Clinical trial results:
A randomized, placebo-controlled, multi-center phase I/II trial to assess the safety and efficacy of nintedanib (BIBF 1120) added to low-dose cytarabine in elderly patients with AML unfit for an intensive induction therapy

Summary

EudraCT number	2011-001086-41
Trial protocol	DE
Global end of trial date	27 July 2021

Results information

Result version number	v1 (current)
This version publication date	09 August 2022
First version publication date	09 August 2022

Trial information

Trial identification

Sponsor protocol code	UKM10_0014

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01488344
WHO universal trial number (UTN)	U1111-1122-6147

Notes:

Sponsors

Sponsor organisation name	Universitätsklinikum Münster
Sponsor organisation address	Albert-Schweitzer-Campus 1, Münster, Germany, 48149
Public contact	Medizinische Klinik A, Universitätsklinikum Münster, christoph.schliemann@ukmuenster.de
Scientific contact	Medizinische Klinik A, Universitätsklinikum Münster, christoph.schliemann@ukmuenster.de

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	14 July 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 July 2021
Global end of trial reached?	Yes
Global end of trial date	27 July 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective was to evaluate the safety and efficacy of nintedanib added to low-dose cytarabine (LDAC) in a phase 1/2 study in patients 60 years or older with newly diagnosed or relapsed/refractory (r/r) acute myeloid leukemia (AML) ineligible for intensive chemotherapy.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and the ICH Guidelines in Good Clinical Practice. The study was not started before the competent ethics committee had given a favorable opinion. Written informed consent was obtained from all patients and the study was only conducted as approved by the ethics committee and the competent authority. Amendments were only implemented after approval.

Background therapy:

LDAC is used as standard treatment in elderly patients with newly diagnosed or relapsed/refractory AML ineligible for intensive chemotherapy. Patients in this study received the investigational drug nintedanib or placebo in addition to LDAC.

Evidence for comparator:

In phase II, placebo plus LDAC treatment was used as a control to assess the treatment effect of nintedanib plus LDAC.

Actual start date of recruitment	02 April 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 44
Worldwide total number of subjects	44
EEA total number of subjects	44

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)	4
From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited for Phase I of the study between April 2012 and October 2013 at the University Hospital Münster (UKM). For phase II, patients were recruited from eight hospitals throughout Germany between May 2017 and September 2019.

Pre-assignment

Screening details:

The study included patients 60 years or older with newly diagnosed or relapsed/refractory AML ineligible for intensive chemotherapy.

Period 1

Period 1 title	Overall trial (Phase I and Phase II) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase I - 100 mg Nintedanib (DL 1)

Arm description:

Phase I patients in dose level (DL) 1 received 100 mg nintedanib plus LDAC.

Arm type	Experimental
Investigational medicinal product name	Nintedanib
Investigational medicinal product code	
Other name	BIBF1120
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

The patients in DL 1 reveived 100 mg Nintedanib (BIBF1120) orally twice daily for 28 days of a 28-day cycle in combination with low-dose cytarabine (LDAC). LDAC was administered from days 1-10 of of a 28-day cycle at 20 mg twice daily by subcutaneous injection.

Arm title	Phase I - 150 mg Nintedanib (DL 2)

Arm description:

Phase I patients in DL 2 received 150 mg nintedanib plus LDAC.

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:

The patients in DL 2 reveived 150 mg Nintedanib (BIBF1120) orally twice daily for 28 days of a 28-day cycle in combination with LDAC. LDAC was administered from days 1-10 of of a 28-day cycle at 20 mg twice daily by subcutaneous injection.

Arm title	Phase I - 200 mg Nintedanib (DL 3)

Arm description:

Phase I patients in DL 3 received 200 mg nintedanib plus LDAC.

Arm type	Experimental

Investigational medicinal product name	Nintedanib
Investigational medicinal product code	
Other name	BIBF1120
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

The patients in DL 3 reveived 200 mg Nintedanib (BIBF1120) orally twice daily for 28 days of a 28-day cycle in combination with LDAC. LDAC was administered from days 1-10 of of a 28-day cycle at 20 mg twice daily by subcutaneous injection.

Arm title	Phase II - 200 mg Nintedanib

Arm description:

Phase II patients in the experimental arm received 200 mg nintedanib plus LDAC.

Arm type	Experimental
Investigational medicinal product name	Nintedanib
Investigational medicinal product code	
Other name	BIBF1120
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

The patients in this arm received 200 mg Nintedanib (BIBF1120) orally twice daily for 28 days of a 28-day cycle in combination with low-dose cytarabine (LDAC). LDAC was administered from days 1-10 of of a 28-day cycle at 20 mg twice daily by subcutaneous injection.

Arm title	Phase II - Placebo

Arm description:

Phase II patients in the comparator arm received placebo plus LDAC.

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:

The patients in this arm received the placebo orally twice daily for 28 days of a 28- day cycle in combination with low-dose cytarabine (LDAC). LDAC was administered from days 1-10 of of a 28-day cycle at 20 mg twice daily by subcutaneous injection.

Number of subjects in period 1[1]	Phase I - 100 mg Nintedanib (DL 1)	Phase I - 150 mg Nintedanib (DL 2)	Phase I - 200 mg Nintedanib (DL 3)
Started	3	3	6
Completed	1	2	0
Not completed	2	1	6
Consent withdrawn by subject	-	-	3
Relapse	-	-	-
Patient decision	-	-	-
Disease progression	2	-	2
Death	-	-	-

AE / AML progression / death	-	-	-
AE / general physical health deterioration / death	-	-	-
Suspected unexpected serious adverse reaction	-	1	1
AML progression	-	-	-
Consent withdrawn by patient	-	-	-
Adverse event (AE)	-	-	-
AE / consent withdrawn by patient	-	-	-

Number of subjects in period 1[1]	Phase II - 200 mg Nintedanib	Phase II - Placebo
Started	15	15
Completed	0	0
Not completed	15	15
Consent withdrawn by subject	-	-
Relapse	1	2
Patient decision	-	1
Disease progression	-	-
Death	2	2
AE / AML progression / death	-	1
AE / general physical health deterioration / death	1	-
Suspected unexpected serious adverse reaction	-	-
AML progression	7	7
Consent withdrawn by patient	2	1
Adverse event (AE)	1	1
AE / consent withdrawn by patient	1	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: One patient in DL 2 of Phase I did not receive study medication due to death from AML progression shortly after informed consent and was replaced. One randomized patient in Phase II did not receive allocated intervention because the patient withdrew consent immediately after giving consent and before the start of the first cycle.

Baseline characteristics

Reporting groups	
Reporting group title	Phase I - 100 mg Nintedanib (DL 1)
Reporting group description:	
Phase I patients in dose level (DL) 1 received 100 mg nintedanib plus LDAC.	
Reporting group title	Phase I - 150 mg Nintedanib (DL 2)
Reporting group description:	
Phase I patients in DL 2 received 150 mg nintedanib plus LDAC.	
Reporting group title	Phase I - 200 mg Nintedanib (DL 3)
Reporting group description:	
Phase I patients in DL 3 received 200 mg nintedanib plus LDAC.	
Reporting group title	Phase II - 200 mg Nintedanib
Reporting group description:	
Phase II patients in the experimental arm received 200 mg nintedanib plus LDAC.	
Reporting group title	Phase II - Placebo
Reporting group description:	
Phase II patients in the comparator arm received placebo plus LDAC.	

Reporting group values	Phase I - 100 mg Nintedanib (DL 1)	Phase I - 150 mg Nintedanib (DL 2)	Phase I - 200 mg Nintedanib (DL 3)
Number of subjects	3	3	6
Age categorical Units: Subjects			
Adults (18-64 years)	1	1	0
From 65-84 years	2	2	6
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	2	0	4
Male	1	3	2

Reporting group values	Phase II - 200 mg Nintedanib	Phase II - Placebo	Total
Number of subjects	15	15	42
Age categorical Units: Subjects			
Adults (18-64 years)	1	1	4
From 65-84 years	14	14	38
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	8	7	21
Male	7	8	21

End points

End points reporting groups

Reporting group title	Phase I - 100 mg Nintedanib (DL 1)
Reporting group description:	
Phase I patients in dose level (DL) 1 received 100 mg nintedanib plus LDAC.	
Reporting group title	Phase I - 150 mg Nintedanib (DL 2)
Reporting group description:	
Phase I patients in DL 2 received 150 mg nintedanib plus LDAC.	
Reporting group title	Phase I - 200 mg Nintedanib (DL 3)
Reporting group description:	
Phase I patients in DL 3 received 200 mg nintedanib plus LDAC.	
Reporting group title	Phase II - 200 mg Nintedanib
Reporting group description:	
Phase II patients in the experimental arm received 200 mg nintedanib plus LDAC.	
Reporting group title	Phase II - Placebo
Reporting group description:	
Phase II patients in the comparator arm received placebo plus LDAC.	

Primary: Dose limiting toxicities

End point title	Dose limiting toxicities[1][2]

End point description:

Toxicity was assessed by Common Terminology Criteria for Adverse Events (CTCAE) criteria. A dose limiting toxicity (DLT) was defined as every severe adverse reaction CTC grade IV with possible or definite relationship to nintedanib. Designated exceptions for DLT determination included therapy-related cytopenias as signs of an intended anti-leukemic activity and cytopenia-associated complications (neutropenic fever, neutropenic infections, and thrombocytopenic bleedings). However, these complications could constitute a DLT if occurring in an unexpected high frequency. Furthermore, complications such as neutropenic infections, thrombocytopenic bleedings, deterioration of the general condition, laboratory abnormalities, death, tumor lysis syndrome, or organ failure, were also excluded from DLT determination, whenever these were clearly attributable to AML progression in the judgment of the investigator.

End point type	Primary

End point timeframe:

The determination of the maximum tolerated dose (MTD) was based on the occurrence of DLTs in the first treatment cycle.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No analytical statistics were performed to evaluate the safety of the study in phase I.

[2] - 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: The DLTs were only evaluated in phase I.

End point values	Phase I - 100 mg Nintedanib (DL 1)	Phase I - 150 mg Nintedanib (DL 2)	Phase I - 200 mg Nintedanib (DL 3)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	3	6	
Units: dose limiting toxicities (DLTs)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Overall survival

End point title	Overall survival[3]

End point description:

Overall survival (OS) is defined as the time interval from day one of study treatment to the day of death. For a patient who was not known to have died by the end of follow-up, observation of OS was censored on the date the patient was last known to be alive.

End point type	Primary

End point timeframe:

day 1 of study treatment to the day of death.

Notes:

[3] - 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: The OS was only evaluated in phase II.

End point values	Phase II - 200 mg Nintedanib	Phase II - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: month				
median (confidence interval 95%)	3.4 (2.3 to 8.8)	3.6 (2.1 to 99999)		

Statistical analyses

Statistical analysis title	primary endpoint (OS)

Statistical analysis description:

The OS was compared between both treatment arms (ITT) by calculating a 95% confidence interval for the hazard ratio by using a Cox-regression with treatment arm and AML status (newly diagnosed vs. r/r) as independent variables. No noticeable difference in OS between the treatment arms could be detected. The corresponding HR for nintedanib vs placebo was 1.19 and the adjusted confirmatory 95% CI was 0.55-2.56.

Comparison groups	Phase II - 200 mg Nintedanib v Phase II - Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.96 [4]
Method	Logrank

Notes:

[4] - The non-stratified univariate comparison of OS between both treatment arms resulted in a HR of 1.02 (95% CI 0.48-2.15, univariate logrank test p=0.96).

Secondary: Overall survival (r/r AML)

End point title	Overall survival (r/r AML)[5]

End point description:

Comparison of OS in patients with relapsed or refractory (r/r) AML.

End point type	Secondary

End point timeframe:

day 1 of study treatment to the day of death.

Notes:

[5] - 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: The OS was only evaluated in phase II.

End point values	Phase II - 200 mg Nintedanib	Phase II - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: month				
median (confidence interval 95%)	3.0 (1.6 to 99999)	3.6 (2.1 to 99999)		

Statistical analyses

Statistical analysis title	secondary endpoint (OS - r/r AML)

Statistical analysis description:

In the 22 patients enrolled into the phase II part of the study with r/r AML, median OS was 3.0 months in the nintedanib arm and 3.6 months in the placebo arm (HR 1.54, 95% CI, 0.61-3.86; logrank P = 0.36).

Comparison groups	Phase II - 200 mg Nintedanib v Phase II - Placebo
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36
Method	Logrank

Secondary: Overall survival (newly diagnosed AML)

End point title	Overall survival (newly diagnosed AML)[6]

End point description:

Comparison of OS in patients with newly diagnosed AML.

End point type	Secondary

End point timeframe:

day 1 of study treatment to the day of death.

Notes:

[6] - 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: The OS was only evaluated in phase II.

End point values	Phase II - 200 mg Nintedanib	Phase II - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: month				
median (confidence interval 95%)	8.2 (5.9 to 99999)	5.6 (2.1 to 99999)		

Statistical analyses

Statistical analysis title	secondary endpoint (OS - newly diagnosed AML)

Statistical analysis description:

No noticeable difference in OS in the subgroup of patients with newly diagnosed AML could be detected between the two treatment arms. Median OS was 8.2 months in the nintedanib arm and 5.6 months in the placebo arm (HR 0.55, 95% CI, 0.12-2.51; logrank P = 0.44).

Comparison groups	Phase II - 200 mg Nintedanib v Phase II - Placebo
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.44
Method	Logrank

Secondary: Overall response rate

End point title	Overall response rate[7]

End point description:

The overall response rate (ORR) is defined as proportion of patients who achieve either a complete remission (CR), a complete remission with incomplete platelet recovery (CRp) or a complete remission with incomplete neutrophil recovery (CRi).

End point type	Secondary

End point timeframe:

Any time point during study participation.

Notes:

[7] - 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: The ORR was only evaluated in phase II.

End point values	Phase II - 200 mg Nintedanib	Phase II - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: Patients	1	2		

Statistical analyses

Statistical analysis title	secondary endpoint (ORR)

Statistical analysis description:

Three patients reached an overall response. Using a competing risk approach to compare the cumulative

incidence with death to treatment discontinuation without prior overall response (nintedanib n=3, placebo n=3) as a competing event, the Gray's k-sample test p-value for ORR was p=0.743. Because of the small number of responses, the estimates of the subdistribution and cause-specific hazard ratios are not reported here, and the Gray’s k-sample p-values cannot be reasonably interpreted.

Comparison groups	Phase II - 200 mg Nintedanib v Phase II - Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.743
Method	Gray's k-sample test

Secondary: Complete remission

End point title	Complete remission[8]

End point description:

Patients who have achieved a complete remission (CR).

End point type	Secondary

End point timeframe:

Any time point during study participation.

Notes:

[8] - 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: The CR was only evaluated in phase II.

End point values	Phase II - 200 mg Nintedanib	Phase II - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: Patients	1	2		

Statistical analyses

Statistical analysis title	secondary endpoint (CR)

Statistical analysis description:

All three responders achieved a CR. Using a competing risk approach to compare the cumulative incidence with death to treatment discontinuation without prior overall response (nintedanib n=3, placebo n=3) as a competing event, the Gray's k-sample test p-value for CR was p=0.743. Because of the small number of responses, the estimates of the subdistribution and cause-specific hazard ratios are not reported here, and the Gray’s k-sample p-values cannot be reasonably interpreted.

Comparison groups	Phase II - 200 mg Nintedanib v Phase II - Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.743
Method	Gray's k-sample test

Secondary: Relapse-free survival

End point title	Relapse-free survival[9]

End point description:

Relapse-free survival (RFS) is defined as the time interval from the first day a patient achieved CR / CRi / CRp until relapse or death from any course, whatever occurs first. For a patient who was not known to have died or had relapsed by the end of follow-up, observation of RFS was censored on the date the patient was last known to be alive and in CR.

End point type	Secondary

End point timeframe:

first day of CR / CRi / CRp until relapse or death from any course.

Notes:

[9] - 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: The RFS was only evaluated in phase II.

End point values	Phase II - 200 mg Nintedanib	Phase II - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	2		
Units: Patients	1	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from the time of signing the informed consent until 28 days after last protocol treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Safety group: Phase I - 100 mg Nintedanib (DL 1)

Reporting group description:

Study patients who received at least one dose of nintedanib in DL 1 of Phase I.

Reporting group title	Safety group: Phase I - 150 mg Nintedanib (DL 2)

Reporting group description:

Study patients who received at least one dose of nintedanib in DL 2 of Phase I.

Reporting group title	Safety group: Phase I - 200 mg Nintedanib (DL 3)

Reporting group description:

Study patients who received at least one dose of nintedanib in DL 3 of Phase I.

Reporting group title	Safety group: Phase II - 200 mg Nintedanib

Reporting group description:

Study patients who received at least one dose of nintedanib in Phase II.

Reporting group title	Safety group: Phase II - Placebo

Reporting group description:

Study patients who received at least one dose of placebo in Phase II.

Serious adverse events	Safety group: Phase I - 100 mg Nintedanib (DL 1)	Safety group: Phase I - 150 mg Nintedanib (DL 2)	Safety group: Phase I - 200 mg Nintedanib (DL 3)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	3 / 3 (100.00%)	5 / 6 (83.33%)
number of deaths (all causes)	3	3	6
number of deaths resulting from adverse events	0	1	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Vascular disorders			
Circulatory collapse			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Haematoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Orthostatic hypotension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Pyrexia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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

Investigations			
General physical condition decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Haemoglobin decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Injury, poisoning and procedural complications			
Refractoriness to platelet transfusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Transfusion related complication			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
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 failure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Febrile neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 3 (66.67%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fissure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
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			
Renal failure acute			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Febrile infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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 infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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			
Hypercalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (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

Serious adverse events	Safety group: Phase II - 200 mg Nintedanib	Safety group: Phase II - Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 15 (60.00%)	12 / 15 (80.00%)	
number of deaths (all causes)	14	14	
number of deaths resulting from adverse events	3	6	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease progression			

subjects affected / exposed	0 / 15 (0.00%)	2 / 15 (13.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Fatigue			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 15 (0.00%)	2 / 15 (13.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
General physical condition decreased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Refractoriness to platelet transfusion			

subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion related complication			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 15 (13.33%)	5 / 15 (33.33%)	
occurrences causally related to treatment / all	0 / 5	2 / 7	
deaths causally related to treatment / all	0 / 1	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pancytopenia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Febrile infection			

subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 15 (13.33%)	2 / 15 (13.33%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Sepsis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Safety group: Phase I - 100 mg Nintedanib (DL 1)	Safety group: Phase I - 150 mg Nintedanib (DL 2)	Safety group: Phase I - 200 mg Nintedanib (DL 3)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	3 / 3 (100.00%)	6 / 6 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bone neoplasm			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Intra-abdominal haematoma			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Peripheral coldness			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Phlebitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Thrombophlebitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	1 / 6 (16.67%)
occurrences (all)	2	1	1

Chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Chills			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Injection site reaction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Mucosal inflammation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oedema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	2 / 6 (33.33%)
occurrences (all)	2	1	2
Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Peripheral swelling			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	2 / 6 (33.33%)
occurrences (all)	0	2	2
Immune system disorders			
Conjunctivitis			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Breast swelling			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pelvic pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blister			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 6 (50.00%)
occurrences (all)	0	0	3
Dyspnoea exertional			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	2	1	0
Haemoptysis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pharyngeal erythema			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Rhinorrhoea			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Psychiatric disorders			
Disorientation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Restlessness			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	2 / 6 (33.33%)
occurrences (all)	1	1	2
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Blood bilirubin increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Blood creatinine increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Blood urea increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Blood uric acid increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Heart rate irregular			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Liver function test increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oxygen saturation decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Transaminases increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Burns second degree			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Joint injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Periorbital haematoma			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Thermal burn			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Sinus tachycardia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Tachycardia paroxysmal			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dysgeusia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Hypotonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Paraesthesia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Tremor			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lymphadenitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lymph node pain			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Atrial flutter			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vestibular disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Abdominal pain upper			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Anal fissure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Aphthous ulcer			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	3	0	1
Diarrhoea			

subjects affected / exposed	0 / 3 (0.00%)	2 / 3 (66.67%)	5 / 6 (83.33%)
occurrences (all)	0	5	8
Dry mouth			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	0
Dysphagia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eructation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Faeces hard			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gingival bleeding			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Haematochezia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Mouth haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	2 / 6 (33.33%)
occurrences (all)	0	1	2
Mouth ulceration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	3 / 6 (50.00%)
occurrences (all)	3	1	5
Oral mucosal erythema			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Oral pain			

subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Proctalgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Rectal haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Stomatitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	3 / 6 (50.00%)
occurrences (all)	2	3	5
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Purpura			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Skin ulcer			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	3
Back pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 6 (33.33%)
occurrences (all)	1	0	2
Chest wall haematoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Flank pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Joint swelling			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Abscess soft tissue			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Bacterial disease carrier			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Device related infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Enterococcal infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fungal skin infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Herpes simplex			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lip infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lung infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Oral candidiasis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oral herpes			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Paronychia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pathogen resistance			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pelvic infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Soft tissue infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vaginal infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Appetite disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Decreased appetite			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	3 / 6 (50.00%)
occurrences (all)	1	0	3
Dehydration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hyperuricaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Safety group: Phase II - 200 mg Nintedanib	Safety group: Phase II - Placebo	
Total subjects affected by non-serious			

adverse events subjects affected / exposed	14 / 15 (93.33%)	14 / 15 (93.33%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Bone neoplasm subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	
Vascular disorders Haematoma subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 15 (0.00%) 0	
Hypertension subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 15 (0.00%) 0	
Hypotension subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	
Intra-abdominal haematoma subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	
Peripheral coldness subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	
Phlebitis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	
Thrombophlebitis subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 15 (0.00%) 0	
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	
Chest pain subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	
Chills			

subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Fatigue			
subjects affected / exposed	4 / 15 (26.67%)	2 / 15 (13.33%)	
occurrences (all)	5	4	
Injection site reaction			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Mucosal inflammation			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	2	2	
Non-cardiac chest pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Oedema			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Oedema peripheral			
subjects affected / exposed	1 / 15 (6.67%)	2 / 15 (13.33%)	
occurrences (all)	1	3	
Pain			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
Peripheral swelling			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	2 / 15 (13.33%)	2 / 15 (13.33%)	
occurrences (all)	5	2	
Immune system disorders			
Conjunctivitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			

Breast swelling			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Pelvic pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Blister			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 15 (6.67%)	3 / 15 (20.00%)	
occurrences (all)	1	3	
Dyspnoea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Dyspnoea exertional			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Epistaxis			
subjects affected / exposed	1 / 15 (6.67%)	3 / 15 (20.00%)	
occurrences (all)	1	3	
Haemoptysis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Pharyngeal erythema			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Rhinorrhoea			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Dry skin			

subjects affected / exposed	0 / 15 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Psychiatric disorders			
Disorientation			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Insomnia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Restlessness			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Blood bilirubin increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Blood creatinine increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Blood urea increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Blood uric acid increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Heart rate irregular			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Liver function test increased			

subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Oxygen saturation decreased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Transaminases increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Weight decreased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Burns second degree			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Joint injury			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Periorbital haematoma			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Thermal burn			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Sinus tachycardia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Tachycardia			

subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Tachycardia paroxysmal			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Dysgeusia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	0 / 15 (0.00%)	3 / 15 (20.00%)	
occurrences (all)	0	7	
Hypotonia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Paraesthesia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Tremor			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Lymphadenitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Lymph node pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Thrombocytopenia			

subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Atrial flutter			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
Vestibular disorder			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Abdominal pain			
subjects affected / exposed	2 / 15 (13.33%)	2 / 15 (13.33%)	
occurrences (all)	2	2	
Abdominal pain upper			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Anal fissure			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Aphthous ulcer			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Constipation			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
Diarrhoea			
subjects affected / exposed	7 / 15 (46.67%)	5 / 15 (33.33%)	
occurrences (all)	39	8	
Dry mouth			

subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Dysphagia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Eructation			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Faeces hard			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	2	
Flatulence			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	2	
Gingival bleeding			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Haematochezia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Mouth haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Mouth ulceration			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	6 / 15 (40.00%)	4 / 15 (26.67%)	
occurrences (all)	29	8	
Oral mucosal erythema			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Oral pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Proctalgia			

subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Rectal haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Stomatitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	8 / 15 (53.33%)	0 / 15 (0.00%)	
occurrences (all)	10	0	
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Purpura			
subjects affected / exposed	2 / 15 (13.33%)	1 / 15 (6.67%)	
occurrences (all)	3	1	
Rash			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Skin ulcer			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Pollakiuria			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Back pain			

subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Chest wall haematoma			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Flank pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Joint swelling			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Muscle spasms			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Muscular weakness			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Myalgia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	0 / 15 (0.00%)	3 / 15 (20.00%)	
occurrences (all)	0	3	
Infections and infestations			
Abscess soft tissue			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Bacterial disease carrier			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	

Device related infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	2	
Enterococcal infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Fungal skin infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Herpes simplex			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Infection			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Lip infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Lung infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Oral candidiasis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Oral herpes			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Paronychia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Pathogen resistance			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	

Pelvic infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Soft tissue infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Urinary tract infection			
subjects affected / exposed	1 / 15 (6.67%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
Vaginal infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Appetite disorder			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Decreased appetite			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Dehydration			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Hyperglycaemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Hyperuricaemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 March 2013	Protocol amendment 1 was done in response to a new IB for nintedanib from Boehringer Ingelheim (version 12). Changes were made to the inclusion/exclusion criteria to take into account the risk for hollow organ perforation upon therapy with nintedanib, among other minor changes to the protocol and clarifications.
28 September 2016	After the completion of Phase I and before the start of Phase II, the protocol was amended. The study design for phase II was changed to a double-blind, placebo-controlled study part. Patients should be randomized 1:1 to receive either LDAC plus nintedanib or LDAC plus placebo with overall survival rather than CR rate as the primary endpoint. Prof. Utz Krug was in phase I the coordinating investigator of the study. He was replaced by Prof. Christoph Schliemann before the start of phase II.

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 total, only 30 randomized patients were analyzed in the full-analysis set. The initial sample size of 100 patients was not reached due to discontinuation of recruitment due to new drugs for this disease and slow recruitment.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27716819