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	v2 (current)
This version publication date	12 January 2020
First version publication date	27 November 2019
Version creation reason	

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	Argentina: 7
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	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/m^2 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	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel 200 mg/m^2 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/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.

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/m^2 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/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 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/m^2 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/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.

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/m^2 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
Progressive disease	185	173
Protocol deviation	1	-
Physician decision	6	18
Other than listed	10	11
Adverse event, serious fatal	26	26
Adverse event, non-fatal	38	37
Consent withdrawn by subject	27	15
Lost to follow-up	-	2

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 the patients who were randomised after successfully completing the screening period and received at least one 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/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 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/m^2 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/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.

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/m^2 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
Progressive disease	21	21
Physician decision	1	1
Other than listed	4	5
Adverse event, serious fatal	3	2
Study terminated by sponsor	8	11
Adverse event, non-fatal	4	4
Consent withdrawn by subject	1	2

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/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 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.

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/m^2 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/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.

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/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 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.

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/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 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:

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:

Gastrointestial 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 excat 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/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 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/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 USlicensed 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)	193	184	3
number of deaths resulting from adverse events	5	2	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
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
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
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
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
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
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
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
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
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
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 diseas			
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
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	1 / 1	0 / 0	0 / 0

treatment / all			
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
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
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
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	1 / 1	0 / 0	0 / 0

treatment / all			
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
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
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
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	0 / 1	0 / 0	0 / 0

treatment / all			
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
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
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

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)	2		
number of deaths resulting from adverse events	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			
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			
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		
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		
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			
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			
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			

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			
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 deterioratio				
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 coagulati			
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 diseas				
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			
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			

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		
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		
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			
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			
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			
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			
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			
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			

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%)
Vascular disorders			
Hypertension			
subjects affected / exposed	49 / 335 (14.63%)	51 / 328 (15.55%)	3 / 42 (7.14%)
occurrences (all)	69	86	3
Investigations			
Platelet count decreased			
subjects affected / exposed	41 / 335 (12.24%)	33 / 328 (10.06%)	0 / 42 (0.00%)
occurrences (all)	96	68	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
Neutrophil count decreased			
subjects affected / exposed	39 / 335 (11.64%)	42 / 328 (12.80%)	0 / 42 (0.00%)
occurrences (all)	121	121	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	5 / 335 (1.49%)	17 / 328 (5.18%)	0 / 42 (0.00%)
occurrences (all)	8	31	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	38 / 335 (11.34%)	32 / 328 (9.76%)	0 / 42 (0.00%)
occurrences (all)	48	37	0
Dyspnoea			
subjects affected / exposed	22 / 335 (6.57%)	31 / 328 (9.45%)	0 / 42 (0.00%)
occurrences (all)	25	35	0
Epistaxis			
subjects affected / exposed	38 / 335 (11.34%)	32 / 328 (9.76%)	0 / 42 (0.00%)
occurrences (all)	46	38	0
Haemoptysis			
subjects affected / exposed	17 / 335 (5.07%)	10 / 328 (3.05%)	0 / 42 (0.00%)
occurrences (all)	19	11	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
Thrombocytopenia			

subjects affected / exposed	44 / 335 (13.13%)	47 / 328 (14.33%)	1 / 42 (2.38%)
occurrences (all)	108	85	1
Neutropenia			
subjects affected / exposed	61 / 335 (18.21%)	52 / 328 (15.85%)	0 / 42 (0.00%)
occurrences (all)	129	108	0
Leukopenia			
subjects affected / exposed	18 / 335 (5.37%)	23 / 328 (7.01%)	0 / 42 (0.00%)
occurrences (all)	42	52	0
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
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	60 / 335 (17.91%)	45 / 328 (13.72%)	1 / 42 (2.38%)
occurrences (all)	89	72	1
Nausea			
subjects affected / exposed	73 / 335 (21.79%)	75 / 328 (22.87%)	2 / 42 (4.76%)
occurrences (all)	154	128	2
Vomiting			
subjects affected / exposed	56 / 335 (16.72%)	37 / 328 (11.28%)	1 / 42 (2.38%)
occurrences (all)	94	51	1
Constipation			
subjects affected / exposed	51 / 335 (15.22%)	44 / 328 (13.41%)	1 / 42 (2.38%)

occurrences (all)	66	56	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	15 / 335 (4.48%)	18 / 328 (5.49%)	1 / 42 (2.38%)
occurrences (all)	22	22	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
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	155 / 335 (46.27%)	149 / 328 (45.43%)	0 / 42 (0.00%)
occurrences (all)	188	176	0
Rash			
subjects affected / exposed	17 / 335 (5.07%)	16 / 328 (4.88%)	1 / 42 (2.38%)
occurrences (all)	17	19	1
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
Back pain			
subjects affected / exposed	22 / 335 (6.57%)	14 / 328 (4.27%)	1 / 42 (2.38%)
occurrences (all)	23	18	1

Myalgia			
subjects affected / exposed	38 / 335 (11.34%)	29 / 328 (8.84%)	0 / 42 (0.00%)
occurrences (all)	76	54	0
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			
Hyperglycaemia			
subjects affected / exposed	21 / 335 (6.27%)	28 / 328 (8.54%)	0 / 42 (0.00%)
occurrences (all)	42	53	0
Decreased appetite			
subjects affected / exposed	54 / 335 (16.12%)	54 / 328 (16.46%)	2 / 42 (4.76%)
occurrences (all)	81	75	2

Non-serious adverse events	US-licensed Avastin® (post-switch)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 46 (47.83%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
White blood cell count decreased			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Neutrophil count decreased			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Alanine aminotransferase increased			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	2		

Gamma-glutamyltransferase increased			
subjects affected / exposed	6 / 46 (13.04%)		
occurrences (all)	6		
Weight decreased			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Blood cholesterol increased			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
Haemoglobin decreased			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 46 (10.87%)		
occurrences (all)	5		
Dyspnoea			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Haemoptysis			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 46 (8.70%)		
occurrences (all)	4		

Thrombocytopenia subjects affected / exposed occurrences (all)	4 / 46 (8.70%) 4		
Neutropenia subjects affected / exposed occurrences (all)	2 / 46 (4.35%) 2		
Leukopenia subjects affected / exposed occurrences (all)	2 / 46 (4.35%) 2		
Nervous system disorders			
Neuropathy peripheral subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Headache subjects affected / exposed occurrences (all)	2 / 46 (4.35%) 2		
Paraesthesia subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Dysgeusia subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Nausea 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	1 / 46 (2.17%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	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		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		

Myalgia subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 1 / 46 (2.17%) 1 0 / 46 (0.00%) 0 0 / 46 (0.00%) 0		
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all) Decreased appetite subjects affected / exposed occurrences (all)	 4 / 46 (8.70%) 4 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	• "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	• In the section relating to chemotherapy, the text "In case of anticipated toxicity, the Investigator may start paclitaxel at a dose of 175 mg/m^2 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	

17 January 2018	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.

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: