



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 |
|-----------------------|---------|

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 |
|----------|---|

| | |
|---|----|
| 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 |
|------------------|---------------------------------------|

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 |
|------------------|---------------------------------------|

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 |
|------------------|--------------------------------------|

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 |
|------------------|---------------------------------------|

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 |
|------------------|---------------------------------------|

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 |
|------------------|---------------------------------------|

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 |
|------------------|---------------------------------|

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 |
|------------------|--------------------------------|

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 |
|---------------------|---|---|---|

| 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 | 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 | 31 |
| 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 |
| 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). | |

| 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] |
|-----------------|--|

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 |
|----------------|---------|

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] |
|-----------------|--|

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 |
|----------------|---------|

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] |
|-----------------|---|

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 |
|----------------|-----------|

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] |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Phase I Group I Nintedanib, 100 mg 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 I Nintedanib, 150 mg 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 I Nintedanib, 200 mg 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 II Nintedanib, 50 mg 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 II Nintedanib, 100 mg 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 II Nintedanib, 150 mg 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 II Nintedanib, 200 mg 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 Nintedanib, 200 mg 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 Sorafenib, 400mg 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).

| 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 erythrodysaesthesia 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 |
|-----------------------------------|--|---|---|

| | | | |
|--|--|---|--|
| 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 / 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 | 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 |

| | | | |
|---------------------------------------|----------------|----------------|----------------|
| 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 | 0 / 3 (0.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Productive cough | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Depressed mood | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 4 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Amylase increased | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 4 (0.00%) | 2 / 4 (50.00%) |
| occurrences (all) | 2 | 0 | 2 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood albumin decreased | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 4 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 4 (25.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 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 occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Hepatic pain subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Jaundice subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Portal vein thrombosis subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Dermatitis acneiform subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Dry skin subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Erythema subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Hyperhidrosis subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Hyperkeratosis subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Night sweats subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 4 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Palmar-plantar erythrodysaesthesia 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 | 0 / 8 (0.00%) | 0 / 62 (0.00%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 62 (0.00%) | 0 / 31 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tremor | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 62 (0.00%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 5 / 62 (8.06%) | 1 / 31 (3.23%) |
| occurrences (all) | 0 | 11 | 1 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 62 (3.23%) | 4 / 31 (12.90%) |
| occurrences (all) | 0 | 2 | 6 |
| Ear and labyrinth disorders | | | |
| Cerumen impaction | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 62 (0.00%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Deafness | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 62 (0.00%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye disorders | | | |
| Eye discharge | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 62 (0.00%) | 0 / 31 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 62 (3.23%) | 2 / 31 (6.45%) |
| occurrences (all) | 0 | 2 | 2 |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 62 (1.61%) | 1 / 31 (3.23%) |
| occurrences (all) | 1 | 1 | 1 |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 15 / 62 (24.19%) | 9 / 31 (29.03%) |
| occurrences (all) | 3 | 21 | 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 | 0 / 8 (0.00%) | 0 / 62 (0.00%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 62 (0.00%) | 1 / 31 (3.23%) |
| occurrences (all) | 0 | 0 | 1 |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 62 (1.61%) | 1 / 31 (3.23%) |
| occurrences (all) | 0 | 1 | 1 |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 4 / 62 (6.45%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 4 / 62 (6.45%) | 2 / 31 (6.45%) |
| occurrences (all) | 0 | 7 | 2 |
| Back pain | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 6 / 62 (9.68%) | 3 / 31 (9.68%) |
| occurrences (all) | 1 | 6 | 4 |
| Flank pain | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 62 (0.00%) | 1 / 31 (3.23%) |
| occurrences (all) | 0 | 0 | 1 |
| Groin pain | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 62 (1.61%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Joint swelling | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 62 (3.23%) | 1 / 31 (3.23%) |
| occurrences (all) | 0 | 2 | 1 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 3 / 62 (4.84%) | 3 / 31 (9.68%) |
| occurrences (all) | 0 | 3 | 4 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 7 / 62 (11.29%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 7 | 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