



Clinical trial results:

A Phase III, Randomised, Double-blind, Multicentre Study to Compare the Efficacy, Safety, Pharmacokinetics and Immunogenicity between SB8 (proposed bevacizumab biosimilar) and Avastin® in Subjects with Metastatic or Recurrent Non-squamous Non-small Cell Lung Cancer

Summary

EudraCT number	2015-004026-34
Trial protocol	DE HU PL ES
Global end of trial date	09 August 2018

Results information

Result version number	v1 (current)
This version publication date	22 January 2020
First version publication date	22 January 2020

Trial information

Trial identification

Sponsor protocol code	SB8-G31-NSCLC
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Samsung Bioepis Co., Ltd.
Sponsor organisation address	107, Cheomdan-daero, Incheon, Korea, Republic of,
Public contact	Hye Jung Na, Samsung Bioepis Co., Ltd., +82 3180614224, nahjpost@samsung.com
Scientific contact	Hye Jung Na, Samsung Bioepis Co., Ltd., +82 3180614224, nahjpost@samsung.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	09 August 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	09 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the equivalence of SB8 to Avastin®, in terms of the best overall response rate (ORR) by 24 weeks of chemotherapy in subjects with metastatic or recurrent non squamous NSCLC.

Protection of trial subjects:

The study and clinical study protocols were reviewed and approved by Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for each study centre.

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the latest International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP) and applicable local regulatory requirements and laws.

The nature and purpose of the study was fully explained to each subject and written informed consent was obtained from each subject before the subject was entered into the study. The consent documents for the study were reviewed and approved by the appropriate IEC or IRB prior to use.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 July 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Korea, Republic of: 29
Country: Number of subjects enrolled	Ukraine: 155
Country: Number of subjects enrolled	Russian Federation: 254
Country: Number of subjects enrolled	Belarus: 47
Country: Number of subjects enrolled	Georgia: 57
Country: Number of subjects enrolled	Serbia: 29
Country: Number of subjects enrolled	Taiwan: 11
Country: Number of subjects enrolled	Thailand: 26
Country: Number of subjects enrolled	Poland: 19
Country: Number of subjects enrolled	Romania: 44
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	Germany: 26
Country: Number of subjects enrolled	Hungary: 51
Worldwide total number of subjects	763
EEA total number of subjects	155

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)	524
From 65 to 84 years	239
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants who meet the eligibility criteria were randomly assigned to one of the two treatments of this study.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	SB8 (proposed bevacizumab biosimilar)

Arm description:

Administered SB8 every 3 weeks until disease progression, unacceptable toxicity occurred, death, or EOS at a dose of 15 mg/kg body weight concurrently with chemotherapy (paclitaxel 200 mg/m² and carboplatin AUC 6 by IV infusion on Day 1 of every 3-week cycle) for at least 4 cycles and up to 6 cycles then received SB8 maintenance (mono-) therapy

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

Dosage and administration details:

Dose regimen: 15 mg/kg every 3 weeks

Mode of administration: Intravenous infusion

Arm title	EU Avastin
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Arm description:

Administered Avastin every 3 weeks until disease progression, unacceptable toxicity occurred, death, or EOS at a dose of 15 mg/kg body weight concurrently with chemotherapy (paclitaxel 200 mg/m² and carboplatin AUC 6 by IV infusion on Day 1 of every 3-week cycle) for at least 4 cycles and up to 6 cycles then received Avastin maintenance (mono-) therapy

Arm type	Active comparator
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose regimen: 15 mg/kg every 3 weeks

Mode of administration: Intravenous infusion

Number of subjects in period 1	SB8 (proposed bevacizumab biosimilar)	EU Avastin
Started	379	384
Discontinued during induction treatment	121	107
Completed induction treatment	258	277
Discontinued during maintenance treatment	223	239
Was ongoing at the time of end of study	35	38
Completed	35	38
Not completed	344	346
Consent withdrawn by subject	18	19
Death	28	35
Other	21	18
Non-compliance with study treatment	5	9
Adverse event	51	35
Progressive disease	221	225
Lost to follow-up	-	5

Baseline characteristics

Reporting groups

Reporting group title	SB8 (proposed bevacizumab biosimilar)
Reporting group description: Administered SB8 every 3 weeks until disease progression, unacceptable toxicity occurred, death, or EOS at a dose of 15 mg/kg body weight concurrently with chemotherapy (paclitaxel 200 mg/m ² and carboplatin AUC 6 by IV infusion on Day 1 of every 3-week cycle) for at least 4 cycles and up to 6 cycles then received SB8 maintenance (mono-) therapy	
Reporting group title	EU Avastin
Reporting group description: Administered Avastin every 3 weeks until disease progression, unacceptable toxicity occurred, death, or EOS at a dose of 15 mg/kg body weight concurrently with chemotherapy (paclitaxel 200 mg/m ² and carboplatin AUC 6 by IV infusion on Day 1 of every 3-week cycle) for at least 4 cycles and up to 6 cycles then received Avastin maintenance (mono-) therapy	

Reporting group values	SB8 (proposed bevacizumab biosimilar)	EU Avastin	Total
Number of subjects	379	384	763
Age categorical Units: Subjects			
Adults (18-64 years)	255	269	524
From 65-84 years	124	115	239
Age continuous Units: years			
arithmetic mean	60.2	60.0	
standard deviation	± 8.95	± 9.18	-
Gender categorical Units: Subjects			
Female	127	128	255
Male	252	256	508

End points

End points reporting groups

Reporting group title	SB8 (proposed bevacizumab biosimilar)
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Reporting group description:

Administered SB8 every 3 weeks until disease progression, unacceptable toxicity occurred, death, or EOS at a dose of 15 mg/kg body weight concurrently with chemotherapy (paclitaxel 200 mg/m² and carboplatin AUC 6 by IV infusion on Day 1 of every 3-week cycle) for at least 4 cycles and up to 6 cycles then received SB8 maintenance (mono-) therapy

Reporting group title	EU Avastin
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Reporting group description:

Administered Avastin every 3 weeks until disease progression, unacceptable toxicity occurred, death, or EOS at a dose of 15 mg/kg body weight concurrently with chemotherapy (paclitaxel 200 mg/m² and carboplatin AUC 6 by IV infusion on Day 1 of every 3-week cycle) for at least 4 cycles and up to 6 cycles then received Avastin maintenance (mono-) therapy

Subject analysis set title	Per-protocol Set
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Subject analysis set type	Per protocol
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Subject analysis set description:

The Per-Protocol Set consisted of all FAS subjects who completed at least first 2 cycles of combination chemotherapy with a tumour assessment and did not have any major protocol deviations that impacted the primary efficacy assessment. Major protocol deviations that led to the exclusion from the PPS were pre-specified, and the PPS was determined prior to unblinding treatment codes.

Primary: best ORR

End point title	best ORR
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End point description:

The best ORR was defined as the proportion of subjects whose best overall response was either CR or PR according to RECIST v1.1 during the induction treatment period by 24 weeks. If a subject had either CR or PR at least once during induction treatment period by 24 weeks, the subject was considered as responder.

End point type	Primary
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End point timeframe:

The primary efficacy endpoint was the best ORR during induction treatment period by 24 weeks of chemotherapy.

End point values	SB8 (proposed bevacizumab biosimilar)	EU Avastin	Per-protocol Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	337	328	665	
Units: number	169	147	316	

Statistical analyses

Statistical analysis title	Equivalence test
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Comparison groups	EU Avastin v SB8 (proposed bevacizumab biosimilar)
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Number of subjects included in analysis	665
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Risk difference (RD)
Point estimate	5.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	12.9

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were reported from the time the ICF was signed until the EOT visit. After the EOT visit, only SAEs were reported. AEs which were accidentally entered in the Electronic Data Capture (EDC) after the EOT visit, were not excluded in the analysis.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	SB8 (proposed bevacizumab biosimilar)
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Reporting group description:

Administered SB8 every 3 weeks until disease progression, unacceptable toxicity occurred, death, or EOS at a dose of 15 mg/kg body weight concurrently with chemotherapy (paclitaxel 200 mg/m² and carboplatin AUC 6 by IV infusion on Day 1 of every 3-week cycle) for at least 4 cycles and up to 6 cycles then received SB8 maintenance (mono-) therapy

Reporting group title	EU Avastin
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Reporting group description:

Administered Avastin every 3 weeks until disease progression, unacceptable toxicity occurred, death, or EOS at a dose of 15 mg/kg body weight concurrently with chemotherapy (paclitaxel 200 mg/m² and carboplatin AUC 6 by IV infusion on Day 1 of every 3-week cycle) for at least 4 cycles and up to 6 cycles then received Avastin maintenance (mono-) therapy

Serious adverse events	SB8 (proposed bevacizumab biosimilar)	EU Avastin	
Total subjects affected by serious adverse events			
subjects affected / exposed	75 / 378 (19.84%)	81 / 380 (21.32%)	
number of deaths (all causes)	166	171	
number of deaths resulting from adverse events	22	27	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Vascular disorders			
Shock haemorrhagic			
subjects affected / exposed	3 / 378 (0.79%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Hypertension			

subjects affected / exposed	2 / 378 (0.53%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	2 / 378 (0.53%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Internal haemorrhage			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Essential hypertension			

subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	4 / 378 (1.06%)	6 / 380 (1.58%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 4	0 / 6	
Infusion site extravasation			
subjects affected / exposed	2 / 378 (0.53%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 378 (0.00%)	2 / 380 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 378 (0.53%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Anaphylactic reaction			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic shock			
subjects affected / exposed	1 / 378 (0.26%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Drug hypersensitivity			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	4 / 378 (1.06%)	9 / 380 (2.37%)	
occurrences causally related to treatment / all	1 / 4	5 / 9	
deaths causally related to treatment / all	0 / 2	1 / 4	
Pneumothorax			
subjects affected / exposed	3 / 378 (0.79%)	3 / 380 (0.79%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	3 / 378 (0.79%)	5 / 380 (1.32%)	
occurrences causally related to treatment / all	0 / 3	2 / 5	
deaths causally related to treatment / all	0 / 1	2 / 5	
Dyspnoea			

subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 378 (0.26%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atelectasis			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory failure			
subjects affected / exposed	0 / 378 (0.00%)	2 / 380 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			

subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Creatinine renal clearance decreased			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Procedural pneumothorax			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Craniocerebral injury			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suture rupture			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 378 (0.26%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			

subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiovascular insufficiency			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Carotid artery occlusion			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 378 (0.26%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cognitive disorder			

subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 378 (0.26%)	3 / 380 (0.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 3	
Intercostal neuralgia			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brachial plexopathy			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 378 (1.59%)	4 / 380 (1.05%)	
occurrences causally related to treatment / all	2 / 9	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			

subjects affected / exposed	2 / 378 (0.53%)	6 / 380 (1.58%)	
occurrences causally related to treatment / all	2 / 2	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	2 / 378 (0.53%)	2 / 380 (0.53%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 378 (0.53%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 378 (0.00%)	3 / 380 (0.79%)	
occurrences causally related to treatment / all	0 / 0	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Optic atrophy			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 378 (0.53%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 378 (0.26%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			

subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia strangulated			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric hypomotility			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			

subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal haemorrhage			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis chronic			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 378 (0.00%)	2 / 380 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Portal vein thrombosis			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Decubitus ulcer			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 378 (0.26%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis glandularis			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			

subjects affected / exposed	7 / 378 (1.85%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	2 / 378 (0.53%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	1 / 378 (0.26%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	1 / 378 (0.26%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	1 / 378 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			

subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis chronic			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	2 / 378 (0.53%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	0 / 378 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	SB8 (proposed bevacizumab biosimilar)	EU Avastin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	331 / 378 (87.57%)	325 / 380 (85.53%)	
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	39 / 378 (10.32%)	43 / 380 (11.32%)	
occurrences (all)	54	59	
Weight decreased			
subjects affected / exposed	37 / 378 (9.79%)	28 / 380 (7.37%)	
occurrences (all)	37	30	
Aspartate aminotransferase increased			
subjects affected / exposed	32 / 378 (8.47%)	27 / 380 (7.11%)	
occurrences (all)	51	43	
Alanine aminotransferase increased			
subjects affected / exposed	30 / 378 (7.94%)	34 / 380 (8.95%)	
occurrences (all)	50	48	
Blood urea increased			
subjects affected / exposed	28 / 378 (7.41%)	19 / 380 (5.00%)	
occurrences (all)	51	40	
Platelet count decreased			

subjects affected / exposed occurrences (all)	18 / 378 (4.76%) 22	19 / 380 (5.00%) 30	
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	49 / 378 (12.96%) 65	39 / 380 (10.26%) 50	
Nervous system disorders Neuropathy peripheral subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	38 / 378 (10.05%) 39 32 / 378 (8.47%) 33 26 / 378 (6.88%) 29 24 / 378 (6.35%) 25	54 / 380 (14.21%) 59 32 / 380 (8.42%) 34 29 / 380 (7.63%) 51 35 / 380 (9.21%) 36	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all)	94 / 378 (24.87%) 113 75 / 378 (19.84%) 124 59 / 378 (15.61%) 99 39 / 378 (10.32%) 59	95 / 380 (25.00%) 121 69 / 380 (18.16%) 119 46 / 380 (12.11%) 69 23 / 380 (6.05%) 44	
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	52 / 378 (13.76%) 61	45 / 380 (11.84%) 57	

Fatigue subjects affected / exposed occurrences (all)	46 / 378 (12.17%) 58	47 / 380 (12.37%) 59	
Gastrointestinal disorders			
Nausea subjects affected / exposed occurrences (all)	76 / 378 (20.11%) 179	79 / 380 (20.79%) 224	
Diarrhoea subjects affected / exposed occurrences (all)	32 / 378 (8.47%) 41	25 / 380 (6.58%) 27	
Vomiting subjects affected / exposed occurrences (all)	25 / 378 (6.61%) 33	20 / 380 (5.26%) 23	
Constipation subjects affected / exposed occurrences (all)	20 / 378 (5.29%) 25	20 / 380 (5.26%) 26	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea subjects affected / exposed occurrences (all)	25 / 378 (6.61%) 25	30 / 380 (7.89%) 32	
Cough subjects affected / exposed occurrences (all)	25 / 378 (6.61%) 27	21 / 380 (5.53%) 23	
Dysphonia subjects affected / exposed occurrences (all)	24 / 378 (6.35%) 26	16 / 380 (4.21%) 16	
Epistaxis subjects affected / exposed occurrences (all)	20 / 378 (5.29%) 28	14 / 380 (3.68%) 17	
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	184 / 378 (48.68%) 185	185 / 380 (48.68%) 186	
Renal and urinary disorders			
Renal cyst			

subjects affected / exposed	20 / 378 (5.29%)	13 / 380 (3.42%)	
occurrences (all)	20	13	
Proteinuria			
subjects affected / exposed	18 / 378 (4.76%)	24 / 380 (6.32%)	
occurrences (all)	27	40	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	47 / 378 (12.43%)	47 / 380 (12.37%)	
occurrences (all)	118	93	
Myalgia			
subjects affected / exposed	24 / 378 (6.35%)	35 / 380 (9.21%)	
occurrences (all)	37	57	
Musculoskeletal pain			
subjects affected / exposed	19 / 378 (5.03%)	16 / 380 (4.21%)	
occurrences (all)	55	31	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	38 / 378 (10.05%)	35 / 380 (9.21%)	
occurrences (all)	41	48	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2015	This amendment considered US FDA feedback and clarifications on: • Study design and eligibility criteria. • Statistical methods and sample size calculation. • Text was clarified, and editorial/administrative changes were implemented where appropriate.
18 August 2016	This amendment considered clarifications on: • Eligibility criteria. • Text was clarified, and editorial/administrative changes were implemented where appropriate.

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.

None reported

Notes: