PS (0 vs. 1), tumour histology (adenocarcinoma vs. non-adenocarcinoma), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no)

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Analysis based on the investigator's assessment

Comparison groups	Nintedanib plus pemetrexed v Placebo plus pemetrexed
Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0565 [27]
Method	ANOVA

Notes:

[27] - P-value generated from ANOVA model adjusted for baseline ECOG PS (0 vs. 1), tumour histology (adenocarcinoma vs. non-adenocarcinoma), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no)

Secondary: clinical improvement.

End point title	clinical improvement.

End point description:

Clinical improvement was defined as the time from randomisation to deterioration in body weight and/or Eastern Cooperative Oncology group performance score (ECOG PS) whichever occurred first.
Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve.

End point type	Secondary

End point timeframe:

From randomisation until data cut-off (15 February 2013), Up to 30 months

End point values	Nintedanib plus pemetrexed	Placebo plus pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	353[28]	360[29]		
Units: Months				
median (inter-quartile range (Q1-Q3))	7.2 (2.8 to 21.9)	7.5 (1.8 to 24.2)		

Notes:

[28] - RS

[29] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard ratio, confidence interval and p-value obtained from a proportional-hazards model stratified by baseline ECOG PS (0 vs >=1), tumor histology (adenocarcinoma vs. non-adenocarcinoma), brain metastases at baseline (yes vs. no) and prior treatment with bevacizumab (yes vs. no). HR below 1 favors nintedanib

Comparison groups	Nintedanib plus pemetrexed v Placebo plus pemetrexed
Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5068
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.16

Secondary: Quality of Life (QoL)

End point title	Quality of Life (QoL)

End point description:

QoL was measured by standardised questionnaires (EQ-5D, EORTC QLQ-C30, EORTC QLQ-LC13). The EORTC QLQ-C30 comprises of 30 questions, using both multi-item scales and single-item measures. EORTC LC-13 comprises of 13 questions incorporating 1 multi-item scale and a series of single items. The following were the main points of interest: Time to deterioration of cough (QLQ-LC13 question 1), Time to deterioration of
dyspnoea (QLQ-LC13, composite of questions 3 to 5), Time to deterioration of pain (QLQ- C30, composite of questions 9 and 19). Time to deterioration of cough, dyspnoea and pain was defined as the time to a 10-point increase from the baseline score.
Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve.
99999: As only 43.9% of patients had a deterioration of cough by the cut-off date, the 75th percentile was not estimable.

End point type	Secondary

End point timeframe:

From randomisation until data cut-off (15 February 2013), Up to 30 months

End point values	Nintedanib plus pemetrexed	Placebo plus pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	353[30]	360[31]		
Units: Months				
median (inter-quartile range (Q1-Q3))				
Time to deterioration of cough	6 (2.2 to 23.6)	4.3 (1.4 to 99999)		
Time to deterioration of dyspnoea	2.4 (0.9 to 6.4)	2 (0.8 to 5.7)		
Time to deterioration of pain	2.8 (1.2 to 7)	2.7 (1.1 to 8)		

Notes:

[30] - RS

[31] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis evaluating the time to deterioration of cough. HR, CI and p-value obtained from the prop. hazards model stratified by baseline ECOG PS (0 vs >=1), tumour histology (adenocarcinoma vs. non-adenocarcinoma), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no). HR below 1 favors nintedanib.

Comparison groups	Nintedanib plus pemetrexed v Placebo plus pemetrexed
Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1181
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.05

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Analysis evaluating the time to deterioration of dyspnoea. HR, CI and p-value obtained from the prop. hazards model stratified by baseline ECOG PS (0 vs >=1), tumour histology (adenocarcinoma vs. non-adenocarcinoma), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no). HR below 1 favors nintedanib

Comparison groups	Nintedanib plus pemetrexed v Placebo plus pemetrexed

Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4264
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.12

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Analysis evaluating the time to deterioration of pain. HR, CI and p-value obtained from the prop. hazards model stratified by baseline ECOG PS (0 vs >= 1), tumour histology (adenocarcinoma vs. non-adenocarcinoma), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no). HR below 1 favors nintedanib

Comparison groups	Nintedanib plus pemetrexed v Placebo plus pemetrexed
Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8929
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.23

Secondary: Dose Normalised Predose Plasma Concentration at Steady State (Cpre,ss,Norm) of Nintedanib and of Its Metabolites BIBF 1202and BIBF 1202

End point title	Dose Normalised Predose Plasma Concentration at Steady State (Cpre,ss,Norm) of Nintedanib and of Its Metabolites BIBF 1202and BIBF 1202 Glucuronide

End point description:

Geometric mean of dose normalised predose plasma concentration (Cpre,ss,norm) of nintedanib and of its metabolites BIBF 1202 and BIBF 1202 glucuronide evaluated at steady state based on course 2 and 3. If only one value was available and valid, then this value was used for calculation of Cpre,ss,norm. Pharmacokinetic set (PKS): All patients in the treated set who were documented to have received at least 1 dose of nintedanib and who had at least 1 valid drug plasma concentration available.

End point type	Secondary

End point timeframe:

Before the administration of nintedanib or placebo and between a window of 30 mins to an hour after administration of trial drug during Course 2 and between 1 and 3 hours after administration of trial drug during Course 3

End point values	Nintedanib 200 mg bid plus pemetrexed	Nintedanib 150 mg bid Plus pemetrexed		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	188[32]	40[33]		
Units: ng/mL/mg				
geometric mean (geometric coefficient of variation)				
Nintedanib BIBF 1120 (N=188, 39)	0.0883 (± 66.4)	0.103 (± 72.9)		
Nintedanib BIBF 1202 (N=188, 40)	0.131 (± 123)	0.151 (± 125)		
Nintedanib BIBF 1202 glucuronide (N=184, 39)	1.4 (± 169)	1.72 (± 185)		

Notes:

[32] - PKS

[33] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence and Intensity of Adverse Events

End point title	Incidence and Intensity of Adverse Events

End point description:

Incidence and intensity of adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The worst CTCAE grade per patient is reported and MedDRA version 15.1 used.

Serious signs and symptoms of progressive disease were reported as an adverse event in analysis of this endpoint.

Treated set uncut - all randomised patients who were documented to have taken at least 1 dose of study medication . Patients were allocated to the treatment groups according to the treatment actually received.

End point type	Secondary

End point timeframe:

From the first drug administration until 28 days after the last drug administration, up to 36 months

End point values	Nintedanib plus pemetrexed	Placebo plus pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	347[34]	357[35]		
Units: % of participants				
number (not applicable)				
CTCAE grade 1	4.9	9.2		
CTCAE grade 2	22.2	30.5		
CTCAE grade 3	46.1	34.5		
CTCAE grade 4	12.4	7.8		
CTCAE grade 5	9.8	12		

Notes:
[34] - Treated set uncut
[35] - Treated set uncut

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first drug administration until 28 days after the last drug administration, up to 36 months

Adverse event reporting additional description:

One patient in the nintedanib plus pemetrexed treatment arm reported a serious adverse event for which the preferred term was not yet coded until data cut-off (15 February 2013).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Nintedanib plus pemetrexed

Reporting group description:

Nintedanib 200 mg twice daily administered orally in a form of a soft gelatin capsule on day2 to 21 of each 21-day treatment course plus pemetrexed 500 mg/m2 on Day 1 of each 21-day treatment course administered via intravenous infusion. If required the dose of nitedanib could be reduced to 150 mg twice daily (b.i.d.) or 100 mg b.i.d. and two dose reductions for pemetrexed were allowed (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

Reporting group title	Placebo plus pemetrexed

Reporting group description:

Placebo soft gelatin capsule matching that of nintedanib twice daily on day 2 to 21 of each 21-day treatment course administered orally plus pemetrexed 500 mg/m2 on Day 1 of each 21-day treatment course administered via intravenous infusion. If required the dose of placebo could be reduced to 150 mg twice daily (b.i.d.) or 100 mg b.i.d. and two dose reductions for pemetrexed were allowed (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

Serious adverse events	Nintedanib plus pemetrexed	Placebo plus pemetrexed	
Total subjects affected by serious adverse events			
subjects affected / exposed	104 / 347 (29.97%)	117 / 357 (32.77%)	
number of deaths (all causes)	255	266	
number of deaths resulting from adverse events	6	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malignant neoplasm progression			
subjects affected / exposed	2 / 347 (0.58%)	4 / 357 (1.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 3	

Malignant pleural effusion			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to bone			
subjects affected / exposed	0 / 347 (0.00%)	2 / 357 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic pain			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm			
subjects affected / exposed	0 / 347 (0.00%)	2 / 357 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Non-small cell lung cancer			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer metastatic			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion malignant			

subjects affected / exposed	1 / 347 (0.29%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tumour associated fever			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour ulceration			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 347 (0.00%)	2 / 357 (0.56%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 347 (0.00%)	3 / 357 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Raynaud's phenomenon			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 347 (0.00%)	3 / 357 (0.84%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Death			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Disease progression			
subjects affected / exposed	2 / 347 (0.58%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	2 / 347 (0.58%)	3 / 357 (0.84%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	4 / 347 (1.15%)	3 / 357 (0.84%)	
occurrences causally related to treatment / all	0 / 4	2 / 4	
deaths causally related to treatment / all	0 / 2	0 / 0	
Mass			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oedema			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			

subjects affected / exposed	1 / 347 (0.29%)	2 / 357 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 347 (0.86%)	4 / 357 (1.12%)	
occurrences causally related to treatment / all	1 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 347 (0.29%)	2 / 357 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 347 (0.29%)	2 / 357 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Aspiration			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Asthma			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			

subjects affected / exposed	0 / 347 (0.00%)	2 / 357 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 347 (0.58%)	3 / 357 (0.84%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	9 / 347 (2.59%)	11 / 357 (3.08%)	
occurrences causally related to treatment / all	1 / 9	0 / 13	
deaths causally related to treatment / all	0 / 4	0 / 5	
Epistaxis			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemoptysis			
subjects affected / exposed	4 / 347 (1.15%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	3 / 4	0 / 1	
deaths causally related to treatment / all	2 / 2	0 / 1	
Hypoxia			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	5 / 347 (1.44%)	3 / 357 (0.84%)	
occurrences causally related to treatment / all	0 / 5	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			

subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	3 / 347 (0.86%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 347 (0.86%)	4 / 357 (1.12%)	
occurrences causally related to treatment / all	0 / 3	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 347 (0.00%)	2 / 357 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pulmonary oedema			
subjects affected / exposed	1 / 347 (0.29%)	2 / 357 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Respiratory distress			
subjects affected / exposed	1 / 347 (0.29%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Respiratory failure			
subjects affected / exposed	5 / 347 (1.44%)	6 / 357 (1.68%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 5	0 / 6	
Throat irritation			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Affective disorder			

subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	2 / 347 (0.58%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Restlessness			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Haemoglobin decreased			

subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 347 (0.29%)	2 / 357 (0.56%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Chemical injury			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			

subjects affected / exposed	0 / 347 (0.00%)	2 / 357 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation pneumonitis			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 347 (0.58%)	3 / 357 (0.84%)	
occurrences causally related to treatment / all	0 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 347 (0.29%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Cardiac failure			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	1 / 347 (0.29%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Cardiac tamponade			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardio-respiratory arrest			

subjects affected / exposed	2 / 347 (0.58%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cardiopulmonary failure			
subjects affected / exposed	1 / 347 (0.29%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Congestive cardiomyopathy			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	2 / 347 (0.58%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pericardial effusion			
subjects affected / exposed	2 / 347 (0.58%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			

subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system lesion			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system necrosis			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Grand mal convulsion			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial aneurysm			

subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 347 (0.29%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic encephalopathy			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebrobasilar insufficiency			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord paralysis			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	5 / 347 (1.44%)	8 / 357 (2.24%)	
occurrences causally related to treatment / all	3 / 6	3 / 9	
deaths causally related to treatment / all	0 / 0	0 / 1	
Febrile neutropenia			
subjects affected / exposed	7 / 347 (2.02%)	3 / 357 (0.84%)	
occurrences causally related to treatment / all	5 / 7	3 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 347 (0.29%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	3 / 347 (0.86%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normochromic normocytic anaemia			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	3 / 347 (0.86%)	2 / 357 (0.56%)	
occurrences causally related to treatment / all	3 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 347 (0.29%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional			

subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Glaucoma			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 347 (0.58%)	3 / 357 (0.84%)	
occurrences causally related to treatment / all	1 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic obstruction			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 347 (0.86%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			

subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 347 (0.29%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Large intestine perforation			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nausea			
subjects affected / exposed	2 / 347 (0.58%)	2 / 357 (0.56%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	3 / 347 (0.86%)	6 / 357 (1.68%)	
occurrences causally related to treatment / all	3 / 4	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cholecystitis acute			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 347 (0.29%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic function abnormal			

subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	1 / 347 (0.29%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 347 (0.00%)	2 / 357 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	2 / 347 (0.58%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal injury			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Arthritis			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 347 (0.00%)	4 / 357 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Amoebiasis			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 347 (0.00%)	3 / 357 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchopneumonia			

subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious peritonitis			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Liver abscess			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	1 / 347 (0.29%)	2 / 357 (0.56%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 347 (0.58%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung abscess			

subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 347 (0.00%)	2 / 357 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lymphangitis			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	1 / 347 (0.29%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal candidiasis			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	11 / 347 (3.17%)	16 / 357 (4.48%)	
occurrences causally related to treatment / all	3 / 12	1 / 17	
deaths causally related to treatment / all	1 / 2	0 / 6	
Pneumonia pneumococcal			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			

subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 347 (0.29%)	3 / 357 (0.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Sepsis			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	1 / 347 (0.29%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 347 (0.86%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 347 (0.00%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 347 (0.29%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			

subjects affected / exposed	6 / 347 (1.73%)	4 / 357 (1.12%)	
occurrences causally related to treatment / all	3 / 6	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 347 (0.58%)	1 / 357 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 347 (0.58%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	1 / 347 (0.29%)	0 / 357 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Nintedanib plus pemetrexed	Placebo plus pemetrexed	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	320 / 347 (92.22%)	312 / 357 (87.39%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	149 / 347 (42.94%)	87 / 357 (24.37%)	
occurrences (all)	268	140	
Aspartate aminotransferase increased			
subjects affected / exposed	129 / 347 (37.18%)	68 / 357 (19.05%)	
occurrences (all)	242	123	
Blood alkaline phosphatase increased			
subjects affected / exposed	33 / 347 (9.51%)	13 / 357 (3.64%)	
occurrences (all)	45	17	
Haemoglobin decreased			
subjects affected / exposed	41 / 347 (11.82%)	44 / 357 (12.32%)	
occurrences (all)	54	54	
Neutrophil count decreased			
subjects affected / exposed	74 / 347 (21.33%)	47 / 357 (13.17%)	
occurrences (all)	210	110	
Platelet count decreased			
subjects affected / exposed	23 / 347 (6.63%)	13 / 357 (3.64%)	
occurrences (all)	35	31	
Weight decreased			
subjects affected / exposed	23 / 347 (6.63%)	15 / 357 (4.20%)	
occurrences (all)	23	16	
White blood cell count decreased			
subjects affected / exposed	57 / 347 (16.43%)	38 / 357 (10.64%)	
occurrences (all)	133	81	
Nervous system disorders			
Dizziness			
subjects affected / exposed	30 / 347 (8.65%)	39 / 357 (10.92%)	
occurrences (all)	38	46	
Headache			
subjects affected / exposed	44 / 347 (12.68%)	47 / 357 (13.17%)	
occurrences (all)	52	65	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	26 / 347 (7.49%)	23 / 357 (6.44%)	
occurrences (all)	35	33	
Neutropenia			
subjects affected / exposed	27 / 347 (7.78%)	19 / 357 (5.32%)	
occurrences (all)	95	22	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	25 / 347 (7.20%)	31 / 357 (8.68%)	
occurrences (all)	39	39	
Chest pain			
subjects affected / exposed	31 / 347 (8.93%)	29 / 357 (8.12%)	
occurrences (all)	38	40	
Fatigue			
subjects affected / exposed	116 / 347 (33.43%)	127 / 357 (35.57%)	
occurrences (all)	151	174	
Oedema peripheral			
subjects affected / exposed	26 / 347 (7.49%)	30 / 357 (8.40%)	
occurrences (all)	33	45	
Pain			
subjects affected / exposed	17 / 347 (4.90%)	21 / 357 (5.88%)	
occurrences (all)	18	22	
Pyrexia			
subjects affected / exposed	36 / 347 (10.37%)	42 / 357 (11.76%)	
occurrences (all)	55	62	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	15 / 347 (4.32%)	21 / 357 (5.88%)	
occurrences (all)	15	23	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	41 / 347 (11.82%)	27 / 357 (7.56%)	
occurrences (all)	53	29	
Abdominal pain upper			
subjects affected / exposed	16 / 347 (4.61%)	22 / 357 (6.16%)	
occurrences (all)	25	25	

Constipation			
subjects affected / exposed	50 / 347 (14.41%)	65 / 357 (18.21%)	
occurrences (all)	63	73	
Diarrhoea			
subjects affected / exposed	118 / 347 (34.01%)	54 / 357 (15.13%)	
occurrences (all)	259	85	
Nausea			
subjects affected / exposed	126 / 347 (36.31%)	118 / 357 (33.05%)	
occurrences (all)	264	230	
Stomatitis			
subjects affected / exposed	27 / 347 (7.78%)	21 / 357 (5.88%)	
occurrences (all)	38	29	
Vomiting			
subjects affected / exposed	84 / 347 (24.21%)	68 / 357 (19.05%)	
occurrences (all)	203	129	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	55 / 347 (15.85%)	60 / 357 (16.81%)	
occurrences (all)	64	77	
Dyspnoea			
subjects affected / exposed	45 / 347 (12.97%)	70 / 357 (19.61%)	
occurrences (all)	50	82	
Epistaxis			
subjects affected / exposed	24 / 347 (6.92%)	12 / 357 (3.36%)	
occurrences (all)	27	14	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	29 / 347 (8.36%)	29 / 357 (8.12%)	
occurrences (all)	39	38	
Pruritus			
subjects affected / exposed	26 / 347 (7.49%)	33 / 357 (9.24%)	
occurrences (all)	35	49	
Rash			
subjects affected / exposed	22 / 347 (6.34%)	28 / 357 (7.84%)	
occurrences (all)	45	43	
Psychiatric disorders			

Insomnia			
subjects affected / exposed	29 / 347 (8.36%)	37 / 357 (10.36%)	
occurrences (all)	33	37	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	23 / 347 (6.63%)	14 / 357 (3.92%)	
occurrences (all)	24	19	
Back pain			
subjects affected / exposed	37 / 347 (10.66%)	36 / 357 (10.08%)	
occurrences (all)	41	37	
Musculoskeletal pain			
subjects affected / exposed	16 / 347 (4.61%)	20 / 357 (5.60%)	
occurrences (all)	21	22	
Myalgia			
subjects affected / exposed	12 / 347 (3.46%)	27 / 357 (7.56%)	
occurrences (all)	17	35	
Pain in extremity			
subjects affected / exposed	18 / 347 (5.19%)	16 / 357 (4.48%)	
occurrences (all)	22	18	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	21 / 347 (6.05%)	20 / 357 (5.60%)	
occurrences (all)	30	36	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	97 / 347 (27.95%)	89 / 357 (24.93%)	
occurrences (all)	143	125	
Hyperglycaemia			
subjects affected / exposed	24 / 347 (6.92%)	28 / 357 (7.84%)	
occurrences (all)	45	51	
Hypokalaemia			
subjects affected / exposed	20 / 347 (5.76%)	8 / 357 (2.24%)	
occurrences (all)	24	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 June 2009	It was specified that the DMC represented an independent multidisciplinary group consisting of clinicians & biostatistician who, collectively, had expertise in the management of patients with NSCLC &in the conduct &monitoring of randomised clinical trials. It was added that DMC reviewed all serious adverse events in an A/B fashion (i.e. the data were presented to the DMC un-blinded per treatment group without identifying the nintedanib or placebo arm) on an ongoing basis. The dose of folic acid was clarified. In ddition, it was specified that in the USA, folic acid was supplied by the trial sites. Outside of the USA, folic acid was provided by a Contract research organisation appointed by BI. Brain metastases had to be stable for 4 weeks,therefore the exclusion criterion was modified: "Chemo-, hormone-, immunotherapy with monoclonal antibodies, treatment with tyrosine kinase inhibitors, or radiotherapy (except for extremities) within the past 4 weeks prior to treatment with the trial drug". It was clarified that investigator could access the assigned treatment of individual patient if un-blinding was medically indicated.The dose reduction scheme for pemetrexed was modified.It was specified that Quality of life was only assessed in countries where validated translations of the questionnaires were available. The laboratory analysis of bilirubin was changed. It was clarified clarified that measurement of the oral or tympanic body temperature was preferable, but that other locations were allowed if the measurements were not feasible. However, the same location was to be used at each measurement. In addition to date& time of nintedanib / placebo intake,the investigators were required to also collect the time of the most recent food /beverage intake before each dose of nintedanib / placebo for 2 days prior to and on the day of blood sampling. The screening period was extended from 14 days to 21 days for exceptional cases.
07 July 2011	It was clarified that the treatment criteria for liver enzymes is for both AST and ALT. It was clarified that patients in the treatment group pemetrexed + BIBF 1120 cannot change to the treatment group BIBF 1120 monotherapy. It was clarified that the patients and site staff will be un-blinded to patients that were on active treatment as of June 18 2011. The sponsor's trial team involved in the later analysis of the trial remained blinded. For the primary analysis of PFS and supportive inference on OS, the trial database was locked and un-blinded. Recruitment and randomisation was held from 18 June 2011. After the ad hoc interim analysis (cut-off of 14 June 2011), the sponsor stopped recruitment on 29 July 2011. Patients who had completed active therapy by 18 June 2011 remained blinded. Patients on active therapy on 18 June 2011 were un-blinded and thus this procedure did not apply to them. Patients who entered the study after 18 June 2011 were not blinded. Patients interrupting nintedanib therapy for 14 or more consecutive days were not considered non-compliant.After 18 June 2011, Quality of Life (QoL) questionnaires were no longer completed. After 18 June 2011, information on caregiver support was no longer collected. After 18 June 2011, thyroid parameters were no longer determined. For patients entered after 18 June 2011, no PK assessment was done. For patients who were on-treatment with nintedanib before 18 June 2011 and were scheduled for PK assessment after 18 June 2011 and decided to continue combination therapy with nintedanib plus pemetrexed, the PK assessment was to be completed as originally planned. For patients entered after 18 June 2011, no pharmacogenetic blood sampling and analysis was performed.

08 August 2011	It was clarified that the treatment criteria for liver enzymes is for both AST and ALT. It was clarified that patients in the treatment group pemetrexed + BIBF 1120 cannot change to the treatment group BIBF 1120 monotherapy. It was clarified that the patients and site staff will be un-blinded to patients that were on active treatment as of June 18 2011. The sponsor's trial team involved in the later analysis of the trial remained blinded. For the primary analysis of PFS and supportive inference on OS, the trial database was locked and un-blinded. Recruitment and randomisation was held from 18 June 2011. After the ad hoc interim analysis (cut-off of 14 June 2011), the sponsor stopped recruitment on 29 July 2011. Patients who had completed active therapy by 18 June 2011 remained blinded. Patients on active therapy on 18 June 2011 were un-blinded and thus this procedure did not apply to them. Patients who entered the study after 18 June 2011 were not blinded. Patients interrupting nintedanib therapy for 14 or more consecutive days were not considered non-compliant.After 18 June 2011, Quality of Life (QoL) questionnaires were no longer completed. After 18 June 2011, information on caregiver support was no longer collected. After 18 June 2011, thyroid parameters were no longer determined. For patients entered after 18 June 2011, no PK assessment was done. For patients who were on-treatment with nintedanib before 18 June 2011 and were scheduled for PK assessment after 18 June 2011 and decided to continue combination therapy with nintedanib plus pemetrexed, the PK assessment was to be completed as originally planned. For patients entered after 18 June 2011, no pharmacogenetic blood sampling and analysis was performed.
12 February 2014	After the final analysis of PFS and OS had been completed, Amendment 4 changed the definitions for the follow-up period and the end of the whole trial. Instead of follow-up until death or lost to follow-up, patients were now to be followed up for 28 days after the last administration of trial medication (which was the reporting period for AEs). The definition for end-of-trial was thus changed to the point when the last patient had completed his first follow-up visit. Additionally, the Amendment clarified that data on patients who were still on treatment at the time of the final PFS and OS analysis were to be added to this follow-up CTR, following the process of a CTR revision.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
18 June 2011	Recruitment for the study was stopped early based on the results of a pre defined futility analysis.	-

Notes:

Limitations and caveats

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

Recruitment for the study was stopped early based on the results of a pre defined futility analysis.

Notes: