

**Clinical trial results:**

A multicentre, open label, Phase I/randomised Phase II study to evaluate safety, pharmacokinetics and efficacy of BIBF 1120 in comparison with sorafenib for advanced hepatocellular carcinoma patients

Summary

EudraCT number	2009-011925-14
Trial protocol	GB AT DE SK HU NL
Global end of trial date	12 October 2016

Results information

Result version number	v2 (current)
This version publication date	14 November 2021
First version publication date	14 October 2017
Version creation reason	

Trial information**Trial identification**

Sponsor protocol code	1199.37
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01004003
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 8002430127, clintrriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 8002430127, clintrriage.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	28 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 July 2014
Global end of trial reached?	Yes
Global end of trial date	12 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase I part: To evaluate safety, maximum tolerated dose (MTD) and pharmacokinetics (PK) of nintedanib in patients with hepatocellular carcinoma (HCC).

Phase II part: To evaluate the efficacy and safety of nintedanib in patients with HCC without prior systemic treatment compared with sorafenib.

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. If a subject continued to take trial medication, close monitoring was adhered to and all adverse events recorded. Rules were implemented in all trials whereby doses would be reduced if required. Thereafter, if further events were reported, the subject would be withdrawn from the trial. Symptomatic treatment of tumour associated symptoms were allowed throughout.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 October 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 18
Country: Number of subjects enrolled	Germany: 25
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Poland: 13
Country: Number of subjects enrolled	Romania: 8
Country: Number of subjects enrolled	United Kingdom: 92
Worldwide total number of subjects	170
EEA total number of subjects	78

Notes:

Subjects enrolled per age group

In utero	0
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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)	78
From 65 to 84 years	89
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that they (the subjects) met all inclusion/exclusion criteria. Subjects were not to be enrolled if any one of the specific entry criteria were violated.

Period 1

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

Blinding implementation details:

Phase I is the uncontrolled dose escalation design and Phase II is the randomised, active controlled and parallel group design.

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1 Group 1, 100mg Nintedanib Bid

Arm description:

Oral administration of Nintedanib (BIBF 1120) 100 mg soft gelatine capsules twice daily (bid). Phase I: A standard 3+3 dose escalation part to determine the maximal tolerated dose (MTD). Group 1 patients had a baseline Child-Pugh score of 5 or 6, and AST (aspartate aminotransferase) and ALT (alanine transaminase) ≤ 2 times the upper limit of normal (ULN).

Arm type	Experimental
Investigational medicinal product name	Nintedanib 100mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Oral administration of Nintedanib (BIBF 1120) 100 mg soft gelatine capsules twice daily (bid).

Arm title	Phase I Group 1, 150mg Nintedanib Bid
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Arm description:

Oral administration of Nintedanib (BIBF 1120) 150 mg soft gelatine capsules twice daily (bid). Phase I: A standard 3+3 dose escalation part to determine the MTD. Group 1 patients had a baseline Child-Pugh score of 5 or 6, and AST and ALT ≤ 2 times the upper limit of normal (ULN).

Arm type	Experimental
Investigational medicinal product name	Nintedanib 150 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Oral administration of Nintedanib (BIBF 1120) 150 mg soft gelatine capsules twice daily (bid).

Arm title	Phase I Group 1, 200mg Nintedanib Bid
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Arm description:

Oral administration of Nintedanib (BIBF 1120) 200 mg soft gelatine capsules (two capsules of 100mg) twice daily (bid). Phase I: A standard 3+3 dose escalation part to determine the MTD. Group 1 patients had a baseline Child-Pugh score of 5 or 6, and AST and ALT ≤ 2 times the upper limit of normal (ULN).

Arm type	Experimental
Investigational medicinal product name	Nintedanib 200 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Oral administration of Nintedanib (BIBF 1120) 200 mg soft gelatine capsules (two capsules of 100mg) twice daily (bid).

Arm title	Phase I Group 2, 50mg Nintedanib Bid
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Arm description:

Oral administration of Nintedanib (BIBF 1120) 50 mg soft gelatine capsules twice daily (bid). Phase I: A standard 3+3 dose escalation part to determine the MTD. Group 2 patients had a baseline Child-Pugh score of 7, or AST or ALT >2 to ≤5 times ULN.

Arm type	Experimental
Investigational medicinal product name	Nintedanib 50 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Oral administration of Nintedanib (BIBF 1120) 50 mg soft gelatine capsules twice daily (bid).

Arm title	Phase I Group 2, 100mg Nintedanib Bid
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Arm description:

Oral administration of Nintedanib (BIBF 1120) 100 mg soft gelatine capsules twice daily (bid). Phase I: A standard 3+3 dose escalation part to determine the MTD. Group 2 patients had a baseline Child-Pugh score of 7, or AST or ALT >2 to ≤5 times ULN.

Arm type	Experimental
Investigational medicinal product name	Nintedanib 100mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Oral administration of Nintedanib (BIBF 1120) 100 mg soft gelatine capsules twice daily (bid).

Arm title	Phase I Group 2, 150mg Nintedanib Bid
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Arm description:

Oral administration of Nintedanib (BIBF 1120) 150 mg soft gelatine capsules twice daily (bid). Phase I: A standard 3+3 dose escalation part to determine the MTD. Group 2 patients had a baseline Child-Pugh score of 7, or AST or ALT >2 to ≤5 times ULN.

Arm type	Experimental
Investigational medicinal product name	Nintedanib 150mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Oral administration of Nintedanib (BIBF 1120) 150 mg soft gelatine capsules twice daily (bid).

Arm title	Phase I Group 2, 200mg Nintedanib Bid
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Arm description:

Oral administration of Nintedanib (BIBF 1120) 200 mg soft gelatine capsules (two capsules of 100mg) twice daily (bid). Phase I: A standard 3+3 dose escalation part to determine the MTD. Group 2 patients

had a baseline Child-Pugh score of 7, or AST or ALT >2 to ≤5 times ULN.

Arm type	Experimental
Investigational medicinal product name	Nintedanib 200mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Oral administration of Nintedanib (BIBF 1120) 200 mg soft gelatine capsules (two capsules of 100mg) twice daily (bid).

Arm title	Phase II, 200 mg Nintedanib Bid
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Arm description:

Oral administration of Nintedanib (BIBF 1120) 200 mg soft gelatine capsules (two capsules of 100mg) twice daily (bid). Phase II: Patients were randomly assigned to open-label treatment with nintedanib or sorafenib. Patients were stratified for macrovascular invasion (MVI) and/or extra-hepatic spread (EHS). Patients had a baseline Child-Pugh score of 5 or 6, and AST and ALT ≤2 times the upper limit of normal (ULN).

Arm type	Experimental
Investigational medicinal product name	Nintedanib 200mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Oral administration of Nintedanib (BIBF 1120) 200 mg soft gelatine capsules (two capsules of 100mg) twice daily (bid).

Arm title	Phase II, 400 mg Sorafenib Bid
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Arm description:

Oral administration of Sorafenib 400 mg film coated tablets twice daily (bid). Phase II: Patients were randomly assigned to open-label treatment with nintedanib or sorafenib. Patients were stratified for macrovascular invasion (MVI) and/or extra-hepatic spread (EHS). Patients had a baseline Child-Pugh score of 5 or 6, and AST and ALT ≤2 times the upper limit of normal (ULN).

Arm type	Active comparator
Investigational medicinal product name	Sorafenib 400mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Oral administration of Sorafenib 400 mg film coated tablets twice daily (bid).

Number of subjects in period 1^[1]	Phase 1 Group 1, 100mg Nintedanib Bid	Phase I Group 1, 150mg Nintedanib Bid	Phase I Group 1, 200mg Nintedanib Bid
Started	6	3	4
Completed	0	0	0
Not completed	6	3	4
Adverse event, non-fatal	4	2	3
Refused to continue taking trial med.	-	-	-
Unknown	-	-	-

Progressive disease	2	1	1
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Number of subjects in period 1 ^[1]	Phase I Group 2, 50mg Nintedanib Bid	Phase I Group 2, 100mg Nintedanib Bid	Phase I Group 2, 150mg Nintedanib Bid
	Started	3	4
Completed	0	0	0
Not completed	3	4	4
Adverse event, non-fatal	3	2	2
Refused to continue taking trial med.	-	-	-
Unknown	-	-	1
Progressive disease	-	2	1

Number of subjects in period 1 ^[1]	Phase I Group 2, 200mg Nintedanib Bid	Phase II, 200 mg Nintedanib Bid	Phase II, 400 mg Sorafenib Bid
	Started	8	62
Completed	0	2	1
Not completed	8	60	30
Adverse event, non-fatal	7	21	6
Refused to continue taking trial med.	-	-	2
Unknown	-	-	-
Progressive disease	1	39	22

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: Not all enrolled subjects were randomized in the baseline period.

Baseline characteristics

Reporting groups

Reporting group title	Phase 1 Group 1, 100mg Nintedanib Bid
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Reporting group description:

Oral administration of Nintedanib (BIBF 1120) 100 mg soft gelatine capsules twice daily (bid). Phase I: A standard 3+3 dose escalation part to determine the maximal tolerated dose (MTD). Group 1 patients had a baseline Child-Pugh score of 5 or 6, and AST (aspartate aminotransferase) and ALT (alanine transaminase) ≤ 2 times the upper limit of normal (ULN).

Reporting group title	Phase I Group 1, 150mg Nintedanib Bid
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Reporting group description:

Oral administration of Nintedanib (BIBF 1120) 150 mg soft gelatine capsules twice daily (bid). Phase I: A standard 3+3 dose escalation part to determine the MTD. Group 1 patients had a baseline Child-Pugh score of 5 or 6, and AST and ALT ≤ 2 times the upper limit of normal (ULN).

Reporting group title	Phase I Group 1, 200mg Nintedanib Bid
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Reporting group description:

Oral administration of Nintedanib (BIBF 1120) 200 mg soft gelatine capsules (two capsules of 100mg) twice daily (bid). Phase I: A standard 3+3 dose escalation part to determine the MTD. Group 1 patients had a baseline Child-Pugh score of 5 or 6, and AST and ALT ≤ 2 times the upper limit of normal (ULN).

Reporting group title	Phase I Group 2, 50mg Nintedanib Bid
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Reporting group description:

Oral administration of Nintedanib (BIBF 1120) 50 mg soft gelatine capsules twice daily (bid). Phase I: A standard 3+3 dose escalation part to determine the MTD. Group 2 patients had a baseline Child-Pugh score of 7, or AST or ALT > 2 to ≤ 5 times ULN.

Reporting group title	Phase I Group 2, 100mg Nintedanib Bid
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Reporting group description:

Oral administration of Nintedanib (BIBF 1120) 100 mg soft gelatine capsules twice daily (bid). Phase I: A standard 3+3 dose escalation part to determine the MTD. Group 2 patients had a baseline Child-Pugh score of 7, or AST or ALT > 2 to ≤ 5 times ULN.

Reporting group title	Phase I Group 2, 150mg Nintedanib Bid
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Reporting group description:

Oral administration of Nintedanib (BIBF 1120) 150 mg soft gelatine capsules twice daily (bid). Phase I: A standard 3+3 dose escalation part to determine the MTD. Group 2 patients had a baseline Child-Pugh score of 7, or AST or ALT > 2 to ≤ 5 times ULN.

Reporting group title	Phase I Group 2, 200mg Nintedanib Bid
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Reporting group description:

Oral administration of Nintedanib (BIBF 1120) 200 mg soft gelatine capsules (two capsules of 100mg) twice daily (bid). Phase I: A standard 3+3 dose escalation part to determine the MTD. Group 2 patients had a baseline Child-Pugh score of 7, or AST or ALT > 2 to ≤ 5 times ULN.

Reporting group title	Phase II, 200 mg Nintedanib Bid
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Reporting group description:

Oral administration of Nintedanib (BIBF 1120) 200 mg soft gelatine capsules (two capsules of 100mg) twice daily (bid). Phase II: Patients were randomly assigned to open-label treatment with nintedanib or sorafenib. Patients were stratified for macrovascular invasion (MVI) and/or extra-hepatic spread (EHS). Patients had a baseline Child-Pugh score of 5 or 6, and AST and ALT ≤ 2 times the upper limit of normal (ULN).

Reporting group title	Phase II, 400 mg Sorafenib Bid
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Reporting group description:

Oral administration of Sorafenib 400 mg film coated tablets twice daily (bid). Phase II: Patients were randomly assigned to open-label treatment with nintedanib or sorafenib. Patients were stratified for macrovascular invasion (MVI) and/or extra-hepatic spread (EHS). Patients had a baseline Child-Pugh score of 5 or 6, and AST and ALT ≤ 2 times the upper limit of normal (ULN).

Reporting group values	Phase 1 Group 1, 100mg Nintedanib Bid	Phase I Group 1, 150mg Nintedanib Bid	Phase I Group 1, 200mg Nintedanib Bid
Number of subjects	6	3	4
Age categorical Units: Subjects			

Age Continuous			
Treated set:Treated set which included all patients who received at least one single dose of trial medication.			
Units: years			
arithmetic mean	69.7	65.0	66.5
standard deviation	± 6.8	± 7.8	± 4.0
Gender, Male/Female Units: Subjects			
Female	1	1	0
Male	5	2	4

Reporting group values	Phase I Group 2, 50mg Nintedanib Bid	Phase I Group 2, 100mg Nintedanib Bid	Phase I Group 2, 150mg Nintedanib Bid
Number of subjects	3	4	4
Age categorical Units: Subjects			

Age Continuous			
Treated set:Treated set which included all patients who received at least one single dose of trial medication.			
Units: years			
arithmetic mean	72.3	56.3	59.3
standard deviation	± 11.7	± 6.4	± 13.9
Gender, Male/Female Units: Subjects			
Female	0	0	1
Male	3	4	3

Reporting group values	Phase I Group 2, 200mg Nintedanib Bid	Phase II, 200 mg Nintedanib Bid	Phase II, 400 mg Sorafenib Bid
Number of subjects	8	62	31
Age categorical Units: Subjects			

Age Continuous			
Treated set:Treated set which included all patients who received at least one single dose of trial medication.			
Units: years			
arithmetic mean	57.0	65.4	63.1
standard deviation	± 11.0	± 10.0	± 11.8
Gender, Male/Female Units: Subjects			
Female	2	14	5
Male	6	48	26

Reporting group values	Total		
Number of subjects	125		
Age categorical Units: Subjects			
Age Continuous			
Treated set:Treated set which included all patients who received at least one single dose of trial medication.			
Units: years arithmetic mean standard deviation	-		
Gender, Male/Female Units: Subjects			
Female	24		
Male	101		

End points

End points reporting groups

Reporting group title	Phase 1 Group 1, 100mg Nintedanib Bid
Reporting group description: Oral administration of Nintedanib (BIBF 1120) 100 mg soft gelatine capsules twice daily (bid). Phase I: A standard 3+3 dose escalation part to determine the maximal tolerated dose (MTD). Group 1 patients had a baseline Child-Pugh score of 5 or 6, and AST (aspartate aminotransferase) and ALT (alanine transaminase) ≤ 2 times the upper limit of normal (ULN).	
Reporting group title	Phase I Group 1, 150mg Nintedanib Bid
Reporting group description: Oral administration of Nintedanib (BIBF 1120) 150 mg soft gelatine capsules twice daily (bid). Phase I: A standard 3+3 dose escalation part to determine the MTD. Group 1 patients had a baseline Child-Pugh score of 5 or 6, and AST and ALT ≤ 2 times the upper limit of normal (ULN).	
Reporting group title	Phase I Group 1, 200mg Nintedanib Bid
Reporting group description: Oral administration of Nintedanib (BIBF 1120) 200 mg soft gelatine capsules (two capsules of 100mg) twice daily (bid). Phase I: A standard 3+3 dose escalation part to determine the MTD. Group 1 patients had a baseline Child-Pugh score of 5 or 6, and AST and ALT ≤ 2 times the upper limit of normal (ULN).	
Reporting group title	Phase I Group 2, 50mg Nintedanib Bid
Reporting group description: Oral administration of Nintedanib (BIBF 1120) 50 mg soft gelatine capsules twice daily (bid). Phase I: A standard 3+3 dose escalation part to determine the MTD. Group 2 patients had a baseline Child-Pugh score of 7, or AST or ALT > 2 to ≤ 5 times ULN.	
Reporting group title	Phase I Group 2, 100mg Nintedanib Bid
Reporting group description: Oral administration of Nintedanib (BIBF 1120) 100 mg soft gelatine capsules twice daily (bid). Phase I: A standard 3+3 dose escalation part to determine the MTD. Group 2 patients had a baseline Child-Pugh score of 7, or AST or ALT > 2 to ≤ 5 times ULN.	
Reporting group title	Phase I Group 2, 150mg Nintedanib Bid
Reporting group description: Oral administration of Nintedanib (BIBF 1120) 150 mg soft gelatine capsules twice daily (bid). Phase I: A standard 3+3 dose escalation part to determine the MTD. Group 2 patients had a baseline Child-Pugh score of 7, or AST or ALT > 2 to ≤ 5 times ULN.	
Reporting group title	Phase I Group 2, 200mg Nintedanib Bid
Reporting group description: Oral administration of Nintedanib (BIBF 1120) 200 mg soft gelatine capsules (two capsules of 100mg) twice daily (bid). Phase I: A standard 3+3 dose escalation part to determine the MTD. Group 2 patients had a baseline Child-Pugh score of 7, or AST or ALT > 2 to ≤ 5 times ULN.	
Reporting group title	Phase II, 200 mg Nintedanib Bid
Reporting group description: Oral administration of Nintedanib (BIBF 1120) 200 mg soft gelatine capsules (two capsules of 100mg) twice daily (bid). Phase II: Patients were randomly assigned to open-label treatment with nintedanib or sorafenib. Patients were stratified for macrovascular invasion (MVI) and/or extra-hepatic spread (EHS). Patients had a baseline Child-Pugh score of 5 or 6, and AST and ALT ≤ 2 times the upper limit of normal (ULN).	
Reporting group title	Phase II, 400 mg Sorafenib Bid
Reporting group description: Oral administration of Sorafenib 400 mg film coated tablets twice daily (bid). Phase II: Patients were randomly assigned to open-label treatment with nintedanib or sorafenib. Patients were stratified for macrovascular invasion (MVI) and/or extra-hepatic spread (EHS). Patients had a baseline Child-Pugh score of 5 or 6, and AST and ALT ≤ 2 times the upper limit of normal (ULN).	
Subject analysis set title	Group 1
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients had a baseline Child-Pugh score of 5 or 6, and AST and ALT ≤ 2 times the upper limit of normal (ULN).	

Intent to treat is actually Treated Set.

Subject analysis set title	Group 2
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients had a baseline Child-Pugh score of 7, or AST or ALT >2 to ≤5 times ULN.
Intent to treat is actually Treated Set.

Primary: Maximum Tolerated Dose in Phase I

End point title	Maximum Tolerated Dose in Phase I ^[1]
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End point description:

The MTD was defined as the highest dose studied for which the incidence of DLTs was 0/3 or less than 2/6 patients during the first treatment course.

Treated set (TS): The set which included all patients who received at least one single dose of trial medication, including phase I patients from the dose escalation part that were not replaced for MTD determination.

End point type	Primary
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End point timeframe:

4 weeks

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: The endpoint was only planned to be analyzed descriptively.

End point values	Group 1	Group 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9 ^[2]	13 ^[3]		
Units: mg bid	200	200		

Notes:

[2] - TS

[3] - TS

Statistical analyses

No statistical analyses for this end point

Primary: Time to Progression (TTP) in Phase II

End point title	Time to Progression (TTP) in Phase II ^[4]
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End point description:

TTP according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.0 criteria based on central independent review. TTP RECIST 1.0 was defined as the time from randomisation to disease progression according to RECIST 1.0.

End point type	Primary
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End point timeframe:

From randomization until data cut-off (15 July 2014); Up to 1031 days

Notes:

[4] - 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 Phase II subjects were analyzed in this endpoint.

End point values	Phase II, 200 mg Nintedanib Bid	Phase II, 400 mg Sorafenib Bid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62 ^[5]	31 ^[6]		
Units: months				
median (inter-quartile range (Q1-Q3))	5.45 (2.69 to 9.20)	4.63 (2.79 to 20.40)		

Notes:

[5] - Treated set, only phase II participants.

[6] - Treated set, only phase II participants.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Phase II, 200 mg Nintedanib Bid v Phase II, 400 mg Sorafenib Bid
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.437
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.805
upper limit	2.565

Secondary: Incidence of Dose Limiting Toxicity in Phase I

End point title	Incidence of Dose Limiting Toxicity in Phase I ^[7]
End point description:	
Number of patients with dose limiting toxicity are presented	
End point type	Secondary
End point timeframe:	
4 weeks	

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: Only Phase I subjects were analyzed in this endpoint.

End point values	Phase 1 Group 1, 100mg Nintedanib Bid	Phase I Group 1, 150mg Nintedanib Bid	Phase I Group 1, 200mg Nintedanib Bid	Phase I Group 2, 50mg Nintedanib Bid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3 ^[8]	3 ^[9]	3 ^[10]	3 ^[11]
Units: participants	0	0	0	0

Notes:

[8] - TS (Phase I patients from the dose escalation part that were not replaced for MTD determination).

[9] - TS (Phase I patients from the dose escalation part that were not replaced for MTD determination).

[10] - TS (Phase I patients from the dose escalation part that were not replaced for MTD determination).

[11] - TS (Phase I patients from the dose escalation part that were not replaced for MTD determination).

End point values	Phase I Group 2, 100mg Nintedanib Bid	Phase I Group 2, 150mg Nintedanib Bid	Phase I Group 2, 200mg Nintedanib Bid	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4 ^[12]	3 ^[13]	3 ^[14]	
Units: participants	0	0	0	

Notes:

[12] - TS (Phase I patients from the dose escalation part that were not replaced for MTD determination).

[13] - TS (Phase I patients from the dose escalation part that were not replaced for MTD determination).

[14] - TS (Phase I patients from the dose escalation part that were not replaced for MTD determination).

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Tumour Response by RECIST

End point title	Objective Tumour Response by RECIST ^[15]
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End point description:

Objective RECIST 1.0 tumour response was defined as Complete Response (CR) or Partial Response (PR) and was derived from the patient's best objective RECIST 1.0 response based on central independent review. 95% Confidence Interval presented below are computed by Clopper and Pearson method.

End point type	Secondary
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End point timeframe:

From randomization until data cut-off (15 July 2014); Up to 1031 days

Notes:

[15] - 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 Phase II subjects were analyzed in this endpoint.

End point values	Phase II, 200 mg Nintedanib Bid	Phase II, 400 mg Sorafenib Bid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62 ^[16]	31 ^[17]		
Units: percentage of participants				
number (confidence interval 95%)	1.6 (0.0 to 8.7)	6.5 (0.8 to 21.4)		

Notes:

[16] - Treated set, phase II participants only

[17] - Treated set, phase II participants only

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS) ^[18]
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End point description:

PFS by RECIST 1.0 was defined as the duration from date of randomisation to date of progression or death, whichever occurred earlier, based on central independent review.

End point type	Secondary
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End point timeframe:

From randomization until data cut-off (15 July 2014); Up to 1031 days

Notes:

[18] - 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 Phase II subjects were analyzed in this endpoint.

End point values	Phase II, 200 mg Nintedanib Bid	Phase II, 400 mg Sorafenib Bid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62 ^[19]	31 ^[20]		
Units: months				
median (inter-quartile range (Q1-Q3))	5.32 (2.69 to 9.20)	3.94 (2.33 to 7.36)		

Notes:

[19] - Treated set, only phase II participants

[20] - Treated set, only phase II participants

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Phase II, 200 mg Nintedanib Bid v Phase II, 400 mg Sorafenib Bid
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority ^[21]
Parameter estimate	Hazard ratio (HR)
Point estimate	1.351
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.779
upper limit	2.343

Notes:

[21] - Hazard ratio from Cox proportional hazards model stratified by macroscopic vascular invasion, extrahepatic spread, or both present vs both absent. HR below 1 favors Nintedanib.

Secondary: Overall Survival

End point title	Overall Survival ^[22]
End point description:	Overall survival was defined as the duration from date of randomisation to the date of death.
End point type	Secondary
End point timeframe:	From randomization until data cut-off (15 July 2014); Up to 1031 days

Notes:

[22] - 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 Phase II subjects were analyzed in this endpoint.

End point values	Phase II, 200 mg Nintedanib Bid	Phase II, 400 mg Sorafenib Bid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62 ^[23]	31 ^[24]		
Units: months				
median (inter-quartile range (Q1-Q3))	11.86 (6.60 to 25.46)	11.40 (6.51 to 17.25)		

Notes:

[23] - Treated set, only phase II participants

[24] - Treated set, only phase II participants

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Hazard ratio from Cox proportional hazards model stratified by macroscopic vascular invasion, extrahepatic spread, or both present vs both absent.	
Comparison groups	Phase II, 200 mg Nintedanib Bid v Phase II, 400 mg Sorafenib Bid
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority ^[25]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.877
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.522
upper limit	1.473

Notes:

[25] - HR below 1 favors Nintedanib.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first administration of the trial drug and until 28 days after the last administration of nintedanib or sorafenib, up to 1289 days

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Phase I Group I Nintedanib, 100 mg bid
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Reporting group description:

Oral administration of Nintedanib (BIBF 1120) 100 mg soft gelatine capsules twice daily (bid). Phase I: A standard 3+3 dose escalation part to determine the maximal tolerated dose (MTD). Group 1 patients had a baseline Child-Pugh score of 5 or 6, and AST (aspartate aminotransferase) and ALT (alanine transaminase) ≤ 2 times the upper limit of normal (ULN).

Reporting group title	Phase I Group I Nintedanib, 150 mg bid
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Reporting group description:

Oral administration of Nintedanib (BIBF 1120) 150 mg soft gelatine capsules twice daily (bid). Phase I: A standard 3+3 dose escalation part to determine the MTD. Group 1 patients had a baseline Child-Pugh score of 5 or 6, and AST and ALT ≤ 2 times the upper limit of normal (ULN).

Reporting group title	Phase I Group I Nintedanib, 200 mg bid
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Reporting group description:

Oral administration of Nintedanib (BIBF 1120) 200 mg soft gelatine capsules (two capsules of 100mg) twice daily (bid). Phase I: A standard 3+3 dose escalation part to determine the MTD. Group 1 patients had a baseline Child-Pugh score of 5 or 6, and AST and ALT ≤ 2 times the upper limit of normal (ULN).

Reporting group title	Phase I Group II Nintedanib, 50 mg bid
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Reporting group description:

Oral administration of Nintedanib (BIBF 1120) 50 mg soft gelatine capsules twice daily (bid). Phase I: A standard 3+3 dose escalation part to determine the MTD. Group 2 patients had a baseline Child-Pugh score of 7, or AST or ALT > 2 to ≤ 5 times ULN.

Reporting group title	Phase I Group II Nintedanib, 100 mg bid
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Reporting group description:

Oral administration of Nintedanib (BIBF 1120) 100 mg soft gelatine capsules twice daily (bid). Phase I: A standard 3+3 dose escalation part to determine the MTD. Group 2 patients had a baseline Child-Pugh score of 7, or AST or ALT > 2 to ≤ 5 times ULN.

Reporting group title	Phase I Group II Nintedanib, 150 mg bid
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Reporting group description:

Oral administration of Nintedanib (BIBF 1120) 150 mg soft gelatine capsules twice daily (bid). Phase I: A standard 3+3 dose escalation part to determine the MTD. Group 2 patients had a baseline Child-Pugh score of 7, or AST or ALT > 2 to ≤ 5 times ULN.

Reporting group title	Phase I Group II Nintedanib, 200 mg bid
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Reporting group description:

Oral administration of Nintedanib (BIBF 1120) 200 mg soft gelatine capsules (two capsules of 100mg) twice daily (bid). Phase I: A standard 3+3 dose escalation part to determine the MTD. Group 2 patients had a baseline Child-Pugh score of 7, or AST or ALT > 2 to ≤ 5 times ULN.

Reporting group title	Phase II Nintedanib, 200 mg bid
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Reporting group description:

Oral administration of Nintedanib (BIBF 1120) 200 mg soft gelatine capsules (two capsules of 100mg) twice daily (bid). Phase II: Patients were randomly assigned to open-label treatment with nintedanib or sorafenib. Patients were stratified for macrovascular invasion (MVI) and/or extra-hepatic spread (EHS). Patients had a baseline Child-Pugh score of 5 or 6, and AST and ALT ≤ 2 times the upper limit of normal (ULN).

Reporting group title	Phase II Sorafenib, 400mg bid
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Reporting group description:

Oral administration of Sorafenib 400 mg film coated tablets twice daily (bid). Phase II: Patients were randomly assigned to open-label treatment with nintedanib or sorafenib. Patients were stratified for macrovascular invasion (MVI) and/or extra-hepatic spread (EHS). Patients had a baseline Child-Pugh score of 5 or 6, and AST and ALT ≤ 2 times the upper limit of normal (ULN).

Serious adverse events	Phase I Group I Nintedanib, 100 mg bid	Phase I Group I Nintedanib, 150 mg bid	Phase I Group I Nintedanib, 200 mg bid
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)	1 / 3 (33.33%)	4 / 4 (100.00%)
number of deaths (all causes)	6	3	3
number of deaths resulting from adverse events	1	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm progression			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Metastatic neoplasm			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Tumour haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Tumour thrombosis			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Vascular disorders			
Bleeding varicose vein			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Hypertensive crisis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Surgical and medical procedures			
Hepatectomy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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			
Chest pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Disease progression			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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

Impaired healing			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Multi-organ failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Performance status decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Respiratory, thoracic and mediastinal disorders			
Hyperventilation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Interstitial lung disease			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Pleural effusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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

Respiratory alkalosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 4 (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
Disorientation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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			
Blood bilirubin increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Lipase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Concussion			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Fall			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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			
Acute coronary syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
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 pectoris			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Atrial fibrillation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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 arrest			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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			
Depressed level of consciousness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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 encephalopathy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Loss of consciousness			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Somnolence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Splenic vein thrombosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Thrombocytopenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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			
Glaucoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Macular fibrosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Retinal detachment			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Ascites			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 4 (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
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Gastric varices haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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 haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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 food impaction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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 varices haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Rectal haemorrhage			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Varices oesophageal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 4 (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
Hepatic failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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 pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Hyperbilirubinaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Jaundice			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Skin and subcutaneous tissue disorders			
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Renal and urinary disorders			
Nephrotic syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
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 impairment			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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			
Biliary sepsis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Hepatitis B			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Ludwig angina			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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 bacterial			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Postoperative wound infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Sepsis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 4 (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
Gout			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Hyperkalaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Hypoglycaemia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (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

Serious adverse events	Phase I Group II Nintedanib, 50 mg bid	Phase I Group II Nintedanib, 100 mg bid	Phase I Group II Nintedanib, 150 mg bid
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	2 / 4 (50.00%)	3 / 4 (75.00%)
number of deaths (all causes)	3	4	4
number of deaths resulting from adverse events	1	1	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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 neoplasm progression			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	2 / 4 (50.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Metastatic neoplasm			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Tumour haemorrhage			

subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Tumour thrombosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Vascular disorders			
Bleeding varicose vein			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Hypertensive crisis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Surgical and medical procedures			
Hepatectomy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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			
Chest pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (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
Disease progression			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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 / 4 (0.00%)	0 / 4 (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 / 4 (0.00%)	0 / 4 (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
Impaired healing			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Multi-organ failure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Performance status decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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 / 4 (0.00%)	0 / 4 (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			
Hyperventilation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Interstitial lung disease			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Pleural effusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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

Pneumothorax			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Respiratory alkalosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Disorientation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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			
Blood bilirubin increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Lipase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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			
Clavicle fracture			

subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Concussion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Fall			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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			
Acute coronary syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Angina pectoris			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Atrial fibrillation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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 arrest			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Depressed level of consciousness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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 encephalopathy			

subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Loss of consciousness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Somnolence			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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 / 4 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic vein thrombosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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			
Glaucoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Macular fibrosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Retinal detachment			

subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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			
subjects affected / exposed	2 / 3 (66.67%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	2 / 3 (66.67%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Gastric varices haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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 haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	2 / 4 (50.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal food impaction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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 varices haemorrhage			

subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Rectal haemorrhage			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Varices oesophageal			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (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
Vomiting			
subjects affected / exposed	1 / 3 (33.33%)	1 / 4 (25.00%)	2 / 4 (50.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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 failure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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 pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Hyperbilirubinaemia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Jaundice			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Skin and subcutaneous tissue disorders			
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Renal and urinary disorders			
Nephrotic syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Renal impairment			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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			
Biliary sepsis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Hepatitis B			

subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ludwig angina			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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 bacterial			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Postoperative wound infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Sepsis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Gout			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Hyperkalaemia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Hypoglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Hyponatraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (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

Serious adverse events	Phase I Group II Nintedanib, 200 mg bid	Phase II Nintedanib, 200 mg bid	Phase II Sorafenib, 400mg bid
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 8 (50.00%)	34 / 62 (54.84%)	14 / 31 (45.16%)
number of deaths (all causes)	6	43	22
number of deaths resulting from adverse events	1	9	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (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 neoplasm progression			
subjects affected / exposed	0 / 8 (0.00%)	2 / 62 (3.23%)	3 / 31 (9.68%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Metastatic neoplasm			

subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (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
Tumour haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (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
Tumour thrombosis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Bleeding varicose vein			
subjects affected / exposed	1 / 8 (12.50%)	0 / 62 (0.00%)	0 / 31 (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
Hypertensive crisis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (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
Surgical and medical procedures			
Hepatectomy			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (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
Disease progression			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1

Fatigue			
subjects affected / exposed	0 / 8 (0.00%)	3 / 62 (4.84%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 8 (0.00%)	2 / 62 (3.23%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 2	0 / 0
Impaired healing			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multi-organ failure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (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
Performance status decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	1 / 31 (3.23%)
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, thoracic and mediastinal disorders			
Hyperventilation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (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

Pleural effusion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (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
Pneumothorax			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory alkalosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (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
Disorientation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (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
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 8 (0.00%)	2 / 62 (3.23%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (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
Lipase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (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			
Clavicle fracture			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (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
Concussion			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (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
Angina pectoris			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (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			
Depressed level of consciousness			

subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (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
Hepatic encephalopathy			
subjects affected / exposed	0 / 8 (0.00%)	5 / 62 (8.06%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	2 / 7	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (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
Somnolence			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 8 (0.00%)	3 / 62 (4.84%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	1 / 5	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic vein thrombosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (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
Macular fibrosis			

subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (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
Retinal detachment			
subjects affected / exposed	1 / 8 (12.50%)	0 / 62 (0.00%)	0 / 31 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (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
Ascites			
subjects affected / exposed	1 / 8 (12.50%)	1 / 62 (1.61%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	2 / 62 (3.23%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric varices haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (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
Oesophageal food impaction			

subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	2 / 62 (3.23%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	2 / 62 (3.23%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varices oesophageal			
subjects affected / exposed	1 / 8 (12.50%)	1 / 62 (1.61%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 8 (12.50%)	1 / 62 (1.61%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	0 / 8 (0.00%)	2 / 62 (3.23%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Hepatic pain			

subjects affected / exposed	0 / 8 (0.00%)	2 / 62 (3.23%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (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
Jaundice			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (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
Skin and subcutaneous tissue disorders			
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	1 / 31 (3.23%)
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			
Nephrotic syndrome			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (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
Renal impairment			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Biliary sepsis			

subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (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
Hepatitis B			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (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
Ludwig angina			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (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
Peritonitis bacterial			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (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
Sepsis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 62 (1.61%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (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
Gout			

subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (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
Hyperkalaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (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
Hyponatraemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (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

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

Non-serious adverse events	Phase I Group I Nintedanib, 100 mg bid	Phase I Group I Nintedanib, 150 mg bid	Phase I Group I Nintedanib, 200 mg bid
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	3 / 3 (100.00%)	4 / 4 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Intra-abdominal haematoma			

subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Catheter site bruise			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Chest pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Chills			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Device difficult to use			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	3 / 6 (50.00%)	0 / 3 (0.00%)	3 / 4 (75.00%)
occurrences (all)	3	0	3
Feeling cold			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Gait disturbance			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
General physical health deterioration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Impaired healing			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Inflammation			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Influenza like illness			
subjects affected / exposed	1 / 6 (16.67%)	1 / 3 (33.33%)	3 / 4 (75.00%)
occurrences (all)	1	1	3
Injection site bruising			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Local swelling			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Malaise			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Mucosal inflammation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	1 / 4 (25.00%)
occurrences (all)	0	1	3
Pyrexia			
subjects affected / exposed	2 / 6 (33.33%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	1
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Seasonal allergy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	2 / 4 (50.00%)
occurrences (all)	3	0	3
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Dyspnoea exertional			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Haemoptysis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hiccups			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Increased viscosity of bronchial secretion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Productive cough			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Pulmonary oedema			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Depressed mood			

subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 3 (66.67%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Amylase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 3 (66.67%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Blood albumin decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 3 (66.67%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
Blood bilirubin increased			
subjects affected / exposed	2 / 6 (33.33%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	2	1	0
Blood potassium decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
International normalised ratio increased			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Lipase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Liver function test abnormal			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Transaminases increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Contrast media reaction			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Contusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Sunburn			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Tooth fracture			

subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Nervous system disorders			
Aphonia			
subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 3 (33.33%) 1	1 / 4 (25.00%) 1
Dizziness			
subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Dizziness postural			
subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Dysaesthesia			
subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Dysgeusia			
subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	2 / 4 (50.00%) 2
Dyskinesia			
subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Encephalopathy			
subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Headache			
subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Lethargy			
subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1
Memory impairment			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Sensory disturbance			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Sensory loss			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Transient ischaemic attack			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Deafness			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Eye disorders			

Eye discharge subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Abdominal distension subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 3 (0.00%) 0	3 / 4 (75.00%) 3
Abdominal pain subjects affected / exposed occurrences (all)	3 / 6 (50.00%) 6	1 / 3 (33.33%) 2	2 / 4 (50.00%) 2
Abdominal pain lower subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 3 (33.33%) 1	2 / 4 (50.00%) 3
Abdominal tenderness subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0
Anorectal varices subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0
Ascites subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 3 (33.33%) 1	1 / 4 (25.00%) 1
Constipation subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 3 (0.00%) 0	2 / 4 (50.00%) 4
Diarrhoea subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 8	2 / 3 (66.67%) 3	3 / 4 (75.00%) 7
Dry mouth			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Duodenal ulcer			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	1 / 6 (16.67%)	2 / 3 (66.67%)	0 / 4 (0.00%)
occurrences (all)	1	3	0
Dysphagia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorder			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Gingival bleeding			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Haematemesis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Haematochezia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Melaena			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Nausea			

subjects affected / exposed	1 / 6 (16.67%)	3 / 3 (100.00%)	3 / 4 (75.00%)
occurrences (all)	2	5	8
Oral pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Rectal haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Retching			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Tooth loss			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	1 / 6 (16.67%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	2	1	0
Vomiting			
subjects affected / exposed	2 / 6 (33.33%)	3 / 3 (100.00%)	3 / 4 (75.00%)
occurrences (all)	5	8	15
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hepatic haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Hepatic pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Jaundice			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	1 / 4 (25.00%)
occurrences (all)	0	1	1

Portal vein thrombosis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Dermatitis acneiform subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Dry skin subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Erythema subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Hyperhidrosis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Hyperkeratosis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Night sweats subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1
Palmar-plantar erythrodysesthesia syndrome subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Pruritus subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1
Rash subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1
Skin reaction			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Oliguria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Proteinuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Renal failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Renal failure acute			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Urinary incontinence			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	3
Back pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Flank pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Groin pain			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Joint swelling			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Musculoskeletal stiffness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Pain in extremity			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Pain in jaw			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Pathological fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Spinal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	3
Lower respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	3

Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 3 (33.33%) 1	1 / 4 (25.00%) 3
Oral candidiasis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Tooth abscess subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2	1 / 3 (33.33%) 2	0 / 4 (0.00%) 0
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 3 (0.00%) 0	3 / 4 (75.00%) 6
Dehydration subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Hyperuricaemia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Hypoglycaemia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1
Hypokalaemia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Hyponatraemia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Malnutrition subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0

Non-serious adverse events	Phase I Group II Nintedanib, 50 mg bid	Phase I Group II Nintedanib, 100 mg bid	Phase I Group II Nintedanib, 150 mg bid
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Total subjects affected by non-serious adverse events subjects affected / exposed	3 / 3 (100.00%)	4 / 4 (100.00%)	4 / 4 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Basal cell carcinoma subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Vascular disorders Hypertension subjects affected / exposed occurrences (all) Hypotension subjects affected / exposed occurrences (all) Intra-abdominal haematoma subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0	1 / 4 (25.00%) 1 1 / 4 (25.00%) 1 0 / 4 (0.00%) 0	0 / 4 (0.00%) 0 1 / 4 (25.00%) 1 0 / 4 (0.00%) 0
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Catheter site bruise subjects affected / exposed occurrences (all) Chest pain subjects affected / exposed occurrences (all) Chills subjects affected / exposed occurrences (all) Device difficult to use subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Feeling cold	0 / 3 (0.00%) 0 1 / 3 (33.33%) 1 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 2 / 3 (66.67%) 2 0	0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 1 / 4 (25.00%) 1 1 / 4 (25.00%) 1 0	0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 1 / 4 (25.00%) 1 2 / 4 (50.00%) 2 0

subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
General physical health deterioration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Impaired healing			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Inflammation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Injection site bruising			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Local swelling			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Mucosal inflammation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Oedema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Pain			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Seasonal allergy subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	2 / 4 (50.00%) 3	0 / 4 (0.00%) 0
Dyspnoea subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Dyspnoea exertional subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Epistaxis subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	1 / 4 (25.00%) 1	1 / 4 (25.00%) 2
Haemoptysis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Hiccups subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Increased viscosity of bronchial secretion subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0
Oropharyngeal pain			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Productive cough subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Pulmonary oedema subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Psychiatric disorders Confusional state subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Depressed mood subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Insomnia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1
Amylase increased subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 2	0 / 4 (0.00%) 0	2 / 4 (50.00%) 2
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Blood albumin decreased subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0
Blood bilirubin increased			

subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Blood potassium decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	6
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
International normalised ratio increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Lipase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Liver function test abnormal			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Platelet count decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Transaminases increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			

Contrast media reaction subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Contusion subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1
Fall subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1
Sunburn subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Tooth fracture subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Nervous system disorders Aphonia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Dizziness subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1
Dizziness postural subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	1 / 4 (25.00%) 2
Dysaesthesia subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Dysgeusia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 4 (50.00%) 2	0 / 4 (0.00%) 0
Dyskinesia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Encephalopathy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Lethargy			
subjects affected / exposed	0 / 3 (0.00%)	2 / 4 (50.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Memory impairment			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Sensory disturbance			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Sensory loss			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Syncope			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Transient ischaemic attack			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Ear and labyrinth disorders Cerumen impaction subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Deafness subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Eye disorders Eye discharge subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Abdominal distension subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0
Abdominal pain subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	1 / 4 (25.00%) 2	0 / 4 (0.00%) 0
Abdominal pain lower subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	2 / 4 (50.00%) 3	0 / 4 (0.00%) 0
Abdominal tenderness subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Anorectal varices subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Ascites			

subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	3 / 3 (100.00%)	2 / 4 (50.00%)	3 / 4 (75.00%)
occurrences (all)	6	3	6
Dry mouth			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Duodenal ulcer			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Dysphagia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gingival bleeding			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Haematemesis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Haematochezia			

subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Melaena			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Mouth ulceration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	2 / 3 (66.67%)	1 / 4 (25.00%)	3 / 4 (75.00%)
occurrences (all)	2	1	3
Oral pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Rectal haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Retching			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Stomatitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Tooth loss			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	2 / 3 (66.67%)	2 / 4 (50.00%)	1 / 4 (25.00%)
occurrences (all)	2	2	1
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Hepatic haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hepatic pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Jaundice			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Portal vein thrombosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Dermatitis acneiform			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hyperkeratosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Palmar-plantar erythrodysesthesia syndrome			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0
Pruritus subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	2 / 4 (50.00%) 2
Rash subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1
Skin reaction subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Renal and urinary disorders			
Chromaturia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Oliguria subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Proteinuria subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1
Renal failure subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Renal failure acute subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Urinary incontinence subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Endocrine disorders			
Hypothyroidism subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Back pain			
subjects affected / exposed	2 / 3 (66.67%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	1
Flank pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Groin pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Joint swelling			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pain in jaw			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pathological fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Spinal pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Infections and infestations			
Influenza subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Lower respiratory tract infection subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Oral candidiasis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Tooth abscess subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1	1 / 4 (25.00%) 2
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 4 (50.00%) 3	2 / 4 (50.00%) 2
Dehydration subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0
Hyperuricaemia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1
Hypoglycaemia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Hypokalaemia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Hyponatraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Malnutrition			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Phase I Group II Nintedanib, 200 mg bid	Phase II Nintedanib, 200 mg bid	Phase II Sorafenib, 400mg bid
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 8 (87.50%)	61 / 62 (98.39%)	31 / 31 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 8 (0.00%)	7 / 62 (11.29%)	3 / 31 (9.68%)
occurrences (all)	0	8	3
Hypotension			
subjects affected / exposed	1 / 8 (12.50%)	1 / 62 (1.61%)	1 / 31 (3.23%)
occurrences (all)	2	1	1
Intra-abdominal haematoma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 8 (0.00%)	3 / 62 (4.84%)	2 / 31 (6.45%)
occurrences (all)	0	3	2
Catheter site bruise			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Chest pain			

subjects affected / exposed	1 / 8 (12.50%)	1 / 62 (1.61%)	2 / 31 (6.45%)
occurrences (all)	1	1	2
Chills			
subjects affected / exposed	0 / 8 (0.00%)	3 / 62 (4.84%)	0 / 31 (0.00%)
occurrences (all)	0	3	0
Device difficult to use			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	5 / 8 (62.50%)	32 / 62 (51.61%)	10 / 31 (32.26%)
occurrences (all)	6	40	11
Feeling cold			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
General physical health deterioration			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Impaired healing			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Inflammation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Injection site bruising			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Local swelling			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Malaise			

subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	2 / 31 (6.45%)
occurrences (all)	0	1	2
Mucosal inflammation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	3 / 31 (9.68%)
occurrences (all)	0	0	4
Oedema			
subjects affected / exposed	0 / 8 (0.00%)	4 / 62 (6.45%)	0 / 31 (0.00%)
occurrences (all)	0	4	0
Oedema peripheral			
subjects affected / exposed	2 / 8 (25.00%)	8 / 62 (12.90%)	1 / 31 (3.23%)
occurrences (all)	2	8	1
Pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	10 / 62 (16.13%)	3 / 31 (9.68%)
occurrences (all)	0	14	4
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Seasonal allergy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 8 (25.00%)	3 / 62 (4.84%)	2 / 31 (6.45%)
occurrences (all)	2	3	2
Dyspnoea			
subjects affected / exposed	1 / 8 (12.50%)	4 / 62 (6.45%)	1 / 31 (3.23%)
occurrences (all)	1	5	1
Dyspnoea exertional			
subjects affected / exposed	0 / 8 (0.00%)	3 / 62 (4.84%)	2 / 31 (6.45%)
occurrences (all)	0	3	2
Epistaxis			

subjects affected / exposed	0 / 8 (0.00%)	7 / 62 (11.29%)	3 / 31 (9.68%)
occurrences (all)	0	9	4
Haemoptysis			
subjects affected / exposed	1 / 8 (12.50%)	2 / 62 (3.23%)	0 / 31 (0.00%)
occurrences (all)	1	2	0
Hiccups			
subjects affected / exposed	1 / 8 (12.50%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Increased viscosity of bronchial secretion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	1 / 31 (3.23%)
occurrences (all)	0	2	1
Productive cough			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Pulmonary oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 8 (12.50%)	2 / 62 (3.23%)	1 / 31 (3.23%)
occurrences (all)	1	3	1
Depressed mood			
subjects affected / exposed	0 / 8 (0.00%)	5 / 62 (8.06%)	1 / 31 (3.23%)
occurrences (all)	0	5	1
Insomnia			
subjects affected / exposed	0 / 8 (0.00%)	3 / 62 (4.84%)	1 / 31 (3.23%)
occurrences (all)	0	4	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	8 / 62 (12.90%)	3 / 31 (9.68%)
occurrences (all)	0	9	3
Amylase increased			

subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 8 (25.00%)	11 / 62 (17.74%)	5 / 31 (16.13%)
occurrences (all)	2	15	6
Blood albumin decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 8 (0.00%)	6 / 62 (9.68%)	2 / 31 (6.45%)
occurrences (all)	0	7	2
Blood bilirubin increased			
subjects affected / exposed	2 / 8 (25.00%)	8 / 62 (12.90%)	6 / 31 (19.35%)
occurrences (all)	2	8	6
Blood potassium decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	4 / 62 (6.45%)	2 / 31 (6.45%)
occurrences (all)	0	5	2
International normalised ratio increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Lipase increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	2 / 31 (6.45%)
occurrences (all)	0	1	2
Liver function test abnormal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count decreased			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 62 (1.61%) 1	1 / 31 (3.23%) 1
Platelet count decreased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	2 / 62 (3.23%) 2	2 / 31 (6.45%) 2
Transaminases increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 62 (1.61%) 1	2 / 31 (6.45%) 2
Weight decreased subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	8 / 62 (12.90%) 8	2 / 31 (6.45%) 2
Injury, poisoning and procedural complications			
Contrast media reaction subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 62 (0.00%) 0	0 / 31 (0.00%) 0
Contusion subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 62 (1.61%) 1	0 / 31 (0.00%) 0
Fall subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	3 / 62 (4.84%) 3	2 / 31 (6.45%) 2
Sunburn subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 62 (0.00%) 0	0 / 31 (0.00%) 0
Tooth fracture subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 62 (0.00%) 0	0 / 31 (0.00%) 0
Cardiac disorders			
Atrial fibrillation subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 62 (0.00%) 0	0 / 31 (0.00%) 0
Nervous system disorders			
Aphonia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 62 (0.00%) 0	1 / 31 (3.23%) 1
Dizziness			

subjects affected / exposed	1 / 8 (12.50%)	6 / 62 (9.68%)	3 / 31 (9.68%)
occurrences (all)	1	11	3
Dizziness postural			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Dysaesthesia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	1 / 8 (12.50%)	4 / 62 (6.45%)	3 / 31 (9.68%)
occurrences (all)	1	4	3
Dyskinesia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Encephalopathy			
subjects affected / exposed	2 / 8 (25.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
Headache			
subjects affected / exposed	0 / 8 (0.00%)	8 / 62 (12.90%)	5 / 31 (16.13%)
occurrences (all)	0	14	5
Lethargy			
subjects affected / exposed	0 / 8 (0.00%)	5 / 62 (8.06%)	8 / 31 (25.81%)
occurrences (all)	0	5	8
Memory impairment			
subjects affected / exposed	1 / 8 (12.50%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Sensory disturbance			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Sensory loss			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Syncope			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 62 (0.00%) 0	0 / 31 (0.00%) 0
Transient ischaemic attack subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 62 (0.00%) 0	0 / 31 (0.00%) 0
Tremor subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 62 (0.00%) 0	0 / 31 (0.00%) 0
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	5 / 62 (8.06%) 11	1 / 31 (3.23%) 1
Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	2 / 62 (3.23%) 2	4 / 31 (12.90%) 6
Ear and labyrinth disorders			
Cerumen impaction subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 62 (0.00%) 0	0 / 31 (0.00%) 0
Deafness subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 62 (0.00%) 0	0 / 31 (0.00%) 0
Eye disorders			
Eye discharge subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 62 (0.00%) 0	0 / 31 (0.00%) 0
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	2 / 62 (3.23%) 2	2 / 31 (6.45%) 2
Abdominal distension subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	1 / 62 (1.61%) 1	1 / 31 (3.23%) 1
Abdominal pain subjects affected / exposed occurrences (all)	3 / 8 (37.50%) 3	15 / 62 (24.19%) 21	9 / 31 (29.03%) 11
Abdominal pain lower			

subjects affected / exposed	0 / 8 (0.00%)	3 / 62 (4.84%)	0 / 31 (0.00%)
occurrences (all)	0	3	0
Abdominal pain upper			
subjects affected / exposed	2 / 8 (25.00%)	16 / 62 (25.81%)	4 / 31 (12.90%)
occurrences (all)	3	20	5
Abdominal tenderness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Anorectal varices			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Ascites			
subjects affected / exposed	1 / 8 (12.50%)	3 / 62 (4.84%)	2 / 31 (6.45%)
occurrences (all)	1	3	2
Constipation			
subjects affected / exposed	1 / 8 (12.50%)	9 / 62 (14.52%)	6 / 31 (19.35%)
occurrences (all)	1	12	9
Diarrhoea			
subjects affected / exposed	5 / 8 (62.50%)	43 / 62 (69.35%)	21 / 31 (67.74%)
occurrences (all)	14	98	44
Dry mouth			
subjects affected / exposed	1 / 8 (12.50%)	2 / 62 (3.23%)	3 / 31 (9.68%)
occurrences (all)	1	2	5
Duodenal ulcer			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 62 (1.61%)	1 / 31 (3.23%)
occurrences (all)	1	1	1
Dysphagia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	3 / 31 (9.68%)
occurrences (all)	0	2	3
Flatulence			
subjects affected / exposed	0 / 8 (0.00%)	4 / 62 (6.45%)	1 / 31 (3.23%)
occurrences (all)	0	4	1
Gastritis			

subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	2 / 31 (6.45%)
occurrences (all)	0	1	2
Gastrointestinal disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Gingival bleeding			
subjects affected / exposed	1 / 8 (12.50%)	1 / 62 (1.61%)	3 / 31 (9.68%)
occurrences (all)	1	1	3
Haematemesis			
subjects affected / exposed	2 / 8 (25.00%)	1 / 62 (1.61%)	0 / 31 (0.00%)
occurrences (all)	2	1	0
Haematochezia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Melaena			
subjects affected / exposed	1 / 8 (12.50%)	2 / 62 (3.23%)	0 / 31 (0.00%)
occurrences (all)	1	4	0
Mouth ulceration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Nausea			
subjects affected / exposed	7 / 8 (87.50%)	29 / 62 (46.77%)	9 / 31 (29.03%)
occurrences (all)	8	51	14
Oral pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Rectal haemorrhage			
subjects affected / exposed	1 / 8 (12.50%)	1 / 62 (1.61%)	0 / 31 (0.00%)
occurrences (all)	1	1	0
Retching			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Stomatitis			
subjects affected / exposed	0 / 8 (0.00%)	2 / 62 (3.23%)	3 / 31 (9.68%)
occurrences (all)	0	2	3
Tooth loss			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 62 (0.00%) 0	0 / 31 (0.00%) 0
Toothache subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 62 (0.00%) 0	0 / 31 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	5 / 8 (62.50%) 14	23 / 62 (37.10%) 65	9 / 31 (29.03%) 15
Hepatobiliary disorders			
Drug-induced liver injury subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 62 (0.00%) 0	1 / 31 (3.23%) 2
Hepatic haemorrhage subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 62 (0.00%) 0	0 / 31 (0.00%) 0
Hepatic pain subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	2 / 62 (3.23%) 2	0 / 31 (0.00%) 0
Jaundice subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	2 / 62 (3.23%) 2	0 / 31 (0.00%) 0
Portal vein thrombosis subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 62 (0.00%) 0	2 / 31 (6.45%) 2
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	3 / 62 (4.84%) 3	11 / 31 (35.48%) 11
Dermatitis acneiform subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 62 (0.00%) 0	2 / 31 (6.45%) 3
Dry skin subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	4 / 62 (6.45%) 5	5 / 31 (16.13%) 5
Erythema			

subjects affected / exposed	0 / 8 (0.00%)	3 / 62 (4.84%)	3 / 31 (9.68%)
occurrences (all)	0	3	3
Hyperhidrosis			
subjects affected / exposed	0 / 8 (0.00%)	2 / 62 (3.23%)	2 / 31 (6.45%)
occurrences (all)	0	2	2
Hyperkeratosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Night sweats			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	1 / 8 (12.50%)	1 / 62 (1.61%)	11 / 31 (35.48%)
occurrences (all)	1	1	18
Pruritus			
subjects affected / exposed	0 / 8 (0.00%)	9 / 62 (14.52%)	3 / 31 (9.68%)
occurrences (all)	0	9	4
Rash			
subjects affected / exposed	0 / 8 (0.00%)	6 / 62 (9.68%)	7 / 31 (22.58%)
occurrences (all)	0	6	8
Skin reaction			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	3 / 31 (9.68%)
occurrences (all)	0	1	4
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Oliguria			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Proteinuria			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Renal failure			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 62 (0.00%) 0	0 / 31 (0.00%) 0
Renal failure acute subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 62 (0.00%) 0	1 / 31 (3.23%) 1
Urinary incontinence subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 62 (1.61%) 1	1 / 31 (3.23%) 1
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	4 / 62 (6.45%) 4	0 / 31 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	4 / 62 (6.45%) 7	2 / 31 (6.45%) 2
Back pain subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	6 / 62 (9.68%) 6	3 / 31 (9.68%) 4
Flank pain subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 62 (0.00%) 0	1 / 31 (3.23%) 1
Groin pain subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 62 (1.61%) 1	0 / 31 (0.00%) 0
Joint swelling subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	2 / 62 (3.23%) 2	1 / 31 (3.23%) 1
Muscle spasms subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	3 / 62 (4.84%) 3	3 / 31 (9.68%) 4
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	7 / 62 (11.29%) 7	0 / 31 (0.00%) 0
Musculoskeletal stiffness			

subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 8 (0.00%)	3 / 62 (4.84%)	1 / 31 (3.23%)
occurrences (all)	0	3	1
Pain in extremity			
subjects affected / exposed	0 / 8 (0.00%)	3 / 62 (4.84%)	2 / 31 (6.45%)
occurrences (all)	0	3	2
Pain in jaw			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Pathological fracture			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Spinal pain			
subjects affected / exposed	1 / 8 (12.50%)	1 / 62 (1.61%)	0 / 31 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Lower respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)	4 / 62 (6.45%)	3 / 31 (9.68%)
occurrences (all)	2	11	3
Nasopharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	6 / 62 (9.68%)	0 / 31 (0.00%)
occurrences (all)	0	8	0
Oral candidiasis			
subjects affected / exposed	1 / 8 (12.50%)	4 / 62 (6.45%)	2 / 31 (6.45%)
occurrences (all)	1	4	3
Tooth abscess			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)	2 / 62 (3.23%)	3 / 31 (9.68%)
occurrences (all)	0	2	4

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 8 (62.50%)	23 / 62 (37.10%)	13 / 31 (41.94%)
occurrences (all)	5	27	15
Dehydration			
subjects affected / exposed	0 / 8 (0.00%)	2 / 62 (3.23%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
Hyperuricaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Hypoglycaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Hypokalaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 62 (1.61%)	2 / 31 (6.45%)
occurrences (all)	0	1	5
Hyponatraemia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 62 (3.23%)	2 / 31 (6.45%)
occurrences (all)	0	2	2
Malnutrition			
subjects affected / exposed	0 / 8 (0.00%)	0 / 62 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 April 2010	The EudraCT number was corrected. The Trial Clinical Monitor was changed.
29 April 2011	1) Only patients with liver function in Group 1 (Child-Pugh A and both AST and ALT $\leq 2 \times$ ULN) were eligible for the Phase II part. 2) The Phase II dose for Group 1 patients was available. 3) Choi criteria were replaced by mRECIST for HCC criteria to more accurately reflect disease stabilisation and progression in this indication. 4) Stratification factors were specified. 5) Sampling for plasma protein binding of nintedanib was added because plasma protein concentrations can alter in patients with hepatic impairment. 5) The definition of MTD was updated. 6) The Trial Clinical Monitor was changed. 7) The recommended dose for Phase II (MTD) was identified, and an extension cohort of 11 to 15 Group 2 patients was added to further study the safety of patients from Group 2. 8) The randomisation procedure and analysis set was modified. 9) There was a change in the PK methods (12 instead of 24 hours). 10) The interim safety analysis was performed in Group 1 patients only. 11) Lipase, amylase and phosphate were added to the safety laboratory examinations.
25 January 2012	1) The wording for AE reporting was updated, was a requirement from the German health authority (BfArM) for a protocol submitted in any country. 2) The Food and Drug Administration drug-induced liver injury guidelines were implemented. 3) Continuous HBV testing was added for patients with positive HBV DNA at baseline
25 July 2012	1) The restart criteria following interruption of study medication in Phase II due to AST/ALT/ALKP elevation were corrected. 2) Inclusion criterion 7 was clarified. 3) In sites participating in the Phase I MTD extension cohort, at least 6 patients with Child-Pugh B (7) in the MTD extension cohort for Group 2 had to be included. 4) The planned interim analysis was changed to the primary analysis, to clarify when the primary analysis was to be conducted. Justification for conducting the primary analysis after at least 80% of patients had a TTP event was added. 5) The interim analysis was not performed because the primary analysis was performed instead. 6) The criteria for defining the end of the whole trial were changed from as soon as the last patient has completed his/her last visit, to as soon as at least 50% of the patients have had an overall survival event or the last patient has completed his/her first follow-up visit for overall survival, whichever occurred last. This change was made because overall survival events of at least 50% of patients were considered to provide enough information to estimate the Kaplan-Meier curves, and ensured that all patients were off treatment and not in follow-up for disease progression
04 December 2013	1) Selected secondary and explorative endpoints were modified because PK parameters are considered further endpoints, and safety is summarised separately from secondary endpoints. 2) Selected text was deleted that should have been deleted in Amendment 2. 3) Selected text was revised that was unclear in Amendment 3. 4) An administrative change was made.
31 March 2014	1) The timing of the primary analysis was brought forward slightly because there were an unexpectedly high number of patients censored for TTP events due to early death, lost to follow-up or other treatment. The number of events for overall survival had already been reached. Therefore, the primary analysis was done after approximately 80% of patients (instead of at least 80% of patients) had reached the primary endpoint. 2) Minor corrections were made to 2 of the footnotes to the flow chart for the Phase II part

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported