



Clinical trial results:

A multicenter, randomized, double-blind Phase III trial to evaluate efficacy and safety of BI 695502 plus chemotherapy versus Avastin® plus chemotherapy in patients with advanced nonsquamous Non-Small Cell Lung Cancer

Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2014-002161-30 |
| Trial protocol | HU PT ES DE PL HR GR |
| Global end of trial date | 16 November 2018 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 |
| This version publication date | 27 November 2019 |
| First version publication date | 27 November 2019 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | 1302.5 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02272413 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Boehringer Ingelheim |
| Sponsor organisation address | Binger Strasse 173, Ingelheim am Rhein, Germany, 55216 |
| Public contact | QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com |
| Scientific contact | QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 16 November 2018 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 16 November 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main trial objective was to establish statistical equivalence in terms of efficacy until 18 weeks of first-line treatment with BI 695502 plus chemotherapy versus United States (US)-licensed Avastin® plus chemotherapy followed by maintenance monotherapy with either BI 695502 or US-licensed Avastin® in patients with advanced non-squamous non-small cell lung cancer (nsNSCLC).

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 | 21 July 2015 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 4 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Brazil: 37 |
| Country: Number of subjects enrolled | Bulgaria: 14 |
| Country: Number of subjects enrolled | Chile: 26 |
| Country: Number of subjects enrolled | Croatia: 10 |
| Country: Number of subjects enrolled | Egypt: 38 |
| Country: Number of subjects enrolled | Germany: 1 |
| Country: Number of subjects enrolled | Greece: 30 |
| Country: Number of subjects enrolled | Hungary: 58 |
| Country: Number of subjects enrolled | Italy: 15 |
| Country: Number of subjects enrolled | Japan: 98 |
| Country: Number of subjects enrolled | Korea, Republic of: 15 |
| Country: Number of subjects enrolled | Malaysia: 13 |
| Country: Number of subjects enrolled | Mexico: 56 |
| Country: Number of subjects enrolled | Philippines: 25 |
| Country: Number of subjects enrolled | Poland: 33 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Portugal: 10 |
| Country: Number of subjects enrolled | Romania: 15 |
| Country: Number of subjects enrolled | Russian Federation: 84 |
| Country: Number of subjects enrolled | Serbia: 63 |
| Country: Number of subjects enrolled | South Africa: 14 |
| Country: Number of subjects enrolled | Spain: 26 |
| Country: Number of subjects enrolled | Thailand: 61 |
| Country: Number of subjects enrolled | Turkey: 64 |
| Country: Number of subjects enrolled | Argentina: 7 |
| Country: Number of subjects enrolled | Ukraine: 179 |
| Country: Number of subjects enrolled | United Kingdom: 3 |
| Country: Number of subjects enrolled | United States: 31 |
| Country: Number of subjects enrolled | Vietnam: 4 |
| Worldwide total number of subjects | 1030 |
| EEA total number of subjects | 215 |

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) | 623 |
| From 65 to 84 years | 406 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

Phase III, randomized, double-blind, multicenter, active comparator, parallel 2-arm trial in patients with advanced non-squamous non-small cell lung cancer (nsNSCLC). From 21December2017, Sponsor recommended, patients to be switched from BI 695502 to reference product Avastin® (commercially available) as soon as it was available at clinical site.

Pre-assignment

Screening details:

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

Period 1

| | |
|------------------------------|---|
| Period 1 title | Randomized through Treatment Start |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

This was a double-blind trial. Patients, Investigators, and trial personnel, except the unblinded pharmacist or designated person, remained blinded with regard to the randomized treatment assignments until after final database lock. No unblinding of sites or patients was performed at the time of switching from BI 695502 to Avastin®, to ensure continued unbiased assessments.

Arms

| | |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes |
| Arm title | BI 695502 |

Arm description:

Patients received BI 695502 solution for i.v. infusion, 15 mg/kg bw, every 3 weeks for up to 6 cycles. During the induction cycles, patients also received standard combination chemotherapy consisting of paclitaxel 200 mg/m² body surface area (BSA), followed by carboplatin target area under the curve (AUC) 6 mg/mL*min, with adequate pre- and concomitant medication.

After Cycle 4 to 6, for responding or stabilized patients, maintenance treatment with BI 695502 monotherapy could be started per the original randomization. Patients then received BI 695502 as a single agent until disease progression, death, withdrawal of consent, unacceptable toxicity, or until the Switch Visit (when each patient was switched to receive commercially available Avastin®), whichever occurred earlier.

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | BI 695502 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

A dose of 15 mg/kg bw of BI 695502 was administered by i.v. infusion every 3 weeks (administered over 90 minutes for the first infusion; if well tolerated, administered over 60 minutes for the second infusion and subsequently administered over 30 minutes).

| | |
|--|-----------------------|
| Investigational medicinal product name | Carboplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Carboplatin target AUC dose of 6 mg/mL*min (administered as 30-to 60-minute i.v. infusion) every 3 weeks (21 days, 1 cycle) for up to 6 cycles.

| | |
|--|-----------------------|
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Paclitaxel 200 mg/m² BSA i.v. infusion (administered according to regular institutional practice) every 3 weeks (21 days, 1 cycle) for up to 6 cycles.

| | |
|------------------|----------------------|
| Arm title | US-licensed Avastin® |
|------------------|----------------------|

Arm description:

Patients received US-licensed Avastin® solution for i.v. infusion, 15 mg/kg bw, every 3 weeks for up to 6 cycles. During the induction cycles, patients also received standard combination chemotherapy consisting of paclitaxel 200 mg/m² BSA, followed by carboplatin target AUC 6 mg/mL*min, with adequate pre- and concomitant medication.

After Cycle 4 to 6, for responding or stabilized patients, maintenance treatment with US-licensed Avastin® monotherapy could be started per the original randomization. Patients then received US-licensed Avastin® as a single agent until disease progression, death, withdrawal of consent, unacceptable toxicity, or until the Switch Visit (when each patient was switched to receive commercially available Avastin®), whichever occurred earlier.

| | |
|--|---------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | US-licensed Avastin® |
| Investigational medicinal product code | |
| Other name | Bevacizumab, Avastin® |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

A dose of 15 mg/kg bw of US-licensed Avastin® was administered by i.v. infusion every 3 weeks (administered over 90 minutes for the first infusion; if well tolerated, administered over 60 minutes for the second infusion and subsequently administered over 30 minutes).

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Avastin® |
| Investigational medicinal product code | |
| Other name | Bevacizumab |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

A dose of 15 mg/kg bw of commercially available Avastin® was administered by i.v. infusion every 3 weeks.

| | |
|--|-----------------------|
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Paclitaxel 200 mg/m² BSA i.v. infusion (administered according to regular institutional practice) every 3 weeks (21 days, 1 cycle) for up to 6 cycles.

| | |
|--|-----------------------|
| Investigational medicinal product name | Carboplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Carboplatin target AUC dose of 6 mg/mL*min (administered as 30-to 60-minute i.v. infusion) every 3

weeks (21 days, 1 cycle) for up to 6 cycles.

| Number of subjects in period 1 | BI 695502 | US-licensed Avastin® |
|--------------------------------|-----------|----------------------|
| Started | 338 | 333 |
| Treated | 335 | 328 |
| Completed | 335 | 328 |
| Not completed | 3 | 5 |
| Not treated | 3 | 5 |

Period 2

| | |
|------------------------------|---|
| Period 2 title | Pre-switch period |
| Is this the baseline period? | Yes ^[1] |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

This was a double-blind trial. Patients, Investigators, and trial personnel, except the unblinded pharmacist or designated person, remained blinded with regard to the randomized treatment assignments until after final database lock. No unblinding of sites or patients was performed at the time of switching from BI 695502 to Avastin®, to ensure continued unbiased assessments.

Arms

| | |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes |
| Arm title | BI 695502 |

Arm description:

Patients received BI 695502 solution for i.v. infusion, 15 mg/kg bw, every 3 weeks for up to 6 cycles. During the induction cycles, patients also received standard combination chemotherapy consisting of paclitaxel 200 mg/m² BSA, followed by carboplatin target AUC 6 mg/mL*min, with adequate pre- and concomitant medication.

After Cycle 4 to 6, for responding or stabilized patients, maintenance treatment with BI 695502 monotherapy could be started per the original randomization. Patients then received BI 695502 as a single agent until disease progression, death, withdrawal of consent, unacceptable toxicity, or until the Switch Visit (when each patient was switched to receive commercially available Avastin®), whichever occurred earlier.

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | BI 695502 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

A dose of 15 mg/kg bw of BI 695502 was administered by i.v. infusion every 3 weeks (administered over 90 minutes for the first infusion; if well tolerated, administered over 60 minutes for the second infusion and subsequently administered over 30 minutes).

| | |
|--|-----------------------|
| Investigational medicinal product name | Carboplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Carboplatin target AUC dose of 6 mg/mL*min (administered as 30-to 60-minute i.v. infusion) every 3 weeks (21 days, 1 cycle) for up to 6 cycles.

| | |
|--|-----------------------|
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Paclitaxel 200 mg/m² BSA i.v. infusion (administered according to regular institutional practice) every 3 weeks (21 days, 1 cycle) for up to 6 cycles.

| | |
|------------------|----------------------|
| Arm title | US-licensed Avastin® |
|------------------|----------------------|

Arm description:

Patients received US-licensed Avastin® solution for i.v. infusion, 15 mg/kg bw, every 3 weeks for up to 6 cycles. During the induction cycles, patients also received standard combination chemotherapy consisting of paclitaxel 200 mg/m² BSA, followed by carboplatin target AUC 6 mg/mL*min, with adequate pre- and concomitant medication.

After Cycle 4 to 6, for responding or stabilized patients, maintenance treatment with US-licensed Avastin® monotherapy could be started per the original randomization. Patients then received US-licensed Avastin® as a single agent until disease progression, death, withdrawal of consent, unacceptable toxicity, or until the Switch Visit (when each patient was switched to receive commercially available Avastin®), whichever occurred earlier.

| | |
|--|---------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | US-licensed Avastin® |
| Investigational medicinal product code | |
| Other name | Bevacizumab, Avastin® |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

A dose of 15 mg/kg bw of US-licensed Avastin® was administered by i.v. infusion every 3 weeks (administered over 90 minutes for the first infusion; if well tolerated, administered over 60 minutes for the second infusion and subsequently administered over 30 minutes).

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Avastin® |
| Investigational medicinal product code | |
| Other name | Bevacizumab |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

A dose of 15 mg/kg bw of commercially available Avastin® was administered by i.v. infusion every 3 weeks.

| | |
|--|-----------------------|
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Paclitaxel 200 mg/m² BSA i.v. infusion (administered according to regular institutional practice) every 3 weeks (21 days, 1 cycle) for up to 6 cycles.

| | |
|--|-----------------------|
| Investigational medicinal product name | Carboplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Carboplatin target AUC dose of 6 mg/mL*min (administered as 30-to 60-minute i.v. infusion) every 3 weeks (21 days, 1 cycle) for up to 6 cycles.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 2 (pre-switch period) is selected as baseline period as baseline characteristics were recorded based on participants who were treated and started pre-switch period (335 and 328).

| Number of subjects in period 2^[2] | BI 695502 | US-licensed Avastin® |
|---|-----------|----------------------|
| Started | 335 | 328 |
| Completed | 42 | 46 |
| Not completed | 293 | 282 |
| Adverse event, serious fatal | 26 | 26 |
| Consent withdrawn by subject | 27 | 15 |
| Physician decision | 6 | 18 |
| Adverse event, non-fatal | 38 | 37 |
| Progressive disease | 185 | 173 |
| Lost to follow-up | - | 2 |
| Other than listed | 10 | 11 |
| Protocol deviation | 1 | - |

Notes:

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

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

Period 3

| | |
|------------------------------|---|
| Period 3 title | Post-switch period |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

This was a double-blind trial. Patients, Investigators, and trial personnel, except the unblinded pharmacist or designated person, remained blinded with regard to the randomized treatment assignments until after final database lock. No unblinding of sites or patients was performed at the time of switching from BI 695502 to Avastin®, to ensure continued unbiased assessments.

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|-----------|
| Arm title | BI 695502 |
|------------------|-----------|

Arm description:

Patients received BI 695502 solution for i.v. infusion, 15 mg/kg bw, every 3 weeks for up to 6 cycles. During the induction cycles, patients also received standard combination chemotherapy consisting of paclitaxel 200 mg/m² BSA, followed by carboplatin target AUC 6 mg/mL*min, with adequate pre- and concomitant medication.

After Cycle 4 to 6, for responding or stabilized patients, maintenance treatment with BI 695502 monotherapy could be started per the original randomization. Patients then received BI 695502 as a single agent until disease progression, death, withdrawal of consent, unacceptable toxicity, or until the Switch Visit (when each patient was switched to receive commercially available Avastin®), whichever occurred earlier.

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | BI 695502 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

A dose of 15 mg/kg bw of BI 695502 was administered by i.v. infusion every 3 weeks (administered over 90 minutes for the first infusion; if well tolerated, administered over 60 minutes for the second infusion and subsequently administered over 30 minutes).

| | |
|--|-----------------------|
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Paclitaxel 200 mg/m² BSA i.v. infusion (administered according to regular institutional practice) every 3 weeks (21 days, 1 cycle) for up to 6 cycles.

| | |
|--|-----------------------|
| Investigational medicinal product name | Carboplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Carboplatin target AUC dose of 6 mg/mL*min (administered as 30-to 60-minute i.v. infusion) every 3 weeks (21 days, 1 cycle) for up to 6 cycles.

| | |
|------------------|----------------------|
| Arm title | US-licensed Avastin® |
|------------------|----------------------|

Arm description:

Patients received US-licensed Avastin® solution for i.v. infusion, 15 mg/kg bw, every 3 weeks for up to 6 cycles. During the induction cycles, patients also received standard combination chemotherapy consisting of paclitaxel 200 mg/m² BSA, followed by carboplatin target AUC 6 mg/mL*min, with adequate pre- and concomitant medication.

After Cycle 4 to 6, for responding or stabilized patients, maintenance treatment with US-licensed Avastin® monotherapy could be started per the original randomization. Patients then received US-licensed Avastin® as a single agent until disease progression, death, withdrawal of consent, unacceptable toxicity, or until the Switch Visit (when each patient was switched to receive commercially available Avastin®), whichever occurred earlier.

| | |
|--|---------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | US-licensed Avastin® |
| Investigational medicinal product code | |
| Other name | Bevacizumab, Avastin® |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

A dose of 15 mg/kg bw of US-licensed Avastin® was administered by i.v. infusion every 3 weeks (administered over 90 minutes for the first infusion; if well tolerated, administered over 60 minutes for the second infusion and subsequently administered over 30 minutes).

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Avastin® |
| Investigational medicinal product code | |
| Other name | Bevacizumab |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

A dose of 15 mg/kg bw of commercially available Avastin® was administered by i.v. infusion every 3 weeks.

| | |
|--|-----------------------|
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Paclitaxel 200 mg/m² BSA i.v. infusion (administered according to regular institutional practice) every 3 weeks (21 days, 1 cycle) for up to 6 cycles.

| | |
|--|-----------------------|
| Investigational medicinal product name | Carboplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Carboplatin target AUC dose of 6 mg/mL*min (administered as 30-to 60-minute i.v. infusion) every 3 weeks (21 days, 1 cycle) for up to 6 cycles.

| Number of subjects in period 3 | BI 695502 | US-licensed Avastin® |
|--------------------------------|-----------|----------------------|
| Started | 42 | 46 |
| Completed | 0 | 0 |
| Not completed | 42 | 46 |
| Adverse event, serious fatal | 3 | 2 |
| Consent withdrawn by subject | 1 | 2 |
| Physician decision | 1 | 1 |
| Adverse event, non-fatal | 4 | 4 |
| Study terminated by sponsor | 8 | 11 |
| Progressive disease | 21 | 21 |
| Other than listed | 4 | 5 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | BI 695502 |
|-----------------------|-----------|

Reporting group description:

Patients received BI 695502 solution for i.v. infusion, 15 mg/kg bw, every 3 weeks for up to 6 cycles. During the induction cycles, patients also received standard combination chemotherapy consisting of paclitaxel 200 mg/m² BSA, followed by carboplatin target AUC 6 mg/mL*min, with adequate pre- and concomitant medication.

After Cycle 4 to 6, for responding or stabilized patients, maintenance treatment with BI 695502 monotherapy could be started per the original randomization. Patients then received BI 695502 as a single agent until disease progression, death, withdrawal of consent, unacceptable toxicity, or until the Switch Visit (when each patient was switched to receive commercially available Avastin®), whichever occurred earlier.

| | |
|-----------------------|----------------------|
| Reporting group title | US-licensed Avastin® |
|-----------------------|----------------------|

Reporting group description:

Patients received US-licensed Avastin® solution for i.v. infusion, 15 mg/kg bw, every 3 weeks for up to 6 cycles. During the induction cycles, patients also received standard combination chemotherapy consisting of paclitaxel 200 mg/m² BSA, followed by carboplatin target AUC 6 mg/mL*min, with adequate pre- and concomitant medication.

After Cycle 4 to 6, for responding or stabilized patients, maintenance treatment with US-licensed Avastin® monotherapy could be started per the original randomization. Patients then received US-licensed Avastin® as a single agent until disease progression, death, withdrawal of consent, unacceptable toxicity, or until the Switch Visit (when each patient was switched to receive commercially available Avastin®), whichever occurred earlier.

| Reporting group values | BI 695502 | US-licensed Avastin® | Total |
|------------------------|-----------|----------------------|-------|
| Number of subjects | 335 | 328 | 663 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|--|--------|--------|-----|
| Age Continuous | | | |
| Full Analysis Set (FAS): The FAS contained all randomized patients who received at least 1 dose of trial drug and who had a baseline tumor assessment. | | | |
| Units: years | | | |
| arithmetic mean | 61.2 | 61.3 | |
| standard deviation | ± 9.89 | ± 9.22 | - |
| Sex: Female, Male | | | |
| FAS | | | |
| Units: Subjects | | | |
| Female | 121 | 125 | 246 |
| Male | 214 | 203 | 417 |
| Race (NIH/OMB) | | | |
| FAS | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 64 | 71 | 135 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 1 | 1 | 2 |
| White | 258 | 248 | 506 |
| More than one race | 0 | 0 | 0 |

| | | | |
|-------------------------|-----|-----|-----|
| Unknown or Not Reported | 12 | 8 | 20 |
| Ethnicity (NIH/OMB) | | | |
| FAS | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 43 | 34 | 77 |
| Not Hispanic or Latino | 284 | 285 | 569 |
| Unknown or Not Reported | 8 | 9 | 17 |

End points

End points reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | BI 695502 |
|-----------------------|-----------|

Reporting group description:

Patients received BI 695502 solution for i.v. infusion, 15 mg/kg bw, every 3 weeks for up to 6 cycles. During the induction cycles, patients also received standard combination chemotherapy consisting of paclitaxel 200 mg/m² body surface area (BSA), followed by carboplatin target area under the curve (AUC) 6 mg/mL*min, with adequate pre- and concomitant medication.

After Cycle 4 to 6, for responding or stabilized patients, maintenance treatment with BI 695502 monotherapy could be started per the original randomization. Patients then received BI 695502 as a single agent until disease progression, death, withdrawal of consent, unacceptable toxicity, or until the Switch Visit (when each patient was switched to receive commercially available Avastin®), whichever occurred earlier.

| | |
|-----------------------|----------------------|
| Reporting group title | US-licensed Avastin® |
|-----------------------|----------------------|

Reporting group description:

Patients received US-licensed Avastin® solution for i.v. infusion, 15 mg/kg bw, every 3 weeks for up to 6 cycles. During the induction cycles, patients also received standard combination chemotherapy consisting of paclitaxel 200 mg/m² BSA, followed by carboplatin target AUC 6 mg/mL*min, with adequate pre- and concomitant medication.

After Cycle 4 to 6, for responding or stabilized patients, maintenance treatment with US-licensed Avastin® monotherapy could be started per the original randomization. Patients then received US-licensed Avastin® as a single agent until disease progression, death, withdrawal of consent, unacceptable toxicity, or until the Switch Visit (when each patient was switched to receive commercially available Avastin®), whichever occurred earlier.

| | |
|-----------------------|-----------|
| Reporting group title | BI 695502 |
|-----------------------|-----------|

Reporting group description:

Patients received BI 695502 solution for i.v. infusion, 15 mg/kg bw, every 3 weeks for up to 6 cycles. During the induction cycles, patients also received standard combination chemotherapy consisting of paclitaxel 200 mg/m² BSA, followed by carboplatin target AUC 6 mg/mL*min, with adequate pre- and concomitant medication.

After Cycle 4 to 6, for responding or stabilized patients, maintenance treatment with BI 695502 monotherapy could be started per the original randomization. Patients then received BI 695502 as a single agent until disease progression, death, withdrawal of consent, unacceptable toxicity, or until the Switch Visit (when each patient was switched to receive commercially available Avastin®), whichever occurred earlier.

| | |
|-----------------------|----------------------|
| Reporting group title | US-licensed Avastin® |
|-----------------------|----------------------|

Reporting group description:

Patients received US-licensed Avastin® solution for i.v. infusion, 15 mg/kg bw, every 3 weeks for up to 6 cycles. During the induction cycles, patients also received standard combination chemotherapy consisting of paclitaxel 200 mg/m² BSA, followed by carboplatin target AUC 6 mg/mL*min, with adequate pre- and concomitant medication.

After Cycle 4 to 6, for responding or stabilized patients, maintenance treatment with US-licensed Avastin® monotherapy could be started per the original randomization. Patients then received US-licensed Avastin® as a single agent until disease progression, death, withdrawal of consent, unacceptable toxicity, or until the Switch Visit (when each patient was switched to receive commercially available Avastin®), whichever occurred earlier.

| | |
|-----------------------|-----------|
| Reporting group title | BI 695502 |
|-----------------------|-----------|

Reporting group description:

Patients received BI 695502 solution for i.v. infusion, 15 mg/kg bw, every 3 weeks for up to 6 cycles. During the induction cycles, patients also received standard combination chemotherapy consisting of paclitaxel 200 mg/m² BSA, followed by carboplatin target AUC 6 mg/mL*min, with adequate pre- and concomitant medication.

After Cycle 4 to 6, for responding or stabilized patients, maintenance treatment with BI 695502 monotherapy could be started per the original randomization. Patients then received BI 695502 as a single agent until disease progression, death, withdrawal of consent, unacceptable toxicity, or until the Switch Visit (when each patient was switched to receive commercially available Avastin®), whichever occurred earlier.

| | |
|--|----------------------|
| Reporting group title | US-licensed Avastin® |
| Reporting group description: | |
| Patients received US-licensed Avastin® solution for i.v. infusion, 15 mg/kg bw, every 3 weeks for up to 6 cycles. During the induction cycles, patients also received standard combination chemotherapy consisting of paclitaxel 200 mg/m ² BSA, followed by carboplatin target AUC 6 mg/mL*min, with adequate pre- and concomitant medication. | |
| After Cycle 4 to 6, for responding or stabilized patients, maintenance treatment with US-licensed Avastin® monotherapy could be started per the original randomization. Patients then received US-licensed Avastin® as a single agent until disease progression, death, withdrawal of consent, unacceptable toxicity, or until the Switch Visit (when each patient was switched to receive commercially available Avastin®), whichever occurred earlier. | |

Primary: Best Overall Response Rate (ORR), Based on Unconfirmed Response Assessment, as Assessed by Central Imaging Review Until 18 Weeks After the Start of Treatment

| | |
|---|---|
| End point title | Best Overall Response Rate (ORR), Based on Unconfirmed Response Assessment, as Assessed by Central Imaging Review Until 18 Weeks After the Start of Treatment |
| End point description: | |
| ORR was defined as the percentage of patients who achieved at least one visit response of complete response (CR) or partial response (PR) after the start of treatment. The response criteria evaluation was carried out according to RECIST 1.1. CR and PR did not need to be confirmed by a subsequent tumor assessment due to blinded central assessment. CR: Disappearance of all target lesions since baseline; PR: At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters. Tumor assessments were performed prior to trial drug administration. The FAS contained all randomized patients who received at least 1 dose of trial drug and who had a baseline tumor assessment. Best ORR (CR+PR) is reported for observed values. | |
| End point type | Primary |
| End point timeframe: | |
| Tumor assessment scans were performed at baseline, Cycle 3 (Week 6), Cycle 5 (Week 12) and at Week 18 ±14 days. Best ORR evaluated until confirmed disease progression, unacceptable toxicity, death or up to 18 weeks, whichever happened earlier. | |

| End point values | BI 695502 | US-licensed Avastin® | | |
|-----------------------------------|--------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 335 ^[1] | 328 ^[2] | | |
| Units: Percentage of patients (%) | | | | |
| number (not applicable) | 54.0 | 63.1 | | |

Notes:

[1] - FAS

[2] - FAS

Statistical analyses

| | |
|--|----------------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | |
| Analysis was based on a log-binomial regression model with subsequent transformation of the estimated parameter (ratio of best ORR) respective CIs to the ratio scale. The model included the following explanatory variables: treatment, sex (male versus female), smoking status (never smoked versus current/ex-smoker), NSCLC stage (recurrent versus Stage IV) and ethnicity (East Asian origin versus Non-East Asian). | |
| Comparison groups | BI 695502 v US-licensed Avastin® |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 663 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[3] |
| Method | Log-binomial regression |
| Parameter estimate | Ratio of best ORR |
| Point estimate | 0.855 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.7697 |
| upper limit | 0.9506 |

Notes:

[3] - The null hypothesis was to be rejected in favor of equivalence if the 2-sided 90% confidence interval (CI) for the ratio in best ORR between the treatments was entirely contained within the equivalence margins of 0.736 to 1.359.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

Analysis was based on a log-binomial regression model with subsequent transformation of the estimated parameter (ratio of best ORR) respective CIs to the ratio scale. The model included the following explanatory variables: treatment, sex (male versus female), smoking status (never smoked versus current/ex-smoker), NSCLC stage (recurrent versus Stage IV) and ethnicity (East Asian origin versus Non-East Asian).

| | |
|---|----------------------------------|
| Comparison groups | BI 695502 v US-licensed Avastin® |
| Number of subjects included in analysis | 663 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[4] |
| Method | Log-binomial regression |
| Parameter estimate | Ratio of best ORR |
| Point estimate | 0.855 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7543 |
| upper limit | 0.97 |

Notes:

[4] - Additional analysis of the primary endpoint was performed for Japan according to a local protocol amendment Japan. For the submission in Japan, to conclude on equivalence, the 2-sided 95% CI for the ratio of best ORR between the treatments had to be entirely contained within the equivalence margins of 0.736 to 1.359.

Secondary: Percentage of Patients with Selected Treatment-Emergent Adverse Events (AE) (TEAEs) For Comparability Assessment of BI 695502 and US-licensed Avastin®

| | |
|-----------------|--|
| End point title | Percentage of Patients with Selected Treatment-Emergent Adverse Events (AE) (TEAEs) For Comparability Assessment of BI 695502 and US-licensed Avastin® |
|-----------------|--|

End point description:

The following selected adverse events (AEs) were evaluated for comparability assessment of BI 695502 and US-licensed Avastin®: Infusion reactions (anaphylactic/hypersensitivity/infusion-related reactions), Thromboembolic events (arterial or venous), Febrile neutropenia, Gastrointestinal perforations, Hypertension, Proteinuria, Pulmonary hemorrhage, Other hemorrhages (not including pulmonary hemorrhages), Wound-healing complications/abscess/fistulas. The analysis of AEs was based on the concept of TEAEs. For non-switched patients, all AEs that started or worsened in severity on or after the first dose of trial drug and prior to the date of last administration of trial medication + 16 weeks inclusive were defined as TEAEs. Treated Set (TS) contained all patients who signed informed consent and who received at least 1 dose of trial drug.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From first dose of trial drug until 16 weeks after the last dose of trial medication, up to 218 days.

| End point values | BI 695502 | US-licensed Avastin® | | |
|--|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 335 ^[5] | 328 ^[6] | | |
| Units: Percentage of patients (%) | | | | |
| number (confidence interval 95%) | | | | |
| AtLeast 1 AE selected for Comparability Assessment | 52.50 (47.04 to 57.99) | 45.10 (39.65 to 50.68) | | |
| Infusion reactions | 16.70 (12.88 to 21.15) | 13.10 (9.65 to 17.25) | | |
| Thromboembolic events | 6.60 (4.16 to 9.77) | 5.50 (3.28 to 8.53) | | |
| Febrile neutropenia | 3.90 (2.08 to 6.54) | 3.40 (1.69 to 5.92) | | |
| Gastrointestinal perforations | 2.10 (0.84 to 4.26) | 0.60 (0.07 to 2.19) | | |
| Hypertension | 15.50 (11.82 to 19.85) | 16.20 (12.34 to 20.60) | | |
| Proteinuria | 15.80 (12.08 to 20.18) | 14.60 (10.99 to 18.93) | | |
| Pulmonary haemorrhage | 1.20 (0.33 to 3.03) | 0.90 (0.19 to 2.65) | | |
| Other hemorrhages | 20.00 (15.85 to 24.69) | 16.20 (12.34 to 20.60) | | |
| Wound-healing complications/abscess/fistulas | 2.70 (1.24 to 5.04) | 2.10 (0.86 to 4.35) | | |

Notes:

[5] - TS

[6] - TS

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|----------------------------------|
| Statistical analysis description: | |
| At least 1 AE selected for comparability assessment, risk ratio X (BI 695502) versus Y (US-licensed Avastin®) was defined as $(a/(a+b))/(c/(c+d))$, where 'a' was the number of patients with TEAEs selected for comparability within treatment group X, 'a+b' was the total number of patients in treatment group X, 'c' was the number of patients with TEAEs selected for comparability within treatment group Y and 'c+d' was the total number of patients in treatment group Y. | |
| Comparison groups | BI 695502 v US-licensed Avastin® |
| Number of subjects included in analysis | 663 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Method | Score exact method |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.99 |
| upper limit | 1.37 |

| | |
|--|----------------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Statistical analysis description: | |
| Infusion reactions, risk ratio X (BI 695502) versus Y (US-licensed Avastin®) was defined as $(a/(a+b))/(c/(c+d))$, where 'a' was the number of patients with TEAEs selected for comparability within treatment group X, 'a+b' was the total number of patients in treatment group X, 'c' was the number of patients with TEAEs selected for comparability within treatment group Y and 'c+d' was the total number of patients in treatment group Y. | |
| Comparison groups | BI 695502 v US-licensed Avastin® |
| Number of subjects included in analysis | 663 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Method | Score exact method |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.88 |
| upper limit | 1.88 |

| | |
|---|----------------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Statistical analysis description: | |
| Thromboembolic events, risk ratio X (BI 695502) versus Y (US-licensed Avastin®) was defined as $(a/(a+b))/(c/(c+d))$, where 'a' was the number of patients with TEAEs selected for comparability within treatment group X, 'a+b' was the total number of patients in treatment group X, 'c' was the number of patients with TEAEs selected for comparability within treatment group Y and 'c+d' was the total number of patients in treatment group Y. | |
| Comparison groups | BI 695502 v US-licensed Avastin® |
| Number of subjects included in analysis | 663 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Method | Score exact method |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.64 |
| upper limit | 2.32 |

| | |
|---|------------------------|
| Statistical analysis title | Statistical Analysis 4 |
| Statistical analysis description: | |
| Febrile neutropenia, risk ratio X (BI 695502) versus Y (US-licensed Avastin®) was defined as $(a/(a+b))/(c/(c+d))$, where 'a' was the number of patients with TEAEs selected for comparability within treatment group X, 'a+b' was the total number of patients in treatment group X, 'c' was the number of patients with TEAEs selected for comparability within treatment group Y and 'c+d' was the total number | |

patients in treatment group Y.

| | |
|---|----------------------------------|
| Comparison groups | BI 695502 v US-licensed Avastin® |
| Number of subjects included in analysis | 663 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Method | Score exact method |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.51 |
| upper limit | 2.76 |

Statistical analysis title

Statistical Analysis 5

Statistical analysis description:

Gastrointestinal perforations, risk ratio X (BI 695502) versus Y (US-licensed Avastin®) was defined as $(a/(a+b))/(c/(c+d))$, where 'a' was the number of patients with TEAEs selected for comparability within treatment group X, 'a+b' was the total number of patients in treatment group X, 'c' was the number of patients with TEAEs selected for comparability within treatment group Y and 'c+d' was the total number of patients in treatment group Y.

| | |
|---|----------------------------------|
| Comparison groups | BI 695502 v US-licensed Avastin® |
| Number of subjects included in analysis | 663 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Method | Score exact method |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 3.43 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.79 |
| upper limit | 32.82 |

Statistical analysis title

Statistical Analysis 6

Statistical analysis description:

Hypertension, risk ratio X (BI 695502) versus Y (US-licensed Avastin®) was defined as $(a/(a+b))/(c/(c+d))$, where 'a' was the number of patients with TEAEs selected for comparability within treatment group X, 'a+b' was the total number of patients in treatment group X, 'c' was the number of patients with TEAEs selected for comparability within treatment group Y and 'c+d' was the total number of patients in treatment group Y.

| | |
|---|----------------------------------|
| Comparison groups | BI 695502 v US-licensed Avastin® |
| Number of subjects included in analysis | 663 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Method | Score exact method |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.96 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.66 |
| upper limit | 1.39 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 7 |
|-----------------------------------|------------------------|

Statistical analysis description:

Proteinuria, risk ratio X (BI 695502) versus Y (US-licensed Avastin®) was defined as $(a/(a+b))/(c/(c+d))$, where 'a' was the number of patients with TEAEs selected for comparability within treatment group X, 'a+b' was the total number of patients in treatment group X, 'c' was the number of patients with TEAEs selected for comparability within treatment group Y and 'c+d' was the total number of patients in treatment group Y.

| | |
|---|----------------------------------|
| Comparison groups | BI 695502 v US-licensed Avastin® |
| Number of subjects included in analysis | 663 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Method | Score exact method |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.74 |
| upper limit | 1.57 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 8 |
|-----------------------------------|------------------------|

Statistical analysis description:

Pulmonary haemorrhage, risk ratio X (BI 695502) versus Y (US-licensed Avastin®) was defined as $(a/(a+b))/(c/(c+d))$, where 'a' was the number of patients with TEAEs selected for comparability within treatment group X, 'a+b' was the total number of patients in treatment group X, 'c' was the number of patients with TEAEs selected for comparability within treatment group Y and 'c+d' was the total number of patients in treatment group Y.

| | |
|---|----------------------------------|
| Comparison groups | BI 695502 v US-licensed Avastin® |
| Number of subjects included in analysis | 663 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Method | Score exact method |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.28 |
| upper limit | 10.79 |

| | |
|---|----------------------------------|
| Statistical analysis title | Statistical Analysis 9 |
| Statistical analysis description: | |
| Other hemorrhages, risk ratio X (BI 695502) versus Y (US-licensed Avastin®) was defined as $(a/(a+b))/(c/(c+d))$, where 'a' was the number of patients with TEAEs selected for comparability within treatment group X, 'a+b' was the total number of patients in treatment group X, 'c' was the number of patients with TEAEs selected for comparability within treatment group Y and 'c+d' was the total number of patients in treatment group Y. | |
| Comparison groups | BI 695502 v US-licensed Avastin® |
| Number of subjects included in analysis | 663 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Method | Score exact method |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.24 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.88 |
| upper limit | 1.74 |

| | |
|--|----------------------------------|
| Statistical analysis title | Statistical Analysis 10 |
| Statistical analysis description: | |
| Wound healing complications/ abscesses/ fistulas, risk ratio X (BI 695502) versus Y (US-licensed Avastin®) was defined as $(a/(a+b))/(c/(c+d))$, where 'a' was the number of patients with TEAEs selected for comparability within treatment group X, 'a+b' was the total number of patients in treatment group X, 'c' was the number of patients with TEAEs selected for comparability within treatment group Y and 'c+d' was the total number of patients in treatment group Y. | |
| Comparison groups | BI 695502 v US-licensed Avastin® |
| Number of subjects included in analysis | 663 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Method | Score exact method |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.26 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.47 |
| upper limit | 3.57 |

Secondary: Progression-Free Survival (PFS) Time as Determined by Investigator Assessment

| | |
|-----------------|---|
| End point title | Progression-Free Survival (PFS) Time as Determined by Investigator Assessment |
|-----------------|---|

End point description:

PFS was defined as the time from randomization until disease progression as determined by Investigator assessment or death from any cause, whichever occurred first during the pre-switch period. Disease progression was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Progression was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also

have demonstrated an absolute increase of at least 5 millimeters. Tumor assessments were performed prior to trial drug administration. PFS was calculated using the Kaplan-Meier technique.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Tumor scans performed at baseline, Cycle 3 (Week 6), Cycle 5 (Week 12), Cycle 7 (Week 18), then every 3 cycles (~9 weeks) until confirmed disease progression. Analysis performed for pre-switch period only; maximum duration of up to 35 cycles (105 weeks).

| End point values | BI 695502 | US-licensed Avastin® | | |
|----------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 335 ^[7] | 328 ^[8] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 8.34 (7.49 to 8.77) | 9.00 (8.34 to 10.38) | | |

Notes:

[7] - FAS

[8] - FAS

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Analysis based on a Cox-proportional hazards regression model. The model included the following explanatory variables: treatment, sex (male versus female), smoking status (never smoked versus current/ex-smoker), NSCLC stage (recurrent versus Stage IV) and ethnicity (East Asian origin versus non East Asian).

| | |
|---|-------------------------------------|
| Comparison groups | BI 695502 v US-licensed Avastin® |
| Number of subjects included in analysis | 663 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Method | Cox-proportional hazards regression |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.02 |
| upper limit | 1.45 |

Secondary: Overall Survival (OS) Time

| | |
|-----------------|----------------------------|
| End point title | Overall Survival (OS) Time |
|-----------------|----------------------------|

End point description:

OS was defined as the time randomization until death from any cause during the pre-switch period. OS was calculated using the Kaplan-Meier technique.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline until death due to any cause, ie., up to 35 cycles (105 weeks).

| End point values | BI 695502 | US-licensed Avastin® | | |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 335 ^[9] | 328 ^[10] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 15.57 (14.16 to 17.25) | 19.48 (15.87 to 20.73) | | |

Notes:

[9] - FAS

[10] - FAS

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|-----------------------------------|------------------------|
|-----------------------------------|------------------------|

Statistical analysis description:

Analysis based on a Cox-proportional hazards regression model. The model included the following explanatory variables: treatment, sex (male versus female), smoking status (never smoked versus current/ex-smoker), NSCLC stage (recurrent versus Stage IV) and ethnicity (East Asian origin versus non East Asian).

| | |
|---|-------------------------------------|
| Comparison groups | BI 695502 v US-licensed Avastin® |
| Number of subjects included in analysis | 663 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Method | Cox-proportional hazards regression |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1 |
| upper limit | 1.51 |

Secondary: Duration of Response (DOR) as Determined by Investigator Assessment

| | |
|-----------------|---|
| End point title | Duration of Response (DOR) as Determined by Investigator Assessment |
|-----------------|---|

End point description:

DOR was the time from first documented CR or PR until time of progression as determined by Investigator assessment during the pre-switch period. Tumor assessments were performed prior to trial drug administration. DOR was calculated using the Kaplan-Meier technique.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Tumor scans performed at baseline, Cycle 3 (Week 6), Cycle 5 (Week 12), Cycle 7 (Week 18), then every 3 cycles (~9 weeks) until confirmed disease progression., ie up to 35 cycles (105 weeks).

| | | | | |
|----------------------------------|---------------------|----------------------|--|--|
| End point values | BI 695502 | US-licensed Avastin® | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 175 ^[11] | 187 ^[12] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 7.66 (7.03 to 9.03) | 8.94 (7.26 to 10.28) | | |

Notes:

[11] - FAS patients with an objective response

[12] - FAS patients with an objective response

Statistical analyses

| | |
|--|-------------------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | |
| Analysis based on a Cox-proportional hazards regression model. The model included the following explanatory variables: treatment, sex (male versus female), smoking status (never smoked versus current/ex-smoker), NSCLC stage (recurrent versus Stage IV) and ethnicity (East Asian origin versus non East Asian). | |
| Comparison groups | BI 695502 v US-licensed Avastin® |
| Number of subjects included in analysis | 362 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Method | Cox-proportional hazards regression |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.88 |
| upper limit | 1.48 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For Pre-switch period: From first dose of trial drug until 112 days (16 weeks) after the last dose of trial medication, up to 218 days. For post-switch period: From the first dose of Avastin® until end of treatment (EOT) visit, up to 127 days.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 21.1 |

Reporting groups

| | |
|-----------------------|------------------------|
| Reporting group title | BI 695502 (pre-switch) |
|-----------------------|------------------------|

Reporting group description:

Patients received BI 695502 solution for i.v. infusion, 15 mg/kg bw, every 3 weeks for up to 6 cycles. During the induction cycles, patients also received standard combination chemotherapy consisting of paclitaxel 200 mg/m² BSA, followed by carboplatin target AUC 6 mg/mL*min, with adequate pre- and concomitant medication. After Cycle 4 to 6, for responding or stabilized patients, maintenance treatment with BI 695502 monotherapy could be started per the original randomization. Patients then received BI 695502 as a single agent until disease progression, death, withdrawal of consent, unacceptable toxicity, or until the Switch Visit (when each patient was switched to receive commercially available Avastin®), whichever occurred earlier.

| | |
|-----------------------|-----------------------------------|
| Reporting group title | US-licensed Avastin® (pre-switch) |
|-----------------------|-----------------------------------|

Reporting group description:

Patients received US-licensed Avastin® solution for i.v. infusion, 15 mg/kg bw, every 3 weeks for up to 6 cycles. During the induction cycles, patients also received standard combination chemotherapy consisting of paclitaxel 200 mg/m² BSA, followed by carboplatin target AUC 6 mg/mL*min, with adequate pre- and concomitant medication. After Cycle 4 to 6, for responding or stabilized patients, maintenance treatment with US-licensed Avastin® monotherapy could be started per the original randomization. Patients then received US-licensed Avastin® as a single agent until disease progression, death, withdrawal of consent, unacceptable toxicity, or until the Switch Visit (when each patient was switched to receive commercially available Avastin®), whichever occurred earlier.

| | |
|-----------------------|-------------------------|
| Reporting group title | BI 695502 (post-switch) |
|-----------------------|-------------------------|

Reporting group description:

Patients switched from BI 695502 to receive commercially available Avastin®.

| | |
|-----------------------|------------------------------------|
| Reporting group title | US-licensed Avastin® (post-switch) |
|-----------------------|------------------------------------|

Reporting group description:

Patients switched from US-licensed Avastin® to receive commercially available Avastin®.

| Serious adverse events | BI 695502 (pre-switch) | US-licensed Avastin® (pre-switch) | BI 695502 (post-switch) |
|---|------------------------|-----------------------------------|-------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 108 / 335 (32.24%) | 89 / 328 (27.13%) | 5 / 42 (11.90%) |
| number of deaths (all causes) | 22 | 17 | 3 |
| number of deaths resulting from adverse events | 5 | 2 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bladder transitional cell carcinoma | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Brain neoplasm | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Intracranial tumour haemorrhage | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 4 / 335 (1.19%) | 6 / 328 (1.83%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 3 / 4 | 3 / 6 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Shock haemorrhagic | | | |
| subjects affected / exposed | 3 / 335 (0.90%) | 0 / 328 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 1 / 328 (0.30%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Internal haemorrhage | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Microembolism | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Peripheral embolism | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Arterial thrombosis | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Embolism venous | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Vascular stenosis | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Vasoconstriction | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Anaphylactic shock | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Drug hypersensitivity | | | |

| | | | |
|---|------------------|-----------------|----------------|
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 11 / 335 (3.28%) | 5 / 328 (1.52%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 9 / 11 | 3 / 6 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 6 / 335 (1.79%) | 4 / 328 (1.22%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 2 / 6 | 1 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 5 / 335 (1.49%) | 7 / 328 (2.13%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 2 / 7 | 0 / 9 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 5 / 335 (1.49%) | 1 / 328 (0.30%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 3 / 335 (0.90%) | 2 / 328 (0.61%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |

| | | | | |
|---|-----------------|-----------------|----------------|--|
| Pulmonary haemorrhage | | | | |
| subjects affected / exposed | 3 / 335 (0.90%) | 1 / 328 (0.30%) | 1 / 42 (2.38%) | |
| occurrences causally related to treatment / all | 2 / 3 | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 | |
| Acquired tracheo-oesophageal fistula | | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 | |
| Bronchial fistula | | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 | |
| Chronic obstructive pulmonary diseases | | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 | |
| Pneumonia aspiration | | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 | |
| Aspiration | | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 | |
| Atelectasis | | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 | |
| Bronchospasm | | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 | |
| Epistaxis | | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Idiopathic pulmonary fibrosis | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Pulmonary necrosis | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Psychiatric disorders | | | |
| Delirium | | | |
| subjects affected / exposed | 3 / 335 (0.90%) | 3 / 328 (0.91%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anxiety | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Suicide attempt | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Investigations | | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 5 / 335 (1.49%) | 1 / 328 (0.30%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 4 / 7 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Platelet count decreased | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 2 / 335 (0.60%) | 2 / 328 (0.61%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Blood magnesium decreased | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Injury, poisoning and procedural complications | | | |
| Clavicle fracture | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Infusion related reaction | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Procedural pneumothorax | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Fall | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 2 / 328 (0.61%) | 0 / 42 (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 |
| Meniscus injury | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Congenital, familial and genetic disorders | | | |
| Pyloric stenosis | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Chest pain | | | |
| subjects affected / exposed | 3 / 335 (0.90%) | 0 / 328 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 2 / 335 (0.60%) | 5 / 328 (1.52%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Pain | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 1 / 328 (0.30%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden cardiac death | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Sudden death | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Asthenia | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 3 / 328 (0.91%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioratio | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 myocardial infarction | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 3 / 328 (0.91%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Cardiac failure acute | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Arrhythmia | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 failure | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery occlusion | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 tamponade | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 0 / 328 (0.00%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 0 / 328 (0.00%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial rupture | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 0 / 328 (0.00%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebral infarction | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 1 / 328 (0.30%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 1 / 328 (0.30%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemiparesis | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Intracranial pressure increased | | | |

| | | | |
|---|------------------|------------------|----------------|
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Spinal cord compression | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Brain oedema | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Seizure | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 13 / 335 (3.88%) | 11 / 328 (3.35%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 3 / 14 | 4 / 11 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| Anaemia | | | |

| | | | |
|---|-----------------|------------------|----------------|
| subjects affected / exposed | 6 / 335 (1.79%) | 11 / 328 (3.35%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 8 | 1 / 13 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 4 / 335 (1.19%) | 9 / 328 (2.74%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 1 / 6 | 0 / 11 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 4 / 335 (1.19%) | 5 / 328 (1.52%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone marrow failure | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 2 / 328 (0.61%) | 0 / 42 (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 |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 2 / 328 (0.61%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Disseminated intravascular coagulati | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Deafness bilateral | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Eye disorders | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| Retinal artery occlusion | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 4 / 335 (1.19%) | 2 / 328 (0.61%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 3 / 335 (0.90%) | 2 / 328 (0.61%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | 6 / 328 (1.83%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 6 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Anal incontinence | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Constipation | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 1 / 328 (0.30%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticular perforation | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Diverticulum intestinal | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Duodenal perforation | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Duodenal ulcer | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 1 / 328 (0.30%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric ulcer | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Gastrointestinal perforation | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Colitis | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Dyspepsia | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Ileus paralytic | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Oesophagobronchial fistula | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 0 / 328 (0.00%) | 1 / 42 (2.38%) |
| 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 perforation | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 0 / 328 (0.00%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Bile duct obstruction | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Hepatitis toxic | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Hepatocellular injury | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Jaundice cholestatic | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Liver injury | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 | | | |
| Hyperhidrosis | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Renal and urinary disorders | | | |
| Bladder obstruction | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Hydronephrosis | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 2 / 328 (0.61%) | 0 / 42 (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 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |

| | | | |
|---|-----------------|-----------------|----------------|
| Exposed bone in jaw | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Myalgia | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Bone pain | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 | | | |
| Pneumonia | | | |
| subjects affected / exposed | 9 / 335 (2.69%) | 9 / 328 (2.74%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 2 / 11 | 0 / 10 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| Lung infection | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 2 / 335 (0.60%) | 2 / 328 (0.61%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | 0 / 328 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Anal abscess | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Anorectal infection | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Appendicitis perforated | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Klebsiella infection | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 1 / 328 (0.30%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Lung abscess | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 335 (0.30%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Osteomyelitis | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary mycosis | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 tract infection | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 0 / 328 (0.00%) | 0 / 42 (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 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 1 / 328 (0.30%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Campylobacter gastroenteritis | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Gastroenteritis | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 tract infection bacteria | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Sepsis | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 335 (0.00%) | 0 / 328 (0.00%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 4 / 335 (1.19%) | 3 / 328 (0.91%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 1 / 328 (0.30%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | 1 / 328 (0.30%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 2 / 328 (0.61%) | 0 / 42 (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 |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 / 335 (0.00%) | 2 / 328 (0.61%) | 0 / 42 (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 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Hypocalcaemia | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 335 (0.00%) | 2 / 328 (0.61%) | 0 / 42 (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 |
| Hypochloraemia | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 335 (0.00%) | 1 / 328 (0.30%) | 0 / 42 (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 |

| Serious adverse events | US-licensed Avastin® (post-switch) | | |
|---|------------------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bladder transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Brain neoplasm | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intracranial tumour haemorrhage | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Shock haemorrhagic | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Internal haemorrhage | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Microembolism | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral embolism | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arterial thrombosis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Embolism venous | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular stenosis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vasoconstriction | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anaphylactic shock | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acquired tracheo-oesophageal fistula | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchial fistula | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|----------------|--|--|--|
| Chronic obstructive pulmonary diseases | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia aspiration | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Aspiration | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atelectasis | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bronchospasm | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Epistaxis | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Idiopathic pulmonary fibrosis | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pulmonary necrosis | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Psychiatric disorders | | | | |

| | | | |
|---|----------------|--|--|
| Delirium | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Blood creatinine increased subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood magnesium decreased subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| White blood cell count decreased subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Clavicle fracture subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Femoral neck fracture subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infusion related reaction subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Procedural pneumothorax subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fall subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|----------------|--|--|--|
| Hip fracture | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Meniscus injury | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Spinal compression fracture | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Congenital, familial and genetic disorders | | | | |
| Pyloric stenosis | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Chest pain | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pyrexia | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Death | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Non-cardiac chest pain | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

| | | | | |
|---|----------------|--|--|--|
| Pain | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sudden cardiac death | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sudden death | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Asthenia | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fatigue | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| General physical health deterioration | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac disorders | | | | |
| Acute myocardial infarction | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrial fibrillation | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac arrest | | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac failure acute | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiopulmonary failure | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Arrhythmia | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac failure | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Coronary artery occlusion | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sinus tachycardia | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac tamponade | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Myocardial ischaemia | | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial rupture | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Headache | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hemiparesis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intracranial pressure increased | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal cord compression | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient ischaemic attack | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Brain oedema | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Seizure | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bone marrow failure | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| Deafness bilateral | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Retinal artery occlusion | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|----------------|--|--|--|
| Nausea | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diarrhoea | | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Anal incontinence | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Constipation | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diverticular perforation | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diverticulum intestinal | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Duodenal perforation | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Duodenal ulcer | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastric ulcer | | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal perforation | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lower gastrointestinal haemorrhage | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Upper gastrointestinal haemorrhage | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Colitis | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dyspepsia | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dysphagia | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ileus paralytic | | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Small intestinal obstruction | | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oesophagobronchial fistula | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oesophageal perforation | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Bile duct obstruction | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatitis toxic | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatocellular injury | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Jaundice cholestatic | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Liver injury | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Bladder obstruction | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal impairment | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Exposed bone in jaw | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myalgia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung infection | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anal abscess | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anorectal infection | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Appendicitis perforated | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Klebsiella infection | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung abscess | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteomyelitis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary mycosis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory tract infection | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Campylobacter gastroenteritis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia bacterial | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory tract infection bacteria | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypokalaemia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypochloraemia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | BI 695502 (pre-switch) | US-licensed Avastin® (pre-switch) | BI 695502 (post-switch) |
|---|------------------------|-----------------------------------|-------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 293 / 335 (87.46%) | 288 / 328 (87.80%) | 20 / 42 (47.62%) |
| Investigations | | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 41 / 335 (12.24%) | 33 / 328 (10.06%) | 0 / 42 (0.00%) |
| occurrences (all) | 96 | 68 | 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 39 / 335 (11.64%) | 42 / 328 (12.80%) | 0 / 42 (0.00%) |
| occurrences (all) | 121 | 121 | 0 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 30 / 335 (8.96%) | 19 / 328 (5.79%) | 0 / 42 (0.00%) |
| occurrences (all) | 113 | 68 | 0 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 24 / 335 (7.16%) | 32 / 328 (9.76%) | 0 / 42 (0.00%) |
| occurrences (all) | 44 | 59 | 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 22 / 335 (6.57%) | 31 / 328 (9.45%) | 1 / 42 (2.38%) |
| occurrences (all) | 55 | 92 | 1 |
| Weight decreased | | | |
| subjects affected / exposed | 21 / 335 (6.27%) | 22 / 328 (6.71%) | 2 / 42 (4.76%) |
| occurrences (all) | 28 | 32 | 2 |
| Blood cholesterol increased | | | |
| subjects affected / exposed | 20 / 335 (5.97%) | 16 / 328 (4.88%) | 1 / 42 (2.38%) |
| occurrences (all) | 51 | 61 | 1 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 19 / 335 (5.67%) | 30 / 328 (9.15%) | 1 / 42 (2.38%) |
| occurrences (all) | 37 | 47 | 1 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 17 / 335 (5.07%) | 25 / 328 (7.62%) | 0 / 42 (0.00%) |
| occurrences (all) | 27 | 50 | 0 |
| Haemoglobin decreased | | | |

| | | | |
|--|----------------------|------------------------|---------------------|
| subjects affected / exposed occurrences (all) | 5 / 335 (1.49%) 8 | 17 / 328 (5.18%) 31 | 0 / 42 (0.00%) 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 49 / 335 (14.63%) | 51 / 328 (15.55%) | 3 / 42 (7.14%) |
| occurrences (all) | 69 | 86 | 3 |
| Nervous system disorders | | | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 62 / 335 (18.51%) | 59 / 328 (17.99%) | 1 / 42 (2.38%) |
| occurrences (all) | 95 | 98 | 1 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 56 / 335 (16.72%) | 53 / 328 (16.16%) | 0 / 42 (0.00%) |
| occurrences (all) | 85 | 77 | 0 |
| Headache | | | |
| subjects affected / exposed | 26 / 335 (7.76%) | 25 / 328 (7.62%) | 1 / 42 (2.38%) |
| occurrences (all) | 34 | 28 | 1 |
| Paraesthesia | | | |
| subjects affected / exposed | 20 / 335 (5.97%) | 19 / 328 (5.79%) | 0 / 42 (0.00%) |
| occurrences (all) | 26 | 23 | 0 |
| Dysgeusia | | | |
| subjects affected / exposed | 13 / 335 (3.88%) | 17 / 328 (5.18%) | 0 / 42 (0.00%) |
| occurrences (all) | 13 | 18 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 112 / 335 (33.43%) | 84 / 328 (25.61%) | 2 / 42 (4.76%) |
| occurrences (all) | 244 | 189 | 2 |
| Neutropenia | | | |
| subjects affected / exposed | 61 / 335 (18.21%) | 52 / 328 (15.85%) | 0 / 42 (0.00%) |
| occurrences (all) | 129 | 108 | 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 44 / 335 (13.13%) | 47 / 328 (14.33%) | 1 / 42 (2.38%) |
| occurrences (all) | 108 | 85 | 1 |
| Leukopenia | | | |
| subjects affected / exposed | 18 / 335 (5.37%) | 23 / 328 (7.01%) | 0 / 42 (0.00%) |
| occurrences (all) | 42 | 52 | 0 |
| Gastrointestinal disorders | | | |

| | | | |
|--|---------------------------|---------------------------|---------------------|
| Nausea subjects affected / exposed occurrences (all) | 73 / 335 (21.79%) 154 | 75 / 328 (22.87%) 128 | 2 / 42 (4.76%) 2 |
| Diarrhoea subjects affected / exposed occurrences (all) | 60 / 335 (17.91%) 89 | 45 / 328 (13.72%) 72 | 1 / 42 (2.38%) 1 |
| Vomiting subjects affected / exposed occurrences (all) | 56 / 335 (16.72%) 94 | 37 / 328 (11.28%) 51 | 1 / 42 (2.38%) 1 |
| Constipation subjects affected / exposed occurrences (all) | 51 / 335 (15.22%) 66 | 44 / 328 (13.41%) 56 | 1 / 42 (2.38%) 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 38 / 335 (11.34%) 48 | 32 / 328 (9.76%) 37 | 0 / 42 (0.00%) 0 |
| Epistaxis subjects affected / exposed occurrences (all) | 38 / 335 (11.34%) 46 | 32 / 328 (9.76%) 38 | 0 / 42 (0.00%) 0 |
| Dyspnoea subjects affected / exposed occurrences (all) | 22 / 335 (6.57%) 25 | 31 / 328 (9.45%) 35 | 0 / 42 (0.00%) 0 |
| Haemoptysis subjects affected / exposed occurrences (all) | 17 / 335 (5.07%) 19 | 10 / 328 (3.05%) 11 | 0 / 42 (0.00%) 0 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia subjects affected / exposed occurrences (all) | 155 / 335 (46.27%) 188 | 149 / 328 (45.43%) 176 | 0 / 42 (0.00%) 0 |
| Rash subjects affected / exposed occurrences (all) | 17 / 335 (5.07%) 17 | 16 / 328 (4.88%) 19 | 1 / 42 (2.38%) 1 |
| Psychiatric disorders | | | |
| Insomnia subjects affected / exposed occurrences (all) | 15 / 335 (4.48%) 22 | 18 / 328 (5.49%) 22 | 1 / 42 (2.38%) 1 |

| | | | |
|---|-------------------|-------------------|-----------------|
| Renal and urinary disorders | | | |
| Proteinuria | | | |
| subjects affected / exposed | 51 / 335 (15.22%) | 46 / 328 (14.02%) | 8 / 42 (19.05%) |
| occurrences (all) | 122 | 130 | 8 |
| Fatigue | | | |
| subjects affected / exposed | 54 / 335 (16.12%) | 53 / 328 (16.16%) | 2 / 42 (4.76%) |
| occurrences (all) | 70 | 68 | 2 |
| Asthenia | | | |
| subjects affected / exposed | 22 / 335 (6.57%) | 29 / 328 (8.84%) | 1 / 42 (2.38%) |
| occurrences (all) | 34 | 45 | 1 |
| Malaise | | | |
| subjects affected / exposed | 19 / 335 (5.67%) | 13 / 328 (3.96%) | 0 / 42 (0.00%) |
| occurrences (all) | 36 | 24 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 17 / 335 (5.07%) | 21 / 328 (6.40%) | 0 / 42 (0.00%) |
| occurrences (all) | 18 | 21 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 40 / 335 (11.94%) | 35 / 328 (10.67%) | 1 / 42 (2.38%) |
| occurrences (all) | 51 | 62 | 1 |
| Myalgia | | | |
| subjects affected / exposed | 38 / 335 (11.34%) | 29 / 328 (8.84%) | 0 / 42 (0.00%) |
| occurrences (all) | 76 | 54 | 0 |
| Back pain | | | |
| subjects affected / exposed | 22 / 335 (6.57%) | 14 / 328 (4.27%) | 1 / 42 (2.38%) |
| occurrences (all) | 23 | 18 | 1 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 18 / 335 (5.37%) | 10 / 328 (3.05%) | 0 / 42 (0.00%) |
| occurrences (all) | 20 | 11 | 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 12 / 335 (3.58%) | 18 / 328 (5.49%) | 1 / 42 (2.38%) |
| occurrences (all) | 14 | 22 | 1 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 54 / 335 (16.12%) | 54 / 328 (16.46%) | 2 / 42 (4.76%) |
| occurrences (all) | 81 | 75 | 2 |

| | | | |
|--|------------------------|------------------------|---------------------|
| Hyperglycaemia subjects affected / exposed occurrences (all) | 21 / 335 (6.27%) 42 | 28 / 328 (8.54%) 53 | 0 / 42 (0.00%) 0 |
|--|------------------------|------------------------|---------------------|

| Non-serious adverse events | US-licensed Avastin® (post- switch) | | |
|---|---|--|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 22 / 46 (47.83%) | | |
| Investigations | | | |
| Platelet count decreased subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | | |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | | |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 2 / 46 (4.35%) 2 | | |
| Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) | 6 / 46 (13.04%) 6 | | |
| Weight decreased subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | | |
| Blood cholesterol increased subjects affected / exposed occurrences (all) | 3 / 46 (6.52%) 3 | | |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 3 / 46 (6.52%) 3 | | |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 3 / 46 (6.52%) 3 | | |

| | | | |
|---|---|--|--|
| Haemoglobin decreased subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | | |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | | |
| Nervous system disorders Neuropathy peripheral subjects affected / exposed occurrences (all) Peripheral sensory neuropathy subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 1 / 46 (2.17%) 1 2 / 46 (4.35%) 2 0 / 46 (0.00%) 0 0 / 46 (0.00%) 0 | | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) | 4 / 46 (8.70%) 4 2 / 46 (4.35%) 2 4 / 46 (8.70%) 4 2 / 46 (4.35%) 2 | | |
| Gastrointestinal disorders | | | |

| | | | |
|--|----------------------|--|--|
| Nausea subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | | |
| Vomiting subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | | |
| Constipation subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 5 / 46 (10.87%) 5 | | |
| Epistaxis subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | | |
| Dyspnoea subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | | |
| Haemoptysis subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | | |
| Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | | |
| Rash subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | | |

| | | | |
|---|-----------------|--|--|
| Renal and urinary disorders | | | |
| Proteinuria | | | |
| subjects affected / exposed | 6 / 46 (13.04%) | | |
| occurrences (all) | 6 | | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | | |
| occurrences (all) | 2 | | |
| Malaise | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences (all) | 0 | | |
| Myalgia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences (all) | 0 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences (all) | 0 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 4 / 46 (8.70%) | | |
| occurrences (all) | 4 | | |

| | | | |
|--|---------------------|--|--|
| Hyperglycaemia subjects affected / exposed occurrences (all) | 4 / 46 (8.70%) 4 | | |
|--|---------------------|--|--|

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|--|
| 01 April 2015 | <ul style="list-style-type: none">• "US-sourced Avastin®" was updated to "US-licensed Avastin®" in order to clearly indicate the product used in this trial.• The description of the requirements for the safety follow-up (SFU) visit was clarified to state that all patients were required to attend the SFU visit after completing trial therapy.• For consistency with the informed consent form (ICF), inclusion criterion 10 was revised to specify that all patients (males and females of childbearing potential) were to continue to use an acceptable form of contraception for 6 months following completion or discontinuation of trial medication, and to add text defining childbearing potential.• The criteria for withdrawal from the trial, discontinuation from trial medication and the requirements for follow-up of patients who discontinue treatment were clarified in line with Federal Drug Agency (FDA) requirements.• It was clarified that patients who were unable to tolerate at least 3 cycles of chemotherapy or those that started a new backbone chemotherapy were not to be withdrawn from the trial but would be discontinued from trial medication. |
| 10 July 2015 | <ul style="list-style-type: none">• In the section relating to chemotherapy, the text "In case of anticipated toxicity, the Investigator may start paclitaxel at a dose of 175 mg/m² BSA and/or carboplatin target AUC 5 mg/mL*min." was changed to "The dose can be reduced in the event of toxicity according to the protocol guideline". This was done to address FDA feedback regarding the starting dose of paclitaxel and/or carboplatin being consistent with prior clinical trials.• In response to FDA feedback, instructions relating to management of patients with severe hypertension, moderate to severe proteinuria, or severe infusion reactions were amended to state that these patients "will not receive further treatment with US-licensed Avastin® or BI 695502 if the event cannot be adequately controlled within 14 days" rather than allowing a 28-day treatment interruption. |

| | |
|------------------|--|
| 19 February 2016 | <ul style="list-style-type: none"> • Japan age requirement changed from “Age ≥20 years at visit 1” to “Age ≥20 years at Screening”. • It was specified that abdominal magnetic resonance imaging scans were to be performed with contrast using gadolinium. • Timing and frequency of, and permitted delays to, treatment cycles was further clarified. • Text was added: “During the induction phase, tumor assessments should be performed before treatment administration of Cycles 3 and 5. If an induction therapy cycle is delayed, the tumor assessment will also be delayed.” • In the event of a treatment cycle delay due to toxicity, it was clarified that the imaging assessment for the primary endpoint was to be performed at Week 18 ±14 days (fixed time point), regardless of the number of cycles administered to date. • The list of reasons patients could be discontinued from the trial drug was updated for consistency with other sections of the protocol, and to clarify that progressive disease required trial drug discontinuation. • To clarify, the following text was added: “Patients discontinued from trial treatment or withdrawn from the trial will not be replaced, regardless of the reason for discontinuation/withdrawal.” • Clarification was added to state that the correct dose of Avastin®/BI 695502 was to be recalculated prior to each infusion. • It was clarified that progression of cancer (underlying disease) was exempted from reporting as an AE. • In the definition of protocol-specified AEs of special interest, for patients with impaired liver function at baseline, the specified elevated levels of liver enzymes to define hepatic injury were clarified. • Text was added to clarify that pregnant participants had to be excluded from the study and to provide detail on the procedure when a patient’s partner became pregnant. |
| 17 January 2018 | <p>As a consequence of the observation of particles for certain investigational medicinal product batches, the Sponsor recommended that patients be switched from BI 695502 to the reference medicinal product (Avastin®) as soon as it was available at the respective clinical site. The following changes relating to the switch were included: A description of the ‘switch visit’ and assessments to be done were added. It was specified that the dose of Avastin® remained the same after the switch from BI 695502 and that the first infusion for all patients after the switch visit should be delivered over 90 minutes. If tolerated the second infusion was to be delivered over 60 minutes, and if this was tolerated all subsequent infusions could be administered over 30 minutes. Text was added to clarify that no unblinding of patients or sites would occur as a result of the switch. Relabeling of commercially available Avastin® was not required, sites were instructed to monitor the storage conditions of Avastin® in accordance with local requirements, and after patients switched from BI 695502/US-Licensed Avastin® to Avastin® drug accountability details were recorded. Text was modified to state that the 18-week SFU visit was to take place 18 weeks after the last dose of trial medication prior to the switch visit. Patients who were receiving treatment with Avastin® at 18 weeks post the last BI 695502/US-Licensed Avastin® dose were not to have a SFU visit. The End of Treatment definition was updated so that patients could continue to receive Avastin® after the SFU. Clarification on statistical methods to be used to analyze data as a result of the switch were added. Patients were informed orally by the Investigator about the switch, and once the updated ICF was available consent was obtained. All added text that the Sponsor highly recommended the use of the same filters as for BI 695502 administration, and to clarify the recommended concentration of Avastin® after switching.</p> |

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.

From 21 December 2017, after Week 18 primary analysis data cut-off, the Sponsor recommended to switch patients from BI 695502/US-licensed Avastin® to Avastin®. The main analyses to report all endpoint and AE results was the pre-switch period.

Notes: