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

Summary

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

Results information

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

Trial information

Trial identification

Sponsor protocol code	1199.93

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01907100
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +001 8002430127, 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	19 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 March 2018
Global end of trial reached?	Yes
Global end of trial date	31 August 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 September 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Egypt: 38
Country: Number of subjects enrolled	South Africa: 6
Country: Number of subjects enrolled	Japan: 31
Country: Number of subjects enrolled	Australia: 56
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	Croatia: 14
Country: Number of subjects enrolled	Czech Republic: 9
Country: Number of subjects enrolled	Denmark: 18
Country: Number of subjects enrolled	France: 49
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	Israel: 11
Country: Number of subjects enrolled	Italy: 84
Country: Number of subjects enrolled	Netherlands: 20
Country: Number of subjects enrolled	Norway: 11
Country: Number of subjects enrolled	Poland: 19
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Russian Federation: 18

Country: Number of subjects enrolled	Spain: 39
Country: Number of subjects enrolled	Sweden: 13
Country: Number of subjects enrolled	Turkey: 12
Country: Number of subjects enrolled	United Kingdom: 64
Country: Number of subjects enrolled	United States: 17
Country: Number of subjects enrolled	Argentina: 11
Country: Number of subjects enrolled	Chile: 17
Country: Number of subjects enrolled	Mexico: 28
Worldwide total number of subjects	645
EEA total number of subjects	388

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	270
From 65 to 84 years	373
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

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

Blinding implementation details:

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo_Phase II

Arm description:

Phase II part: Nintedanib matching placebo 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m2 (100 mg or 500 mg vials) and Cisplatin 75 mg/m2 (50 mL of 1 mg/ml solution) on Day 1 of each 21-day treatment course administered intravenously. If required, the dose of placebo could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

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

Dosage and administration details:

Nintedanib matching placebo 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m2 (100 mg or 500 mg vials) and Cisplatin 75 mg/m2 (50 mL of 1 mg/ml solution) on Day 1 of each 21-day treatment course administered intravenously. If required, the dose of placebo could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

Arm title	Nintedanib_Phase II

Arm description:

Phase II part: Nintedanib 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m2 (100 mg or 500 mg vials) and Cisplatin 75 mg/m2 (50 mL of 1 mg/ml solution) on Day 1 of each 21-day treatment course administered intravenously. If required, the dose of Nintedanib could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

Arm type	Experimental

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

Dosage and administration details:

Nintedanib 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m2 (100 mg or 500 mg vials) and Cisplatin 75 mg/m2 (50 mL of 1 mg/ml solution) on Day 1 of each 21-day treatment course administered intravenously. If required, the dose of Nintedanib could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

Arm title	Placebo_Phase III

Arm description:

Phase III part: Nintedanib matching Placebo 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m2 (100 mg or 500 mg vials) and Cisplatin 75 mg/m2 (50 mL of 1 mg/ml solution) on Day 1 of each 21-day treatment course administered intravenously. If required, the dose of placebo could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

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

Dosage and administration details:

Nintedanib matching placebo 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m2 (100 mg or 500 mg vials) and Cisplatin 75 mg/m2 (50 mL of 1 mg/ml solution) on Day 1 of each 21-day treatment course administered intravenously. If required, the dose of placebo could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

Arm title	Nintedanib_Phase III

Arm description:

Phase III part: Nintedanib 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m2 (100 mg or 500 mg vials) and Cisplatin 75 mg/m2 (50 mL of 1 mg/ml solution) on Day 1 of each 21-day treatment course administered intravenously. If required, the dose of Nintedanib could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

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

Dosage and administration details:

Nintedanib 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m2 (100 mg or 500 mg vials) and Cisplatin 75 mg/m2 (50 mL of 1 mg/ml solution) on Day 1 of each 21-day treatment course administered intravenously. If required, the dose of Nintedanib could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

Number of subjects in period 1[1]	Placebo_Phase II	Nintedanib_Phase II	Placebo_Phase III
Started	43	44	229
Treated Patients	41	44	228
Completed	0	4	82
Not completed	43	40	147
Protocol deviation	-	-	1
Adverse event, serious fatal	-	-	4
Other than reasons specified	1	-	10
PD based on modified RECIST criteria	31	32	95
Adverse event, non-fatal	7	3	26
Consent withdrawn by subject	2	5	10
Lost to follow-up	-	-	-
Not treated	2	-	1

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

Notes:

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

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

Baseline characteristics

Reporting groups	
Reporting group title	Placebo_Phase II
Reporting group description:	
Phase II part: Nintedanib matching placebo 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m2 (100 mg or 500 mg vials) and Cisplatin 75 mg/m2 (50 mL of 1 mg/ml solution) on Day 1 of each 21-day treatment course administered intravenously. If required, the dose of placebo could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.	
Reporting group title	Nintedanib_Phase II
Reporting group description:	
Phase II part: Nintedanib 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m2 (100 mg or 500 mg vials) and Cisplatin 75 mg/m2 (50 mL of 1 mg/ml solution) on Day 1 of each 21-day treatment course administered intravenously. If required, the dose of Nintedanib could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.	
Reporting group title	Placebo_Phase III
Reporting group description:	
Phase III part: Nintedanib matching Placebo 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m2 (100 mg or 500 mg vials) and Cisplatin 75 mg/m2 (50 mL of 1 mg/ml solution) on Day 1 of each 21-day treatment course administered intravenously. If required, the dose of placebo could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.	
Reporting group title	Nintedanib_Phase III
Reporting group description:	
Phase III part: Nintedanib 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m2 (100 mg or 500 mg vials) and Cisplatin 75 mg/m2 (50 mL of 1 mg/ml solution) on Day 1 of each 21-day treatment course administered intravenously. If required, the dose of Nintedanib could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.	

Reporting group values	Placebo_Phase II	Nintedanib_Phase II	Placebo_Phase III
Number of subjects	43	44	229
Age categorical Units: Subjects			

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

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

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

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

End points

End points reporting groups

Reporting group title	Placebo_Phase II

Reporting group description:

Phase II part: Nintedanib matching placebo 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m2 (100 mg or 500 mg vials) and Cisplatin 75 mg/m2 (50 mL of 1 mg/ml solution) on Day 1 of each 21-day treatment course administered intravenously. If required, the dose of placebo could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

Reporting group title	Nintedanib_Phase II

Reporting group description:

Phase II part: Nintedanib 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m2 (100 mg or 500 mg vials) and Cisplatin 75 mg/m2 (50 mL of 1 mg/ml solution) on Day 1 of each 21-day treatment course administered intravenously. If required, the dose of Nintedanib could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

Reporting group title	Placebo_Phase III

Reporting group description:

Phase III part: Nintedanib matching Placebo 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m2 (100 mg or 500 mg vials) and Cisplatin 75 mg/m2 (50 mL of 1 mg/ml solution) on Day 1 of each 21-day treatment course administered intravenously. If required, the dose of placebo could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

Reporting group title	Nintedanib_Phase III

Reporting group description:

Phase III part: Nintedanib 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m2 (100 mg or 500 mg vials) and Cisplatin 75 mg/m2 (50 mL of 1 mg/ml solution) on Day 1 of each 21-day treatment course administered intravenously. If required, the dose of Nintedanib could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

Primary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

This outcome measure presents progression-free survival. Disease progression was defined according to the modified Response Evaluation Criteria in Solid Tumours (RECIST) criteria. Progression-free survival time was calculated as the duration from the date of randomization to the date of disease progression or death, whichever occurred first. For patients with known date of progression (or death): PFS (days) = min (date of progression, date of death) - date of randomization + 1 day. For patients without progression or death, PFS was censored at the last imaging date that showed no disease progression: PFS (days, censored) = date of last imaging showing no progression - date randomization + 1 day. Randomised Set (RS) : This patient set included all randomized patients.

End point type	Primary

End point timeframe:

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

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

Notes:

[1] - RS

[2] - RS

[3] - RS

[4] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

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

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

Notes:

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

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

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

Comparison groups	Placebo_Phase III v Nintedanib_Phase III
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.543 [6]
Method	Proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided

lower limit	0.79
upper limit	1.3

Notes:

[6] - one-sided p-value

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

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

End point type	Secondary

End point timeframe:

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

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

Notes:

[7] - RS

[8] - RS

[9] - RS

[10] - RS

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

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

Comparison groups	Placebo_Phase II v Nintedanib_Phase II
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.4132
Method	Proportional hazards mode
Parameter estimate	Hazard ratio (HR)
Point estimate	0.782
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.433
upper limit	1.412

Notes:

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

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

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

Comparison groups	Placebo_Phase III v Nintedanib_Phase III
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.7306 [13]
Method	Proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.58

Notes:

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

Secondary: Objective response according to modified RECIST− investigator assessment

End point title	Objective response according to modified RECIST− investigator assessment[14]

End point description:

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

End point type	Secondary

End point timeframe:

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

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

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

Notes:

[15] - RS

[16] - RS

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Odds ratio and one−sided p−value are obtained from an un−adjusted logistic regression model (Nintedanib vs Placebo).

Comparison groups	Placebo_Phase III v Nintedanib_Phase III
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	= 0.3189 [18]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.58

Notes:

[17] - Odds ratio above 1 favours nintedanib.

[18] - one-sided p-value

Secondary: Disease control according to modified RECIST− investigator assessment

End point title	Disease control according to modified RECIST− investigator assessment[19]

End point description:

Disease control (best overall response of confirmed CR or PR, or Stable Disease (SD) that lasted ≥36 days) according to modified RECIST. Percentage of Patients with Disease control is presented. This endpoint was only evaluated for Phase III part.

End point type	Secondary

End point timeframe:

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

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

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

Notes:
[20] - RS
[21] - RS

Statistical analyses

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

Notes:
[22] - Odds ratio above 1 favours nintedanib.
[23] - one-sided p-value

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Placebo_Phase II

Reporting group description:

Phase II part: Nintedanib matching placebo 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin
capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m2 (100 mg or 500 mg vials) and Cisplatin 75 mg/m2 (50 mL of 1 mg/ml solution) on Day 1 of
each 21-day treatment course administered intravenously. If required, the dose of placebo could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocoldefined dose-reduction scheme). No dose increase was allowed after a dose reduction.

Reporting group title	Nintedanib_Phase II

Reporting group description:

Phase II part: Nintedanib 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m2 (100 mg or 500 mg vials) and Cisplatin 75 mg/m2 (50 mL of 1 mg/ml solution) on Day 1 of each 21-day treatment course administered intravenously. If required, the dose of Nintedanib could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

Reporting group title	Placebo_Phase III

Reporting group description:

Phase III part: Nintedanib matching Placebo 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m2 (100 mg or 500 mg vials) and Cisplatin 75 mg/m2 (50 mL of 1 mg/ml solution) on Day 1 of
each 21-day treatment course administered intravenously. If required, the dose of placebo could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocoldefined dose-reduction scheme). No dose increase was allowed after a dose reduction.

Reporting group title	Nintedanib_Phase III

Reporting group description:

Phase III part: Nintedanib 200 mg twice daily (b.i.d.) on Day 2 to 21 of each 21-day treatment course administered orally in the form of a soft gelatin capsule (100 mg or 150 mg capsules) plus standard Pemetrexed 500 mg/m2 (100 mg or 500 mg vials) and Cisplatin 75 mg/m2 (50 mL of 1 mg/ml solution) on Day 1 of each 21-day treatment course administered intravenously. If required, the dose of Nintedanib could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

Serious adverse events	Placebo_Phase II	Nintedanib_Phase II	Placebo_Phase III
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 41 (41.46%)	16 / 44 (36.36%)	89 / 228 (39.04%)
number of deaths (all causes)	25	22	63

number of deaths resulting from adverse events	0	1	4
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 44 (2.27%)	2 / 228 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic aneurysm			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic thrombosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jugular vein thrombosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Subclavian artery thrombosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subclavian vein thrombosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vena cava thrombosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis limb			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	2 / 41 (4.88%)	2 / 44 (4.55%)	2 / 228 (0.88%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 2
Basal cell carcinoma			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cancer pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant pleural effusion			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural mesothelioma malignant			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour associated fever			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuroendocrine tumour			
subjects affected / exposed	0 / 41 (0.00%)	1 / 44 (2.27%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	0 / 41 (0.00%)	1 / 44 (2.27%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 41 (2.44%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	1 / 41 (2.44%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Feeling of body temperature change			
subjects affected / exposed	1 / 41 (2.44%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	0 / 41 (0.00%)	1 / 44 (2.27%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Erosive balanitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	0 / 41 (0.00%)	1 / 44 (2.27%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Rib fracture			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 41 (0.00%)	1 / 44 (2.27%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	1 / 41 (2.44%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatinine increased			
subjects affected / exposed	2 / 41 (4.88%)	1 / 44 (2.27%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	1 / 2	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibrin D dimer increased			
subjects affected / exposed	1 / 41 (2.44%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-reactive protein increased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ejection fraction decreased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood potassium decreased			
subjects affected / exposed	1 / 41 (2.44%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 41 (2.44%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glomerular filtration rate decreased			

subjects affected / exposed	0 / 41 (0.00%)	1 / 44 (2.27%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 41 (2.44%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 41 (2.44%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bundle branch block left			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac tamponade			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	2 / 228 (0.88%)

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

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Aplasia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 41 (2.44%)	2 / 44 (4.55%)	8 / 228 (3.51%)
occurrences causally related to treatment / all	0 / 1	0 / 2	5 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Febrile bone marrow aplasia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 44 (0.00%)	3 / 228 (1.32%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 44 (0.00%)	3 / 228 (1.32%)
occurrences causally related to treatment / all	1 / 1	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 44 (0.00%)	2 / 228 (0.88%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	4 / 41 (9.76%)	1 / 44 (2.27%)	7 / 228 (3.07%)
occurrences causally related to treatment / all	4 / 4	2 / 2	7 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Thrombocytopenia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 44 (0.00%)	4 / 228 (1.75%)
occurrences causally related to treatment / all	1 / 1	0 / 0	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone marrow toxicity			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to	0 / 0	0 / 0	0 / 0

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	2 / 228 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic infarction			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone marrow failure			
subjects affected / exposed	1 / 41 (2.44%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphatic obstruction			
subjects affected / exposed	1 / 41 (2.44%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 41 (4.88%)	2 / 44 (4.55%)	6 / 228 (2.63%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pleural effusion			
subjects affected / exposed	0 / 41 (0.00%)	2 / 44 (4.55%)	6 / 228 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 41 (2.44%)	4 / 44 (9.09%)	7 / 228 (3.07%)

occurrences causally related to treatment / all	0 / 1	3 / 4	3 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiccups			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperventilation			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	4 / 228 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 4
Laryngeal oedema			
subjects affected / exposed	1 / 41 (2.44%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0

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

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Visual acuity reduced			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 41 (0.00%)	1 / 44 (2.27%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoacusis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 41 (4.88%)	0 / 44 (0.00%)	2 / 228 (0.88%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	3 / 41 (7.32%)	0 / 44 (0.00%)	7 / 228 (3.07%)
occurrences causally related to treatment / all	3 / 3	0 / 0	7 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 44 (0.00%)	0 / 228 (0.00%)

occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	0 / 41 (0.00%)	1 / 44 (2.27%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	2 / 41 (4.88%)	1 / 44 (2.27%)	4 / 228 (1.75%)
occurrences causally related to treatment / all	2 / 2	2 / 2	4 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 41 (2.44%)	1 / 44 (2.27%)	8 / 228 (3.51%)
occurrences causally related to treatment / all	3 / 3	1 / 1	8 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	2 / 228 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Acute abdomen			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Gastric ulcer			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	2 / 228 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumoperitoneum			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	5 / 228 (2.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 5

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Calculus bladder			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	4 / 228 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrotic syndrome			
subjects affected / exposed	0 / 41 (0.00%)	1 / 44 (2.27%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Stasis dermatitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous emphysema			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash erythematous			
subjects affected / exposed	0 / 41 (0.00%)	1 / 44 (2.27%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)

occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 41 (4.88%)	2 / 44 (4.55%)	8 / 228 (3.51%)
occurrences causally related to treatment / all	2 / 2	1 / 2	2 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hypokalaemia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 44 (0.00%)	2 / 228 (0.88%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesaemia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	3 / 228 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	2 / 228 (0.88%)
occurrences causally related to	0 / 0	0 / 0	0 / 2

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lactic acidosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	0 / 41 (0.00%)	2 / 44 (4.55%)	2 / 228 (0.88%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 44 (2.27%)	2 / 228 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Bronchitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia bacteraemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis norovirus			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal candidiasis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Onychomycosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Oral bacterial infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	4 / 228 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Tooth abscess			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 44 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia klebsiella			
subjects affected / exposed	1 / 41 (2.44%)	0 / 44 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2

Serious adverse events	Nintedanib_Phase III		
Total subjects affected by serious adverse events			
subjects affected / exposed	99 / 227 (43.61%)		
number of deaths (all causes)	64		
number of deaths resulting from adverse events	3		

Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	3 / 227 (1.32%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Aortic aneurysm			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aortic thrombosis			
subjects affected / exposed	2 / 227 (0.88%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Embolism			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Jugular vein thrombosis			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral ischaemia			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Subclavian artery thrombosis			

subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Subclavian vein thrombosis			
subjects affected / exposed	2 / 227 (0.88%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Thrombophlebitis			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vena cava thrombosis			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Venous thrombosis			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Venous thrombosis limb			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cancer pain			

subjects affected / exposed	2 / 227 (0.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Malignant pleural effusion			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural mesothelioma malignant			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour associated fever			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neuroendocrine tumour			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Fatigue			
subjects affected / exposed	2 / 227 (0.88%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	4 / 227 (1.76%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	1 / 1		
Pyrexia			
subjects affected / exposed	4 / 227 (1.76%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	5 / 227 (2.20%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Malaise			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mucosal inflammation			
subjects affected / exposed	2 / 227 (0.88%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Performance status decreased			
subjects affected / exposed	1 / 227 (0.44%)		

occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Chills			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Feeling of body temperature change			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hallucination			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Erosive balanitis			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Rib fracture				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Post procedural haemorrhage				
subjects affected / exposed	0 / 227 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Toxicity to various agents				
subjects affected / exposed	0 / 227 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood creatinine increased				
subjects affected / exposed	3 / 227 (1.32%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Fibrin D dimer increased				
subjects affected / exposed	0 / 227 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Alanine aminotransferase increased				
subjects affected / exposed	2 / 227 (0.88%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
C-reactive protein increased				
subjects affected / exposed	0 / 227 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Ejection fraction decreased			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic enzyme increased			
subjects affected / exposed	2 / 227 (0.88%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			
subjects affected / exposed	3 / 227 (1.32%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Platelet count decreased			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Transaminases increased			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
White blood cell count decreased			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood potassium decreased			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Glomerular filtration rate decreased			

subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 227 (0.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Atrial flutter			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block second degree			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bundle branch block left			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac tamponade			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	1 / 227 (0.44%)		

occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Myocardial infarction			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pericardial effusion			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pericarditis			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sinus tachycardia			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Supraventricular tachycardia			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Angina unstable			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tachyarrhythmia			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		

deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Aplasia			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile bone marrow aplasia			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	4 / 227 (1.76%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Leukopenia			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	6 / 227 (2.64%)		
occurrences causally related to treatment / all	3 / 6		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bone marrow toxicity			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to	1 / 1		

treatment / all				
deaths causally related to treatment / all	0 / 0			
Pancytopenia				
subjects affected / exposed	2 / 227 (0.88%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Splenic infarction				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Bone marrow failure				
subjects affected / exposed	0 / 227 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lymphatic obstruction				
subjects affected / exposed	0 / 227 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	5 / 227 (2.20%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 2			
Pleural effusion				
subjects affected / exposed	4 / 227 (1.76%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	13 / 227 (5.73%)			

occurrences causally related to treatment / all	10 / 13		
deaths causally related to treatment / all	0 / 0		
Cough			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hiccups			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperventilation			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	3 / 227 (1.32%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pulmonary hypertension			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Laryngeal oedema			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		

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

deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 227 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Visual acuity reduced				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Deafness				
subjects affected / exposed	0 / 227 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoacusis				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Constipation				
subjects affected / exposed	2 / 227 (0.88%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	8 / 227 (3.52%)			
occurrences causally related to treatment / all	8 / 8			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	1 / 227 (0.44%)			

occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestine perforation				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	4 / 227 (1.76%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	6 / 227 (2.64%)			
occurrences causally related to treatment / all	4 / 6			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	2 / 227 (0.88%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Acute abdomen				
subjects affected / exposed	0 / 227 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enteritis				
subjects affected / exposed	0 / 227 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer				
subjects affected / exposed	0 / 227 (0.00%)			
occurrences causally related to treatment / all	0 / 0			

deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	0 / 227 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhoids				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Intestinal perforation				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumoperitoneum				
subjects affected / exposed	0 / 227 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	0 / 227 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	9 / 227 (3.96%)			
occurrences causally related to treatment / all	5 / 9			

deaths causally related to treatment / all	0 / 0		
Calculus bladder			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nephrotic syndrome			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Stasis dermatitis			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subcutaneous emphysema			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rash erythematous			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 227 (0.44%)		

occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Flank pain				
subjects affected / exposed	0 / 227 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Muscular weakness				
subjects affected / exposed	0 / 227 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain in extremity				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	4 / 227 (1.76%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				
subjects affected / exposed	1 / 227 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypomagnesaemia				
subjects affected / exposed	0 / 227 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Decreased appetite				
subjects affected / exposed	3 / 227 (1.32%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	2 / 227 (0.88%)			
occurrences causally related to	2 / 2			

treatment / all			
deaths causally related to treatment / all	0 / 0		
Lactic acidosis			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	4 / 227 (1.76%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocarditis			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia bacteraemia			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		

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

Oral bacterial infection			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peritonitis			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	6 / 227 (2.64%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 1		
Tooth abscess			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia klebsiella			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	Placebo_Phase II	Nintedanib_Phase II	Placebo_Phase III
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 41 (100.00%)	44 / 44 (100.00%)	219 / 228 (96.05%)
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 41 (14.63%)	6 / 44 (13.64%)	21 / 228 (9.21%)
occurrences (all)	6	6	26
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	12 / 41 (29.27%)	14 / 44 (31.82%)	46 / 228 (20.18%)
occurrences (all)	26	25	62
Chest pain			
subjects affected / exposed	9 / 41 (21.95%)	7 / 44 (15.91%)	23 / 228 (10.09%)
occurrences (all)	14	8	24
Fatigue			
subjects affected / exposed	15 / 41 (36.59%)	18 / 44 (40.91%)	62 / 228 (27.19%)
occurrences (all)	34	38	85
Mucosal inflammation			
subjects affected / exposed	4 / 41 (9.76%)	7 / 44 (15.91%)	22 / 228 (9.65%)
occurrences (all)	7	9	25
Oedema peripheral			
subjects affected / exposed	5 / 41 (12.20%)	5 / 44 (11.36%)	16 / 228 (7.02%)
occurrences (all)	5	8	19
Pyrexia			
subjects affected / exposed	4 / 41 (9.76%)	7 / 44 (15.91%)	22 / 228 (9.65%)
occurrences (all)	6	13	29
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 41 (9.76%)	8 / 44 (18.18%)	12 / 228 (5.26%)
occurrences (all)	4	8	12
Depression			
subjects affected / exposed	3 / 41 (7.32%)	1 / 44 (2.27%)	2 / 228 (0.88%)
occurrences (all)	3	1	2
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 41 (2.44%)	17 / 44 (38.64%)	10 / 228 (4.39%)
occurrences (all)	2	39	11

Aspartate aminotransferase increased			
subjects affected / exposed	1 / 41 (2.44%)	13 / 44 (29.55%)	9 / 228 (3.95%)
occurrences (all)	1	26	14
Blood creatinine increased			
subjects affected / exposed	4 / 41 (9.76%)	6 / 44 (13.64%)	26 / 228 (11.40%)
occurrences (all)	13	13	39
Blood magnesium decreased			
subjects affected / exposed	6 / 41 (14.63%)	10 / 44 (22.73%)	12 / 228 (5.26%)
occurrences (all)	14	22	14
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 41 (2.44%)	10 / 44 (22.73%)	13 / 228 (5.70%)
occurrences (all)	1	41	15
Neutrophil count decreased			
subjects affected / exposed	3 / 41 (7.32%)	8 / 44 (18.18%)	26 / 228 (11.40%)
occurrences (all)	5	20	47
Weight decreased			
subjects affected / exposed	9 / 41 (21.95%)	8 / 44 (18.18%)	23 / 228 (10.09%)
occurrences (all)	9	11	24
White blood cell count decreased			
subjects affected / exposed	1 / 41 (2.44%)	2 / 44 (4.55%)	15 / 228 (6.58%)
occurrences (all)	1	2	26
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 41 (2.44%)	9 / 44 (20.45%)	6 / 228 (2.63%)
occurrences (all)	1	9	6
Blood glucose increased			
subjects affected / exposed	1 / 41 (2.44%)	5 / 44 (11.36%)	1 / 228 (0.44%)
occurrences (all)	1	5	1
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 41 (0.00%)	3 / 44 (6.82%)	1 / 228 (0.44%)
occurrences (all)	0	3	1
Blood potassium decreased			
subjects affected / exposed	2 / 41 (4.88%)	4 / 44 (9.09%)	0 / 228 (0.00%)
occurrences (all)	2	4	0
Blood urea increased			
subjects affected / exposed	3 / 41 (7.32%)	8 / 44 (18.18%)	10 / 228 (4.39%)

occurrences (all)	3	8	10
Haemoglobin decreased			
subjects affected / exposed	2 / 41 (4.88%)	4 / 44 (9.09%)	2 / 228 (0.88%)
occurrences (all)	2	4	2
Platelet count decreased			
subjects affected / exposed	4 / 41 (9.76%)	8 / 44 (18.18%)	7 / 228 (3.07%)
occurrences (all)	8	22	12
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 41 (21.95%)	16 / 44 (36.36%)	94 / 228 (41.23%)
occurrences (all)	15	28	123
Leukopenia			
subjects affected / exposed	5 / 41 (12.20%)	2 / 44 (4.55%)	28 / 228 (12.28%)
occurrences (all)	5	2	58
Neutropenia			
subjects affected / exposed	9 / 41 (21.95%)	22 / 44 (50.00%)	82 / 228 (35.96%)
occurrences (all)	22	53	170
Thrombocytopenia			
subjects affected / exposed	1 / 41 (2.44%)	7 / 44 (15.91%)	18 / 228 (7.89%)
occurrences (all)	1	11	27
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 41 (14.63%)	15 / 44 (34.09%)	33 / 228 (14.47%)
occurrences (all)	6	15	40
Dyspnoea			
subjects affected / exposed	7 / 41 (17.07%)	7 / 44 (15.91%)	26 / 228 (11.40%)
occurrences (all)	7	7	29
Hiccups			
subjects affected / exposed	3 / 41 (7.32%)	1 / 44 (2.27%)	20 / 228 (8.77%)
occurrences (all)	3	1	27
Epistaxis			
subjects affected / exposed	2 / 41 (4.88%)	1 / 44 (2.27%)	13 / 228 (5.70%)
occurrences (all)	2	1	15
Dysphonia			
subjects affected / exposed	0 / 41 (0.00%)	3 / 44 (6.82%)	2 / 228 (0.88%)
occurrences (all)	0	3	2

Oropharyngeal pain			
subjects affected / exposed	6 / 41 (14.63%)	2 / 44 (4.55%)	4 / 228 (1.75%)
occurrences (all)	6	2	4
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 41 (12.20%)	3 / 44 (6.82%)	18 / 228 (7.89%)
occurrences (all)	5	3	22
Headache			
subjects affected / exposed	4 / 41 (9.76%)	5 / 44 (11.36%)	23 / 228 (10.09%)
occurrences (all)	4	5	23
Dysgeusia			
subjects affected / exposed	11 / 41 (26.83%)	11 / 44 (25.00%)	27 / 228 (11.84%)
occurrences (all)	11	11	31
Lethargy			
subjects affected / exposed	13 / 41 (31.71%)	6 / 44 (13.64%)	5 / 228 (2.19%)
occurrences (all)	13	6	11
Neuropathy peripheral			
subjects affected / exposed	6 / 41 (14.63%)	9 / 44 (20.45%)	18 / 228 (7.89%)
occurrences (all)	6	9	18
Paraesthesia			
subjects affected / exposed	4 / 41 (9.76%)	4 / 44 (9.09%)	19 / 228 (8.33%)
occurrences (all)	4	4	21
Neurotoxicity			
subjects affected / exposed	3 / 41 (7.32%)	1 / 44 (2.27%)	4 / 228 (1.75%)
occurrences (all)	3	1	4
Eye disorders			
Dry eye			
subjects affected / exposed	3 / 41 (7.32%)	0 / 44 (0.00%)	4 / 228 (1.75%)
occurrences (all)	3	0	4
Lacrimation increased			
subjects affected / exposed	4 / 41 (9.76%)	7 / 44 (15.91%)	18 / 228 (7.89%)
occurrences (all)	4	7	18
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	9 / 41 (21.95%)	4 / 44 (9.09%)	24 / 228 (10.53%)
occurrences (all)	14	8	27

Hypoacusis			
subjects affected / exposed	1 / 41 (2.44%)	4 / 44 (9.09%)	4 / 228 (1.75%)
occurrences (all)	1	4	4
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 41 (7.32%)	11 / 44 (25.00%)	10 / 228 (4.39%)
occurrences (all)	5	18	10
Abdominal pain upper			
subjects affected / exposed	3 / 41 (7.32%)	9 / 44 (20.45%)	11 / 228 (4.82%)
occurrences (all)	3	11	11
Constipation			
subjects affected / exposed	19 / 41 (46.34%)	17 / 44 (38.64%)	73 / 228 (32.02%)
occurrences (all)	27	31	96
Diarrhoea			
subjects affected / exposed	15 / 41 (36.59%)	29 / 44 (65.91%)	47 / 228 (20.61%)
occurrences (all)	27	31	61
Dyspepsia			
subjects affected / exposed	11 / 41 (26.83%)	3 / 44 (6.82%)	20 / 228 (8.77%)
occurrences (all)	12	3	20
Nausea			
subjects affected / exposed	34 / 41 (82.93%)	37 / 44 (84.09%)	134 / 228 (58.77%)
occurrences (all)	101	114	234
Stomatitis			
subjects affected / exposed	5 / 41 (12.20%)	3 / 44 (6.82%)	16 / 228 (7.02%)
occurrences (all)	5	3	18
Vomiting			
subjects affected / exposed	20 / 41 (48.78%)	24 / 44 (54.55%)	66 / 228 (28.95%)
occurrences (all)	36	55	115
Dry mouth			
subjects affected / exposed	4 / 41 (9.76%)	2 / 44 (4.55%)	2 / 228 (0.88%)
occurrences (all)	4	2	2
Haemorrhoids			
subjects affected / exposed	0 / 41 (0.00%)	3 / 44 (6.82%)	2 / 228 (0.88%)
occurrences (all)	0	3	2
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 41 (9.76%)	3 / 44 (6.82%)	11 / 228 (4.82%)

occurrences (all)	4	3	11

Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	5 / 41 (12.20%)	6 / 44 (13.64%)	8 / 228 (3.51%)
occurrences (all)	5	6	8
Rash			
subjects affected / exposed	7 / 41 (17.07%)	11 / 44 (25.00%)	23 / 228 (10.09%)
occurrences (all)	7	11	28
Dry skin			
subjects affected / exposed	3 / 41 (7.32%)	0 / 44 (0.00%)	7 / 228 (3.07%)
occurrences (all)	3	0	7
Pruritus			
subjects affected / exposed	1 / 41 (2.44%)	3 / 44 (6.82%)	10 / 228 (4.39%)
occurrences (all)	1	3	10
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	16 / 41 (39.02%)	17 / 44 (38.64%)	66 / 228 (28.95%)
occurrences (all)	24	26	91
Hypokalaemia			
subjects affected / exposed	2 / 41 (4.88%)	4 / 44 (9.09%)	13 / 228 (5.70%)
occurrences (all)	2	6	18
Hypomagnesaemia			
subjects affected / exposed	8 / 41 (19.51%)	13 / 44 (29.55%)	20 / 228 (8.77%)
occurrences (all)	8	13	28
Hyponatraemia			
subjects affected / exposed	2 / 41 (4.88%)	1 / 44 (2.27%)	14 / 228 (6.14%)
occurrences (all)	2	1	15
Hyperglycaemia			
subjects affected / exposed	1 / 41 (2.44%)	2 / 44 (4.55%)	15 / 228 (6.58%)
occurrences (all)	1	2	22
Dehydration			
subjects affected / exposed	3 / 41 (7.32%)	4 / 44 (9.09%)	8 / 228 (3.51%)
occurrences (all)	3	4	8
Hypocalcaemia			
subjects affected / exposed	3 / 41 (7.32%)	0 / 44 (0.00%)	2 / 228 (0.88%)

occurrences (all)	3	0	2

Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 41 (2.44%)	4 / 44 (9.09%)	12 / 228 (5.26%)
occurrences (all)	1	4	12
Upper respiratory tract infection			
subjects affected / exposed	5 / 41 (12.20%)	2 / 44 (4.55%)	6 / 228 (2.63%)
occurrences (all)	6	3	8
Urinary tract infection			
subjects affected / exposed	5 / 41 (12.20%)	0 / 44 (0.00%)	14 / 228 (6.14%)
occurrences (all)	8	0	20
Conjunctivitis			
subjects affected / exposed	2 / 41 (4.88%)	4 / 44 (9.09%)	11 / 228 (4.82%)
occurrences (all)	2	4	11
Influenza			
subjects affected / exposed	2 / 41 (4.88%)	3 / 44 (6.82%)	4 / 228 (1.75%)
occurrences (all)	2	3	4

Non-serious adverse events	Nintedanib_Phase III		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	218 / 227 (96.04%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	26 / 227 (11.45%)		
occurrences (all)	30		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	53 / 227 (23.35%)		
occurrences (all)	79		
Chest pain			
subjects affected / exposed	23 / 227 (10.13%)		
occurrences (all)	24		
Fatigue			
subjects affected / exposed	60 / 227 (26.43%)		
occurrences (all)	81		
Mucosal inflammation			

subjects affected / exposed	16 / 227 (7.05%)		
occurrences (all)	21		
Oedema peripheral			
subjects affected / exposed	16 / 227 (7.05%)		
occurrences (all)	18		
Pyrexia			
subjects affected / exposed	17 / 227 (7.49%)		
occurrences (all)	19		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	11 / 227 (4.85%)		
occurrences (all)	15		
Depression			
subjects affected / exposed	6 / 227 (2.64%)		
occurrences (all)	6		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	35 / 227 (15.42%)		
occurrences (all)	50		
Aspartate aminotransferase increased			
subjects affected / exposed	32 / 227 (14.10%)		
occurrences (all)	49		
Blood creatinine increased			
subjects affected / exposed	21 / 227 (9.25%)		
occurrences (all)	33		
Blood magnesium decreased			
subjects affected / exposed	17 / 227 (7.49%)		
occurrences (all)	19		
Gamma-glutamyltransferase increased			
subjects affected / exposed	25 / 227 (11.01%)		
occurrences (all)	31		
Neutrophil count decreased			
subjects affected / exposed	28 / 227 (12.33%)		
occurrences (all)	45		
Weight decreased			

subjects affected / exposed	20 / 227 (8.81%)		
occurrences (all)	20		
White blood cell count decreased			
subjects affected / exposed	18 / 227 (7.93%)		
occurrences (all)	29		
Blood alkaline phosphatase increased			
subjects affected / exposed	7 / 227 (3.08%)		
occurrences (all)	7		
Blood glucose increased			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences (all)	0		
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
Blood potassium decreased			
subjects affected / exposed	0 / 227 (0.00%)		
occurrences (all)	0		
Blood urea increased			
subjects affected / exposed	9 / 227 (3.96%)		
occurrences (all)	9		
Haemoglobin decreased			
subjects affected / exposed	1 / 227 (0.44%)		
occurrences (all)	1		
Platelet count decreased			
subjects affected / exposed	9 / 227 (3.96%)		
occurrences (all)	20		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	76 / 227 (33.48%)		
occurrences (all)	96		
Leukopenia			
subjects affected / exposed	20 / 227 (8.81%)		
occurrences (all)	50		
Neutropenia			
subjects affected / exposed	83 / 227 (36.56%)		
occurrences (all)	185		

Thrombocytopenia subjects affected / exposed occurrences (all)	13 / 227 (5.73%) 31		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Hiccups subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Dysphonia subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	 29 / 227 (12.78%) 33 34 / 227 (14.98%) 35 8 / 227 (3.52%) 9 20 / 227 (8.81%) 38 4 / 227 (1.76%) 4 6 / 227 (2.64%) 6		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) Lethargy subjects affected / exposed occurrences (all) Neuropathy peripheral	 14 / 227 (6.17%) 15 16 / 227 (7.05%) 17 27 / 227 (11.89%) 32 13 / 227 (5.73%) 21		

subjects affected / exposed	13 / 227 (5.73%)		
occurrences (all)	13		
Paraesthesia			
subjects affected / exposed	20 / 227 (8.81%)		
occurrences (all)	23		
Neurotoxicity			
subjects affected / exposed	8 / 227 (3.52%)		
occurrences (all)	8		
Eye disorders			
Dry eye			
subjects affected / exposed	12 / 227 (5.29%)		
occurrences (all)	12		
Lacrimation increased			
subjects affected / exposed	14 / 227 (6.17%)		
occurrences (all)	14		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	15 / 227 (6.61%)		
occurrences (all)	15		
Hypoacusis			
subjects affected / exposed	7 / 227 (3.08%)		
occurrences (all)	7		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	24 / 227 (10.57%)		
occurrences (all)	31		
Abdominal pain upper			
subjects affected / exposed	14 / 227 (6.17%)		
occurrences (all)	14		
Constipation			
subjects affected / exposed	60 / 227 (26.43%)		
occurrences (all)	81		
Diarrhoea			
subjects affected / exposed	118 / 227 (51.98%)		
occurrences (all)	239		
Dyspepsia			
subjects affected / exposed	14 / 227 (6.17%)		

occurrences (all)	14		
Nausea			
subjects affected / exposed	156 / 227 (68.72%)		
occurrences (all)	274		
Stomatitis			
subjects affected / exposed	22 / 227 (9.69%)		
occurrences (all)	26		
Vomiting			
subjects affected / exposed	96 / 227 (42.29%)		
occurrences (all)	192		
Dry mouth			
subjects affected / exposed	4 / 227 (1.76%)		
occurrences (all)	4		
Haemorrhoids			
subjects affected / exposed	5 / 227 (2.20%)		
occurrences (all)	5		
Gastrooesophageal reflux disease			
subjects affected / exposed	7 / 227 (3.08%)		
occurrences (all)	7		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	12 / 227 (5.29%)		
occurrences (all)	12		
Rash			
subjects affected / exposed	22 / 227 (9.69%)		
occurrences (all)	26		
Dry skin			
subjects affected / exposed	4 / 227 (1.76%)		
occurrences (all)	4		
Pruritus			
subjects affected / exposed	3 / 227 (1.32%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	66 / 227 (29.07%)		
occurrences (all)	97		

Hypokalaemia subjects affected / exposed occurrences (all)	12 / 227 (5.29%) 12		
Hypomagnesaemia subjects affected / exposed occurrences (all)	20 / 227 (8.81%) 27		
Hyponatraemia subjects affected / exposed occurrences (all)	14 / 227 (6.17%) 16		
Hyperglycaemia subjects affected / exposed occurrences (all)	8 / 227 (3.52%) 9		
Dehydration subjects affected / exposed occurrences (all)	4 / 227 (1.76%) 4		
Hypocalcaemia subjects affected / exposed occurrences (all)	4 / 227 (1.76%) 4		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	9 / 227 (3.96%) 10		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	16 / 227 (7.05%) 18		
Urinary tract infection subjects affected / exposed occurrences (all)	12 / 227 (5.29%) 16		
Conjunctivitis subjects affected / exposed occurrences (all)	11 / 227 (4.85%) 11		
Influenza subjects affected / exposed occurrences (all)	5 / 227 (2.20%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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

Notes: