



Clinical trial results: Sorafenib Long Term Extension Program (STEP) Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2007-002604-17 |
| Trial protocol | FR DE ES IT PL GB BE BG |
| Global end of trial date | 24 September 2021 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v2 (current) |
| This version publication date | 16 July 2022 |
| First version publication date | 30 March 2022 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|-------|
| Sponsor protocol code | 12311 |
|-----------------------|-------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00625378 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Bayer AG |
| Sponsor organisation address | Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368 |
| Public contact | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com |
| Scientific contact | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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 | 24 September 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 24 September 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary purpose of the program was to enable patients, currently receiving sorafenib (Nexavar) in a Bayer/Onyx sponsored clinical trial, to continue sorafenib treatment after their respective study had met its primary endpoint and/or had reached the end as defined in the original protocol. An additional objective was the assessment of the safety of Nexavar or Nexavar combination treatment.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects/ /legal representatives. Participating subjects/ /legal representatives signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 21 December 2007 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 26 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Australia: 1 |
| Country: Number of subjects enrolled | Belgium: 2 |
| Country: Number of subjects enrolled | Bulgaria: 2 |
| Country: Number of subjects enrolled | Brazil: 1 |
| Country: Number of subjects enrolled | Canada: 11 |
| Country: Number of subjects enrolled | China: 10 |
| Country: Number of subjects enrolled | Colombia: 1 |
| Country: Number of subjects enrolled | Germany: 10 |
| Country: Number of subjects enrolled | Spain: 10 |
| Country: Number of subjects enrolled | France: 1 |
| Country: Number of subjects enrolled | United Kingdom: 18 |
| Country: Number of subjects enrolled | Hong Kong: 2 |
| Country: Number of subjects enrolled | Italy: 31 |

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Korea, Republic of: 8 |
| Country: Number of subjects enrolled | New Zealand: 1 |
| Country: Number of subjects enrolled | Poland: 70 |
| Country: Number of subjects enrolled | Taiwan: 17 |
| Country: Number of subjects enrolled | Ukraine: 1 |
| Country: Number of subjects enrolled | United States: 7 |
| Worldwide total number of subjects | 204 |
| EEA total number of subjects | 126 |

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) | 109 |
| From 65 to 84 years | 93 |
| 85 years and over | 2 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at multiple centers in 19 countries between 21-Dec-2007 (first subject first visit) and 24-Sep-2021 (last subject last visit).

Pre-assignment

Screening details:

Overall, 206 subjects were transferred from the feeder studies and have signed informed consent for STEP. Of these 206 subjects, 2 subjects were never treated and 204 subjects received the study treatment.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-----------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Sorafenib monotherapy |

Arm description:

Subjects received single-agent sorafenib at the same dose and schedule as in their original Clinical Trial.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Sorafenib |
| Investigational medicinal product code | |
| Other name | Nexavar |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

At the same dose and schedule as in the subjects' original Clinical Trial

| | |
|------------------|---------------------|
| Arm title | Sorafenib+Erlotinib |
|------------------|---------------------|

Arm description:

Subjects received sorafenib and erlotinib combination at the same dose and schedule as in their original Clinical Trial.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Sorafenib |
| Investigational medicinal product code | |
| Other name | Nexavar |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

At the same dose and schedule as in the subjects' original Clinical Trial

| | |
|--|-----------|
| Investigational medicinal product name | Erlotinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

At the same dose and schedule as in the subjects' original Clinical Trial

| Number of subjects in period 1 | Sorafenib monotherapy | Sorafenib+Erlotinib |
|--|------------------------------|----------------------------|
| Started | 203 | 1 |
| Completed | 0 | 0 |
| Not completed | 203 | 1 |
| Disease progression, recurrence or relapse | 88 | - |
| Non-compliant with study medication | 3 | - |
| Adverse event | 22 | - |
| Sponsor decision | 1 | - |
| Missing | 2 | - |
| Multiple toxicities | 1 | - |
| New cancer | 1 | - |
| PTA program | 2 | - |
| Consent withdrawn by subject | 16 | - |
| Investigator's decision | 1 | - |
| Sponsor's decision to stop the trial | 1 | - |
| End of treatment not available | 2 | - |
| Death | 38 | - |
| Switch to commercial drug | 6 | 1 |
| Medical decision | 1 | - |
| Lost to follow-up | 17 | - |
| Recurrent rise in amylase and lipase | 1 | - |

Baseline characteristics

Reporting groups

| | |
|--|-----------------------|
| Reporting group title | Sorafenib monotherapy |
| Reporting group description: | |
| Subjects received single-agent sorafenib at the same dose and schedule as in their original Clinical Trial. | |
| Reporting group title | Sorafenib+Erlotinib |
| Reporting group description: | |
| Subjects received sorafenib and erlotinib combination at the same dose and schedule as in their original Clinical Trial. | |

| Reporting group values | Sorafenib monotherapy | Sorafenib+Erlotinib | Total |
|------------------------|-----------------------|---------------------|-------|
| Number of subjects | 203 | 1 | 204 |
| Age Categorical | | | |
| Units: Subjects | | | |

| | | | |
|---|-------|---------|-----|
| Age Continuous | | | |
| "99999" denotes that value was not calculated due to the only 1 subject in the group. | | | |
| Units: years | | | |
| arithmetic mean | 63.5 | 20.0 | |
| standard deviation | ± 9.6 | ± 99999 | - |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 63 | 0 | 63 |
| Male | 140 | 1 | 141 |
| Race | | | |
| Units: Subjects | | | |
| Asian | 39 | 1 | 40 |
| Hispanic | 2 | 0 | 2 |
| Japanese/American | 1 | 0 | 1 |
| White | 161 | 0 | 161 |
| ECOG performance status | | | |
| Eastern cooperative oncology group (ECOG) performance status: 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work; 2 = Ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours | | | |
| Units: Subjects | | | |
| ECOG 0 | 25 | 1 | 26 |
| ECOG 1 | 16 | 0 | 16 |
| ECOG 2 | 1 | 0 | 1 |
| Missing | 161 | 0 | 161 |

End points

End points reporting groups

| | |
|--|---------------------------|
| Reporting group title | Sorafenib monotherapy |
| Reporting group description: | |
| Subjects received single-agent sorafenib at the same dose and schedule as in their original Clinical Trial. | |
| Reporting group title | Sorafenib+Erlotinib |
| Reporting group description: | |
| Subjects received sorafenib and erlotinib combination at the same dose and schedule as in their original Clinical Trial. | |
| Subject analysis set title | Safety analysis set (SAF) |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| SAF included all subjects who received at least one dose of study medication. | |

Primary: Sorafenib treatment duration within STEP

| | |
|---|---|
| End point title | Sorafenib treatment duration within STEP ^[1] |
| End point description: | |
| Treatment duration was calculated in days as the date of the last dose of any study treatment minus date of the first dose of any study treatment plus one day. | |
| End point type | Primary |
| End point timeframe: | |
| From the date of the first sorafenib dose until the date of the last sorafenib dose, with a mean duration of 25 months and max duration of 153.8 months | |

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: Due to the nature of this trial, only descriptive statistics were performed. Neither confirmatory nor exploratory inferential statistical analyses were pre-specified.

| End point values | Sorafenib monotherapy | Sorafenib+Erlo tinib | | |
|---------------------------------------|-----------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 203 ^[2] | 1 ^[3] | | |
| Units: Months | | | | |
| median (inter-quartile range (Q1-Q3)) | 15.69 (6.41 to 33.19) | 40.13 (40.13 to 40.13) | | |

Notes:

[2] - SAF

[3] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with new treatment-emergent adverse events (TEAEs)

| | |
|-----------------|--|
| End point title | Number of subjects with new treatment-emergent adverse events (TEAEs) ^[4] |
|-----------------|--|

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject or clinical investigation subject administered with a pharmaceutical product. The adverse event did not necessarily have to have a causal relationship with this treatment. A serious adverse event (SAE) was any untoward medical occurrence that at any dose: resulted in death; was life-threatening; required in-patient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability or incapacity; was a congenital anomaly or birth defect; was an important medical event. A new treatment-emergent

adverse event (TEAE) was any AE that had a start date on or after ICF date in STEP and up to 30 days after the last sorafenib dose. A drug-related new TEAE was any new TEAE that had a causal relationship with the study treatment as assessed by the investigator. disc. = discontinuation

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From signing the ICF in STEP until 30 days after the last sorafenib dose, with a mean duration of 26 months

Notes:

[4] - 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: Due to the nature of this trial, only descriptive statistics were performed. Neither confirmatory nor exploratory inferential statistical analyses were pre-specified.

| End point values | Sorafenib monotherapy | Sorafenib+Erlo tinib | | |
|---|-----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 203 ^[5] | 1 ^[6] | | |
| Units: Subjects | | | | |
| Any AE | 166 | 1 | | |
| Serious AE (SAE) | 113 | 1 | | |
| AE leading to dose modification | 64 | 0 | | |
| AE leading to study drug discontinuation | 56 | 0 | | |
| AE leading to death | 37 | 0 | | |
| Sorafenib-related AE | 117 | 1 | | |
| Sorafenib-related SAE | 25 | 1 | | |
| Sorafenib-related AE leading to dose modification | 42 | 0 | | |
| Sorafenib-related AE leading to study drug disc. | 21 | 0 | | |
| Sorafenib-related AE leading to death | 2 | 0 | | |

Notes:

[5] - SAF

[6] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with new TEAEs of CTCAE grades 3 or higher by worst CTCAE grade

| | |
|-----------------|---|
| End point title | Number of subjects with new TEAEs of CTCAE grades 3 or higher by worst CTCAE grade ^[7] |
|-----------------|---|

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject or clinical investigation subject administered with a pharmaceutical product. The AE did not necessarily have to have a causal relationship with this treatment. A new treatment-emergent adverse event (TEAE) was any AE that had a start date on or after ICF date in STEP and up to 30 days after the last sorafenib dose. CTCAE: Common Terminology Criteria Adverse Event.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From signing the ICF in STEP until 30 days after the last sorafenib dose, with a mean duration of 26 months

Notes:

[7] - 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: Due to the nature of this trial, only descriptive statistics were performed. Neither confirmatory nor exploratory inferential statistical analyses were pre-specified.

| End point values | Sorafenib monotherapy | Sorafenib+Erlo tinib | | |
|-----------------------------|-----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 203 ^[8] | 1 ^[9] | | |
| Units: Subjects | | | | |
| Grade 3 | 71 | 1 | | |
| Grade 4 | 17 | 1 | | |
| Grade 5 | 37 | 0 | | |

Notes:

[8] - SAF

[9] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with study drug-related new TEAEs of CTCAE grades 3 or higher by worst CTCAE grade

| | |
|-----------------|---|
| End point title | Number of subjects with study drug-related new TEAEs of CTCAE grades 3 or higher by worst CTCAE grade ^[10] |
|-----------------|---|

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject or clinical investigation subject administered with a pharmaceutical product. The AE did not necessarily have to have a causal relationship with this treatment. A new treatment-emergent adverse event (TEAE) was any AE that had a start date on or after ICF date in STEP and up to 30 days after the last sorafenib dose. A drug-related new TEAE was a new TEAE that had a causal relationship with the study treatment as assessed by the investigator. CTCAE: Common Terminology Criteria Adverse Event.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From signing the ICF in STEP until 30 days after the last sorafenib dose, with a mean duration of 26 months

Notes:

[10] - 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: Due to the nature of this trial, only descriptive statistics were performed. Neither confirmatory nor exploratory inferential statistical analyses were pre-specified.

| End point values | Sorafenib monotherapy | Sorafenib+Erlo tinib | | |
|-----------------------------|-----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 203 ^[11] | 1 ^[12] | | |
| Units: Subjects | | | | |
| Grade 3 | 49 | 1 | | |
| Grade 4 | 6 | 0 | | |
| Grade 5 | 2 | 0 | | |

Notes:

[11] - SAF

[12] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with all adverse events

| | |
|-----------------|--|
| End point title | Number of subjects with all adverse events ^[13] |
|-----------------|--|

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject or clinical investigation subject administered with a pharmaceutical product. The AE did not necessarily have to have a causal relationship with this treatment. A drug-related AE was any AE that had a causal relationship with the study treatment as assessed by the investigator. All AEs in STEP were the combination of AEs ongoing from feeder studies and new TEAEs. disc. = discontinuation

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From signing the ICF in STEP until 30 days after the last sorafenib dose, with a mean duration of 26 months

Notes:

[13] - 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: Due to the nature of this trial, only descriptive statistics were performed. Neither confirmatory nor exploratory inferential statistical analyses were pre-specified.

| End point values | Sorafenib monotherapy | Sorafenib+Erlo tinib | | |
|---|-----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 203 ^[14] | 1 ^[15] | | |
| Units: Subjects | | | | |
| Any AE | 184 | 1 | | |
| Serious AE (SAE) | 114 | 1 | | |
| AE leading to dose modification | 72 | 0 | | |
| AE leading to study drug discontinuation | 56 | 0 | | |
| AE leading to death | 37 | 0 | | |
| Sorafenib-related AE | 159 | 1 | | |
| Sorafenib-related SAE | 26 | 1 | | |
| Sorafenib-related AE leading to dose modification | 53 | 0 | | |
| Sorafenib-related AE leading to study drug disc. | 21 | 0 | | |
| Sorafenib-related AE leading to death | 2 | 0 | | |

Notes:

[14] - SAF

[15] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with all adverse events of CTCAE grades 3 or higher by worst CTCAE grade

| | |
|-----------------|---|
| End point title | Number of subjects with all adverse events of CTCAE grades 3 or higher by worst CTCAE grade ^[16] |
|-----------------|---|

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject or clinical investigation subject administered with a pharmaceutical product. The AE did not necessarily have to have a causal relationship with this treatment. All AEs in STEP were the combination of AEs ongoing from feeder studies and new TEAEs.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From signing the ICF in STEP until 30 days after the last sorafenib dose, with a mean duration of 26 months

Notes:

[16] - 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: Due to the nature of this trial, only descriptive statistics were performed. Neither confirmatory nor exploratory inferential statistical analyses were pre-specified.

| End point values | Sorafenib monotherapy | Sorafenib+Erlo tinib | | |
|-----------------------------|-----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 203 ^[17] | 1 ^[18] | | |
| Units: Subjects | | | | |
| Grade 3 | 81 | 1 | | |
| Grade 4 | 17 | 1 | | |
| Grade 5 | 37 | 0 | | |

Notes:

[17] - SAF

[18] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with study drug-related all adverse events of CTCAE grades 3 or higher by worst CTCAE

| | |
|-----------------|--|
| End point title | Number of subjects with study drug-related all adverse events of CTCAE grades 3 or higher by worst CTCAE ^[19] |
|-----------------|--|

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject or clinical investigation subject administered with a pharmaceutical product. The AE did not necessarily have to have a causal relationship with this treatment. A drug-related AE was any AE that had a causal relationship with the study treatment as assessed by the investigator. All AEs in STEP was a combination of AEs ongoing from feeder studies and new TEAEs.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From signing the ICF in STEP until 30 days after the last sorafenib dose, with a mean duration of 26 months

Notes:

[19] - 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: Due to the nature of this trial, only descriptive statistics were performed. Neither confirmatory nor exploratory inferential statistical analyses were pre-specified.

| End point values | Sorafenib monotherapy | Sorafenib+Erlo tinib | | |
|-----------------------------|-----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 203 ^[20] | 1 ^[21] | | |
| Units: Subjects | | | | |
| Grade 3 | 65 | 1 | | |
| Grade 4 | 6 | 0 | | |
| Grade 5 | 2 | 0 | | |

Notes:

[20] - SAF

[21] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of deaths with primary cause of death

| | |
|---|--|
| End point title | Number of deaths with primary cause of death ^[22] |
| End point description: Primary cause of death included: any cause; progressive disease; toxicity due to study treatment (with at least one AE with outcome death); other (unspecified) or missing cause. | |
| End point type | Primary |
| End point timeframe: From signing the ICF in STEP until completion or discontinuation of the study, with a mean duration of 26 months | |

Notes:

[22] - 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: Due to the nature of this trial, only descriptive statistics were performed. Neither confirmatory nor exploratory inferential statistical analyses were pre-specified.

| End point values | Sorafenib monotherapy | Sorafenib+Erlo tinib | | |
|---------------------------------|-----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 203 ^[23] | 1 ^[24] | | |
| Units: Subjects | | | | |
| Any cause | 62 | 0 | | |
| Progressive disease | 34 | 0 | | |
| Toxicity due to study treatment | 3 | 0 | | |
| Other | 21 | 0 | | |
| Missing | 4 | 0 | | |

Notes:

[23] - SAF

[24] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with abnormal hematological and biochemical laboratory values by worst CTCAE grade

| | |
|---|---|
| End point title | Number of subjects with abnormal hematological and biochemical laboratory values by worst CTCAE grade ^[25] |
| End point description: Subjects with a specific laboratory value that were "not graded" are not included in the table. CTCAE grade was set to "not graded" if the reference ranges or other information necessary to derive grades were unavailable or result had a special character (such as > or <) then the grade. "99999" denotes that value was not countable due to no evaluable data for the subject. | |
| End point type | Primary |
| End point timeframe: From signing the ICF in STEP until 30 days after the last sorafenib dose, with a mean duration of 26 months | |

Notes:

[25] - 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: Due to the nature of this trial, only descriptive statistics were performed. Neither confirmatory nor exploratory inferential statistical analyses were pre-specified.

| End point values | Sorafenib monotherapy | Sorafenib+Erlo tinib | | |
|---------------------------------|-----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 203 ^[26] | 1 ^[27] | | |
| Units: Subjects | | | | |
| Neutrophils (n=165;0) - Grade 1 | 19 | 99999 | | |
| Neutrophils (n=165;0) - Grade 2 | 7 | 99999 | | |
| Neutrophils (n=165;0) - Grade 3 | 0 | 99999 | | |
| Neutrophils (n=165;0) - Grade 4 | 2 | 99999 | | |
| Hemoglobin (n=191;1) - Grade 1 | 67 | 1 | | |
| Hemoglobin (n=191;1) - Grade 2 | 40 | 0 | | |
| Hemoglobin (n=191;1) - Grade 3 | 13 | 0 | | |
| Hemoglobin (n=191;1) - Grade 4 | 8 | 0 | | |
| Lymphopenia (n=187;1) - Grade 1 | 37 | 0 | | |
| Lymphopenia (n=187) - Grade 2 | 37 | 0 | | |
| Lymphopenia (n=187;1) - Grade 3 | 20 | 0 | | |
| Lymphopenia (n=187;1) - Grade 4 | 4 | 1 | | |
| Platelets (n=189;1) - Grade 1 | 48 | 0 | | |
| Platelets (n=189;1) - Grade 2 | 7 | 0 | | |
| Platelets (n=189;1) - Grade 3 | 7 | 0 | | |
| Platelets (n=189;1) - Grade 4 | 17 | 1 | | |
| Leukocytes (n=192;1) - Grade 1 | 40 | 1 | | |
| Leukocytes (n=192;1) - Grade 2 | 12 | 0 | | |
| Leukocytes (n=19;1) - Grade 3 | 2 | 0 | | |
| Leukocytes (n=192;1) - Grade 4 | 1 | 0 | | |
| INR (n=82;0) - Grade 1 | 17 | 99999 | | |
| INR (n=82;0) - Grade 2 | 1 | 99999 | | |
| INR (n=82;0) - Grade 3 | 11 | 99999 | | |
| INR (n=82;0) - Grade 4 | 0 | 99999 | | |
| ALT (n=174;1) - Grade 1 | 66 | 1 | | |
| ALT (n=174;1) - Grade 2 | 13 | 0 | | |
| ALT (n=174;1) - Grade 3 | 7 | 0 | | |
| ALT (n=174;1) - Grade 4 | 0 | 0 | | |
| Amylase (n=178;1) - Grade 1 | 39 | 1 | | |
| Amylase (n=178;1) - Grade 2 | 12 | 0 | | |
| Amylase (n=178;1) - Grade 3 | 8 | 0 | | |
| Amylase (n=178;1) - Grade 4 | 0 | 0 | | |
| AST (n=183;1) - Grade 1 | 88 | 1 | | |
| AST (n=183;1) - Grade 2 | 19 | 0 | | |
| AST (n=183;1) - Grade 3 | 6 | 0 | | |
| AST (n=183;1) - Grade 4 | 0 | 0 | | |
| Lipase (n=165;1) - Grade 1 | 32 | 0 | | |
| Lipase (n=165;1) - Grade 2 | 11 | 1 | | |
| Lipase (n=165;1) - Grade 3 | 28 | 0 | | |
| Lipase (n=165;1) - Grade 4 | 7 | 0 | | |

Notes:

[26] - SAF

[27] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with ECOG performance status by 6-months time intervals

| | |
|--|--|
| End point title | Number of subjects with ECOG performance status by 6-months time intervals ^[28] |
| End point description: Eastern cooperative oncology group (ECOG) performance status: 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work; 2 = Ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours; 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours; 4 = Completely disabled, cannot carry on any self-care, totally confined to bed or chair; 5 = Dead | |
| End point type | Primary |
| End point timeframe: Up to 156 months | |

Notes:

[28] - 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: Due to the nature of this trial, only descriptive statistics were performed. Neither confirmatory nor exploratory inferential statistical analyses were pre-specified.

| End point values | Sorafenib monotherapy | Sorafenib+Erlo tinib | | |
|---------------------------------|-----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 203 ^[29] | 1 ^[30] | | |
| Units: Subjects | | | | |
| Months 1-6 (n=42;1) - Missing | 2 | 0 | | |
| Months 1-6 (n=42;1) - ECOG 0 | 28 | 1 | | |
| Months 1-6 (n=42;1) - ECOG 1 | 11 | 0 | | |
| Months 1-6 (n=42;1) - ECOG 2 | 1 | 0 | | |
| Months 7-12 (n=38;1) - Missing | 3 | 0 | | |
| Months 7-12 (n=38;1) - ECOG 0 | 29 | 1 | | |
| Months 7-12 (n=38;1) - ECOG 1 | 6 | 0 | | |
| Months 13-18 (n=33;1) - Missing | 2 | 0 | | |
| Months 13-18 (n=33;1) - ECOG 0 | 22 | 1 | | |
| Months 13-18 (n=33;1) - ECOG 1 | 7 | 0 | | |
| Months 13-18 (n=33;1) - ECOG 2 | 1 | 0 | | |
| Months 13-18 (n=33;1) - ECOG 3 | 1 | 0 | | |
| Months 19-24 (n=28;1) - Missing | 2 | 0 | | |
| Months 19-24 (n=28;1) - ECOG 0 | 15 | 1 | | |
| Months 19-24 (n=28;1) - ECOG 1 | 9 | 0 | | |
| Months 19-24 (n=28;1) - ECOG 2 | 1 | 0 | | |
| Months 19-24 (N=28;1) - ECOG 5 | 1 | 0 | | |
| Months 25-30 (n=23;1) - Missing | 2 | 0 | | |
| Months 25-30 (n=23;1) - ECOG 0 | 13 | 1 | | |
| Months 25-30 (n=23;1) - ECOG 1 | 7 | 0 | | |
| Months 25-30 (n=23;1) - ECOG 5 | 1 | 0 | | |
| Months 31-36 (n=19;1) - Missing | 1 | 0 | | |
| Months 31-36 (n=19;1) - ECOG 0 | 9 | 1 | | |
| Months 31-36 (n=19;1) - ECOG 1 | 8 | 0 | | |
| Months 31-36 (n=19;1) - ECOG 5 | 1 | 0 | | |
| Months 37-42 (n=19;1) - ECOG 0 | 10 | 1 | | |
| Months 37-42 (n=19;1) - ECOG 1 | 8 | 0 | | |
| Months 37-42 (n=19;1) - ECOG 5 | 1 | 0 | | |
| Months 43-48 (n=16;1) - ECOG 0 | 9 | 0 | | |

| | | | | |
|---|----|---|--|--|
| Months 43-48 (n=16;1) - ECOG 1 | 6 | 0 | | |
| Months 43-48 (n=16;1) - ECOG 5 | 1 | 0 | | |
| Months 49-54 (n=13;1) - ECOG 0 | 7 | 0 | | |
| Months 49-54 (n=13;1) - ECOG 1 | 6 | 0 | | |
| Months 55-60 (n=19;1) - Missing | 2 | 0 | | |
| Months 55-60 (n=19;1) - ECOG 0 | 11 | 0 | | |
| Months 55-60 (n=19;1) - ECOG 1 | 6 | 0 | | |
| Months 61-66 (n=15;1) - Missing | 1 | 0 | | |
| Months 61-66 (n=15;1) - ECOG 0 | 8 | 0 | | |
| Months 61-66 (n=15;1) - ECOG 1 | 6 | 0 | | |
| Months 67-72 (n=14;1) - ECOG 0 | 8 | 0 | | |
| Months 67-72 (n=14;1) - ECOG 1 | 6 | 0 | | |
| Months 73-78 (n=13;1) - ECOG 0 | 7 | 0 | | |
| Months 73-78 (n=13;1) - ECOG 1 | 5 | 0 | | |
| Months 73-78 (n=13;1) - ECOG 2 | 1 | 0 | | |
| Months 79-84 (n=10;1) - ECOG 0 | 6 | 0 | | |
| Months 79-84 (n=10;1) - ECOG 1 | 4 | 0 | | |
| Months 85-90 (n=10;1) - ECOG 0 | 4 | 0 | | |
| Months 85-90 (n=10;1) - ECOG 1 | 5 | 0 | | |
| Months 85-90 (n=10;1) - ECOG 2 | 1 | 0 | | |
| Months 91-96 (n=9;1) - ECOG 0 | 5 | 0 | | |
| Months 91-96 (n=9;1) - ECOG 1 | 4 | 0 | | |
| Months 97-102 (n=8;1) - Missing | 2 | 0 | | |
| Months 97-102 (n=8;1) - ECOG 0 | 4 | 0 | | |
| Months 97-102 (n=8;1) - ECOG 1 | 2 | 0 | | |
| Months 103-108 (n=5;1) - Missing | 1 | 0 | | |
| Months 103-108 (n=5;1) - ECOG 0 | 1 | 0 | | |
| Months 103-108 (n=5;1) - ECOG 1 | 3 | 0 | | |
| Months 109-114 (n=3;1) - ECOG 0 | 1 | 0 | | |
| Months 109-114 (n=3;1) - ECOG 1 | 2 | 0 | | |
| Months 115-120 (n=3;1) - ECOG 0 | 2 | 0 | | |
| Months 115-120 (n=3;1) - ECOG 2 | 1 | 0 | | |
| Months 121-126 (n=3;1) - ECOG 0 | 1 | 0 | | |
| Months 121-126 (n=3;1) - ECOG 1 | 1 | 0 | | |
| Months 121-126 (n=3;1) - ECOG 2 | 1 | 0 | | |
| Months 127-132 (n=3;1) - ECOG 0 | 1 | 0 | | |
| Months 127-132 (n=3;1) - ECOG 1 | 2 | 0 | | |
| Months 133-138 (n=3;1) - ECOG 0 | 1 | 0 | | |
| Months 133-138 (n=3;1) - ECOG 1 | 2 | 0 | | |
| Months 139-144 (n=3;1) - ECOG 0 | 1 | 0 | | |
| Months 139-144 (n=3;1) - ECOG 1 | 1 | 0 | | |
| Months 139-144 (n=3;1) - ECOG 2 | 1 | 0 | | |
| Months 145-150 (n=3;1) - ECOG 0 | 1 | 0 | | |
| Months 145-150 (n=3;1) - ECOG 1 | 1 | 0 | | |
| Months 145-150 (n=3;1) - ECOG 2 | 1 | 0 | | |
| Months 151-156 (n=3;1) - ECOG 0 | 1 | 0 | | |
| Months 151-156 (n=3;1) - ECOG 1 | 1 | 0 | | |
| Months 151-156 (n=3;1) - ECOG 2 | 1 | 0 | | |
| Last available value (n=64;1) - Missing | 9 | 0 | | |
| Last available value (n=64;1) - ECOG 0 | 20 | 1 | | |
| Last available value (n=64;1) - ECOG 1 | 25 | 0 | | |
| Last available value (n=64;1) - ECOG 2 | 4 | 0 | | |

| | | | | |
|--|---|---|--|--|
| Last available value (n=64;1) - ECOG 3 | 1 | 0 | | |
| Last available value (n=64;1) - ECOG 5 | 5 | 0 | | |

Notes:

[29] - SAF

[30] - SAF

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing the ICF in STEP until 30 days after the last sorafenib dose, with a mean duration of 26 months

Adverse event reporting additional description:

Adverse event reporting for the numbers of deaths (all causes) considers all deaths that occurred at any time during the study until the end of the follow up (with a mean duration of 26 months); deaths resulting from adverse events considers both adverse events with CTCAE grade 5 and/or adverse events with outcome 'Fatal'.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 24.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | Sorafenib+Erlotinib |
|-----------------------|---------------------|

Reporting group description:

Subjects received sorafenib and erlotinib combination at the same dose and schedule as in their original Clinical Trial.

| | |
|-----------------------|-----------------------|
| Reporting group title | Sorafenib monotherapy |
|-----------------------|-----------------------|

Reporting group description:

Subjects received single-agent sorafenib at the same dose and schedule as in their original Clinical Trial.

| Serious adverse events | Sorafenib+Erlotinib | Sorafenib monotherapy | |
|---|---------------------|-----------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | 114 / 203 (56.16%) | |
| number of deaths (all causes) | 0 | 62 | |
| number of deaths resulting from adverse events | 0 | 39 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone cancer metastatic | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic myeloid leukaemia | | | |

| | | | |
|---|---------------|-----------------|--|
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clear cell renal cell carcinoma | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatocellular carcinoma | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 4 / 203 (1.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemangioma | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver carcinoma ruptured | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to bone | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant neoplasm of ampulla of Vater | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neoplasm recurrence | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuroendocrine tumour of the lung metastatic | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal neoplasm | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphoedema | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery occlusion | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Stent placement | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 6 / 203 (2.96%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 6 | |
| Disease progression | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Impaired healing | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---------------|-----------------|--|
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 5 / 203 (2.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 5 | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 203 (1.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 3 | |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Apnoea | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 4 / 203 (1.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pleural effusion | | | |

| | | | |
|---|---------------|-----------------|--|
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 203 (1.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 4 / 203 (1.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 4 | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Personality change | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Angiogram | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| International normalised ratio increased | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---------------|-----------------|--|
| Injury, poisoning and procedural complications | | | |
| Limb injury | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Animal bite | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neurological procedural complication | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tendon rupture | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 203 (1.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 203 (1.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiovascular insufficiency | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |

| | | | |
|---|---------------|-----------------|--|
| subjects affected / exposed | 0 / 1 (0.00%) | 5 / 203 (2.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Basal ganglia infarction | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain oedema | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic encephalopathy | | | |

| | | | |
|---|---------------|-----------------|--|
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Migraine | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Presyncope | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord compression | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 8 / 203 (3.94%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Retinal vein occlusion | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---------------|-----------------|--|
| Gastrointestinal disorders | | | |
| Ascites | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 4 / 203 (1.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal obstruction | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis haemorrhagic | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoperitoneum | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subileus | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Bile duct stone | | | |

| | | | |
|---|---------------|-----------------|--|
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 203 (1.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 203 (1.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic lesion | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaundice | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Decubitus ulcer | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |

| | | | |
|---|---------------|-----------------|--|
| Renal failure | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 203 (1.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 203 (1.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neck mass | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Pathological fracture | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abscess limb | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear infection | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Furuncle | | | |

| | | | |
|---|---------------|-----------------|--|
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Groin abscess | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Localised infection | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 9 / 203 (4.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 3 | |
| Perirectal abscess | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 6 / 203 (2.96%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 3 | |
| Staphylococcal infection | | | |

| | | | |
|---|---------------|-----------------|--|
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spontaneous bacterial peritonitis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cachexia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 1 %

| Non-serious adverse events | Sorafenib+Erlotinib | Sorafenib monotherapy | |
|---|---------------------|-----------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | 151 / 203 (74.38%) | |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 203 (1.48%) | |
| occurrences (all) | 0 | 7 | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | 26 / 203 (12.81%) | |
| occurrences (all) | 2 | 26 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 33 / 203 (16.26%) | |
| occurrences (all) | 0 | 41 | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 6 / 203 (2.96%) | |
| occurrences (all) | 0 | 7 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 203 (1.48%) | |
| occurrences (all) | 0 | 3 | |
| Dysphonia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 4 / 203 (1.97%) | |
| occurrences (all) | 0 | 4 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 5 / 203 (2.46%) | |
| occurrences (all) | 0 | 5 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 4 / 203 (1.97%) | |
| occurrences (all) | 0 | 4 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 8 / 203 (3.94%) | |
| occurrences (all) | 0 | 9 | |
| Lipase increased | | | |

| | | | |
|--------------------------------------|---------------|------------------|--|
| subjects affected / exposed | 0 / 1 (0.00%) | 13 / 203 (6.40%) | |
| occurrences (all) | 0 | 15 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 8 / 203 (3.94%) | |
| occurrences (all) | 0 | 10 | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 7 / 203 (3.45%) | |
| occurrences (all) | 0 | 9 | |
| Amylase increased | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 9 / 203 (4.43%) | |
| occurrences (all) | 0 | 13 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 6 / 203 (2.96%) | |
| occurrences (all) | 0 | 6 | |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 10 / 203 (4.93%) | |
| occurrences (all) | 0 | 10 | |
| Nervous system disorders | | | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 203 (1.48%) | |
| occurrences (all) | 0 | 3 | |
| Headache | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 203 (1.48%) | |
| occurrences (all) | 0 | 3 | |
| Lethargy | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 203 (1.48%) | |
| occurrences (all) | 0 | 3 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 203 (1.48%) | |
| occurrences (all) | 0 | 3 | |
| Blood and lymphatic system disorders | | | |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 5 / 203 (2.46%) | |
| occurrences (all) | 0 | 5 | |
| Thrombocytopenia | | | |

| | | | |
|--|---------------|--------------------|--|
| subjects affected / exposed | 0 / 1 (0.00%) | 4 / 203 (1.97%) | |
| occurrences (all) | 0 | 5 | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 15 / 203 (7.39%) | |
| occurrences (all) | 0 | 16 | |
| Gastrointestinal disorders | | | |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 5 / 203 (2.46%) | |
| occurrences (all) | 0 | 6 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 5 / 203 (2.46%) | |
| occurrences (all) | 0 | 13 | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 8 / 203 (3.94%) | |
| occurrences (all) | 0 | 18 | |
| Ascites | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 4 / 203 (1.97%) | |
| occurrences (all) | 0 | 4 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 100 / 203 (49.26%) | |
| occurrences (all) | 0 | 147 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 11 / 203 (5.42%) | |
| occurrences (all) | 0 | 14 | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 12 / 203 (5.91%) | |
| occurrences (all) | 0 | 15 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 203 (1.48%) | |
| occurrences (all) | 0 | 3 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 6 / 203 (2.96%) | |
| occurrences (all) | 0 | 10 | |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |

| | | | |
|---|----------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 1 (100.00%) 1 | 2 / 203 (0.99%) 3 | |
| Alopecia subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 11 / 203 (5.42%) 12 | |
| Dry skin subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 6 / 203 (2.96%) 6 | |
| Palmar-plantar erythrodysesthesia syndrome subjects affected / exposed occurrences (all) | 1 / 1 (100.00%) 1 | 82 / 203 (40.39%) 96 | |
| Pruritus subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 4 / 203 (1.97%) 4 | |
| Rash subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 16 / 203 (7.88%) 19 | |
| Renal and urinary disorders Renal failure subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 5 / 203 (2.46%) 6 | |
| Proteinuria subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 5 / 203 (2.46%) 5 | |
| Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 3 / 203 (1.48%) 3 | |
| Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 3 / 203 (1.48%) 3 | |
| Arthralgia subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 6 / 203 (2.96%) 10 | |
| Muscle spasms | | | |

| | | | |
|------------------------------------|---------------|------------------|--|
| subjects affected / exposed | 0 / 1 (0.00%) | 5 / 203 (2.46%) | |
| occurrences (all) | 0 | 7 | |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 203 (1.48%) | |
| occurrences (all) | 0 | 3 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 16 / 203 (7.88%) | |
| occurrences (all) | 0 | 16 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 5 / 203 (2.46%) | |
| occurrences (all) | 0 | 8 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 203 (1.48%) | |
| occurrences (all) | 0 | 3 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|--|
| 16 March 2011 | Global amendment 02 forming integrated protocol Version 3.0 introduced the following changes: An inclusion criterion was added to allow subjects who received combination treatment with sorafenib (Nexavar) and TACE (transarterial chemoembolization) in their originating study to be eligible for this extension study. The exclusion criterion regarding concurrent anti-cancer chemotherapy was, therefore, modified to clarify that the exclusion did not apply to subjects being treated with sorafenib in combination with TACE. |
| 30 March 2012 | Global amendment 03 forming integrated protocol Version 4.0 introduced the following changes: 1. Inclusion of an Evaluation of Overall Survival. 2. Inclusion of safety as a stated objective with the main objective of this program remained unchanged. |
| 25 March 2014 | Global amendment 04 forming integrated protocol Version 5.0 introduced the following changes: 1. Removal of all references to erlotinib. 2. Removal of references to placebo in association with sorafenib administration. 3. Addition of TACE to the permissible anticancer chemotherapies and addition of guidance on Sorafenib dose modification in combination with TACE. 4. Clarification of which CTC version was used for the grading of liver function abnormalities. |
| 15 May 2018 | Global amendment 07 forming integrated protocol Version 6.0 introduced the following changes: 1. Overall survival (OS) evaluation removed from the study objectives. 2. Safety visits were modified. 3. Laboratory evaluations were modified. 4. Follow-up period was changed. |
| 26 May 2020 | Global amendment 08 forming integrated protocol Version 7.0 introduced the following changes: 1. Added Post-Trial Access Program. 2. Removal of the instructions for dose modifications for the combination of sorafenib with capecitabine and TACE. 3. Added clarification for continuation on study drug. 4. Added clarification for ending the study. 5. Added clarification on last patient last visit date. 6. The timepoint of the performance of the analyses was corrected, last patient last visit was changed to "after the end of the study". |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

No primary endpoints were defined specifically for study STEP as the primary purpose of this study was to enable patients to continue sorafenib treatment. The 26-month long-term follow-up duration was the mean follow-up duration for the subjects.

Notes: