Clinical trial results:
STELLA – A Randomized, Multicenter, Multinational, Double-Blind Study to Assess the Efficacy and Safety of MB02 (Bevacizumab Biosimilar Drug) Versus Avastin® in Combination With Carboplatin and Paclitaxel for the Treatment of Subjects With Stage IIIB/IV Non-squamous Non-Small Cell Lung Cancer (NSCLC)

Summary

EudraCT number	2017-001769-26
Trial protocol	HU BG GR ES
Global end of trial date	27 February 2020

Results information

Result version number	v1 (current)
This version publication date	10 March 2021
First version publication date	10 March 2021

Trial information

Trial identification

Sponsor protocol code	MB02-C-02-17

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03296163
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	mAbxience Research SL
Sponsor organisation address	MANUEL POMBO ANGULO 28, MADRID, Spain, 28050
Public contact	Amalia Florez, mAbxience Research SL, +34 91771 15 00, amalia.florez@mabxience.com
Scientific contact	Ana Del Campo, mAbxience Research SL, +34 91771 15 00, ana.delcampo@mabxience.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	31 March 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 February 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to compare the ORR of MB02 and EU approved Avastin® when they are administered in combination with carboplatin and paclitaxel in subjects with Stage IIIB/IV non-squamous NSCLC as assessed according to RECIST

Protection of trial subjects:

This study was conducted in accordance with the ethical principles in the accepted version of the Declaration of Helsinki and all applicable regulatory authorities' regulations in compliance with International Council for Harmonisation (ICH) good clinical practice (GCP) guidelines (ICH E6), and according to the appropriate regulatory requirements in the countries where the study was conducted. Ethical approval was sought and granted at each centre. All patients provided written informed consent before any study-specific procedures were done.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 January 2018
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	Bulgaria: 6
Country: Number of subjects enrolled	Greece: 10
Country: Number of subjects enrolled	Hungary: 17
Country: Number of subjects enrolled	India: 60
Country: Number of subjects enrolled	Malaysia: 27
Country: Number of subjects enrolled	Philippines: 13
Country: Number of subjects enrolled	Thailand: 27
Country: Number of subjects enrolled	Georgia: 69
Country: Number of subjects enrolled	Russian Federation: 107
Country: Number of subjects enrolled	Serbia: 55
Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	Ukraine: 189
Country: Number of subjects enrolled	Lebanon: 3
Country: Number of subjects enrolled	Brazil: 6
Country: Number of subjects enrolled	Chile: 27
Country: Number of subjects enrolled	Mexico: 6

Worldwide total number of subjects	627
EEA total number of subjects	33

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)	408
From 65 to 84 years	219
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The Screening period for this study was from 23-January-2018, date of the first ICF, through 18-February-2019, the date of last ICF (804 subjects). The recruitment period was from 06-February-2018 through 05-March-2019 (627 subjects).

Pre-assignment

Screening details:

A total of 804 subjects were screened, of which 177 subjects were screening failures. Most screening failures (144 of 177) were the result of subjects failing to meet eligibility criteria (i.e., protocol-specified inclusion [54 subjects] or exclusion [90 subjects] criteria).

Period 1

Period 1 title	Combination Therapy period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	MB02 (Bevacizumab biosimilar) arm

Arm description:

MB02 (test; bevacizumab biosimilar drug sourced from mAbxience Spain), administered as an IV infusion at an intended dose of 15 mg/kg on Day 1 of every 3-week treatment cycle in combination with chemotherapy (carboplatin and paclitaxel).

Arm type	Experimental
Investigational medicinal product name	MB02 (Bevacizumab Biosimilar Drug) + Carboplatin/Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

MB02 (Bevacizumab Biosimilar Drug): 15 mg/kg IV every 3 weeks on Day 1
Carboplatin: Carboplatin AUC 6 IV every 3 weeks on Day 1 for 6 cycles
Paclitaxel: Paclitaxel 200 mg/m2 IV every 3 weeks on Day 1 for 6 cycles

Arm title	Avastin® (EU-Bevacizumab, Ref.product) arm

Arm description:

Avastin® (reference; sourced from the EU), administered as an IV infusion at an intended dose of 15 mg/kg on Day 1 of every 3-week treatment cycle in combination with chemotherapy (carboplatin and paclitaxel).

Arm type	Active comparator
Investigational medicinal product name	EU-approved Avastin® + Carboplatin/Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

EU-approved Avastin®: 15 mg/kg IV every 3 weeks on Day 1
Carboplatin: Carboplatin AUC 6 IV every 3 weeks on Day 1 for 6 cycles
Paclitaxel: Paclitaxel 200 mg/m2 IV every 3 weeks on Day 1 for 6 cycles

Number of subjects in period 1	MB02 (Bevacizumab biosimilar) arm	Avastin® (EU-Bevacizumab, Ref.product) arm
Started	315	312
Completed	207	220
Not completed	108	92
Consent withdrawn by subject	17	12
Physician decision	7	5
Disease progression	27	38
Adverse event, non-fatal	29	20
Subject decision	2	1
Death	14	12
Lost to follow-up	6	2
Did not receive treatment	4	2
Protocol deviation	2	-

Period 2

Period 2 title	Monotherapy
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

After 6 cycles (i.e., at the start of Cycle 7), subjects could have continued to receive MB02/Avastin® monotherapy treatment every 3 weeks until evidence of disease progression or until unacceptable toxic effects developed.

Arms

Are arms mutually exclusive?	Yes
Arm title	Avastin® (EU-Bevacizumab, Ref.product)

Arm description:

Avastin® (reference; sourced from the EU), administered as an IV infusion at an intended dose of 15 mg/kg on Day 1 of every 3-week treatment cycle

Arm type	Active comparator
Investigational medicinal product name	EU-approved Avastin®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

EU-approved Avastin®: 15 mg/kg IV every 3 weeks on Day 1

Arm title	MB02 (Bevacizumab biosimilar) arm

Arm description:

MB02 (test; bevacizumab biosimilar drug sourced from mAbxience Spain), administered as an IV infusion at an intended dose of 15 mg/kg on Day 1 of every 3-week treatment cycle

Arm type	Experimental
Investigational medicinal product name	MB02 (Bevacizumab Biosimilar Drug)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

MB02 (Bevacizumab Biosimilar Drug): 15 mg/kg IV every 3 weeks on Day 1

Number of subjects in period 2	Avastin® (EU-Bevacizumab, Ref.product)	MB02 (Bevacizumab biosimilar) arm
Started	220	207
Completed	74	68
Not completed	146	139
Consent withdrawn by subject	6	5
Physician decision	8	6
Disease progression	106	109
Adverse event, non-fatal	11	10
Subject decision	3	3
Death	8	5
Lost to follow-up	4	1

Baseline characteristics

Reporting groups	
Reporting group title	MB02 (Bevacizumab biosimilar) arm
Reporting group description: MB02 (test; bevacizumab biosimilar drug sourced from mAbxience Spain), administered as an IV infusion at an intended dose of 15 mg/kg on Day 1 of every 3-week treatment cycle in combination with chemotherapy (carboplatin and paclitaxel).	
Reporting group title	Avastin® (EU-Bevacizumab, Ref.product) arm
Reporting group description: Avastin® (reference; sourced from the EU), administered as an IV infusion at an intended dose of 15 mg/kg on Day 1 of every 3-week treatment cycle in combination with chemotherapy (carboplatin and paclitaxel).	

Reporting group values	MB02 (Bevacizumab biosimilar) arm	Avastin® (EU-Bevacizumab, Ref.product) arm	Total
Number of subjects	315	312	627
Age categorical Units: Subjects			
Adults (18-64 years)	206	202	408
From 65-84 years	109	110	219
Age continuous Units: years			
median	61.0	61.0	
inter-quartile range (Q1-Q3)	54.0 to 67.0	56.0 to 67.5	-
Gender categorical Units: Subjects			
Female	122	122	244
Male	193	190	383
Body surface area (BSA) Units: m2			
median	1.780	1.790	
inter-quartile range (Q1-Q3)	1.600 to 1.940	1.595 to 1.940	-

End points

End points reporting groups

Reporting group title	MB02 (Bevacizumab biosimilar) arm
Reporting group description:	
MB02 (test; bevacizumab biosimilar drug sourced from mAbxience Spain), administered as an IV infusion at an intended dose of 15 mg/kg on Day 1 of every 3-week treatment cycle in combination with chemotherapy (carboplatin and paclitaxel).	
Reporting group title	Avastin® (EU-Bevacizumab, Ref.product) arm
Reporting group description:	
Avastin® (reference; sourced from the EU), administered as an IV infusion at an intended dose of 15 mg/kg on Day 1 of every 3-week treatment cycle in combination with chemotherapy (carboplatin and paclitaxel).	
Reporting group title	Avastin® (EU-Bevacizumab, Ref.product)
Reporting group description:	
Avastin® (reference; sourced from the EU), administered as an IV infusion at an intended dose of 15 mg/kg on Day 1 of every 3-week treatment cycle	
Reporting group title	MB02 (Bevacizumab biosimilar) arm
Reporting group description:	
MB02 (test; bevacizumab biosimilar drug sourced from mAbxience Spain), administered as an IV infusion at an intended dose of 15 mg/kg on Day 1 of every 3-week treatment cycle	
Subject analysis set title	Intention-to-treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized subjects.	

Primary: Objective response rate (ORR) at Week 18

End point title	Objective response rate (ORR) at Week 18
End point description:	
Objective response rate was assigned for a subject if the subject displayed either complete response (CR) or partial response (PR) per RECIST version 1.1 at Week 18, as assessed by independent radiological review committee (IRC). Overall Response (OR) = CR + PR.	
End point type	Primary
End point timeframe:	
18 weeks from randomization	

End point values	MB02 (Bevacizumab biosimilar) arm	Avastin® (EU-Bevacizumab, Ref.product) arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	315	312		
Units: percentage of subjects				
number (confidence interval 95%)	40.3 (34.9 to 46.0)	44.6 (39.0 to 50.3)		

Statistical analyses

Statistical analysis title	Equivalence based on risk ratio (RR) with 90% CI

Statistical analysis description:

Equivalence analysis was based on the risk ratio (RR) (MB02/EU-approved Avastin) with an equivalence margin predefined [0.73, 1.36].
The ORR estimate was stratified using the Cochran-Mantel-Haenszel estimate of the RR and corresponding 2-sided 90% and 95% confidence interval (CI).

Comparison groups	MB02 (Bevacizumab biosimilar) arm v Avastin® (EU-Bevacizumab, Ref.product) arm
Number of subjects included in analysis	627
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Risk ratio (RR)
Point estimate	0.91
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.78
upper limit	1.06

Statistical analysis title	Equivalence based on Risk Difference with 90%CI

Statistical analysis description:

The ORR estimate was stratified using the Cochran-Mantel-Haenszel estimate of the risk difference (RD) (MB02-EU-approved Avastin) with an equivalence margin predefined [-12%, 12%] and corresponding 2-sided 90% and 95% confidence interval (CI).

Comparison groups	MB02 (Bevacizumab biosimilar) arm v Avastin® (EU-Bevacizumab, Ref.product) arm
Number of subjects included in analysis	627
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Risk difference (RD)
Point estimate	-4.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	-10.51
upper limit	2.47

Statistical analysis title	Equivalence based on Risk Difference with 95%CI

Statistical analysis description:

The ORR estimate was stratified using the Cochran-Mantel-Haenszel estimate of the risk difference (RD) (MB02-EU-approved Avastin) with an equivalence margin predefined [-12%, 12%] and corresponding 2-sided 90% and 95% confidence interval (CI).

Comparison groups	MB02 (Bevacizumab biosimilar) arm v Avastin® (EU-Bevacizumab, Ref.product) arm

Number of subjects included in analysis	627
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Risk difference (RD)
Point estimate	-4.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.76
upper limit	3.71

Statistical analysis title	Equivalence based on risk ratio (RR) with 95%CI

Statistical analysis description:

Equivalence analysis was based on the risk ratio (RR) (MB02/EU-approved Avastin) with an equivalence margin predefined [0.73, 1.36].
The ORR estimate was stratified using the Cochran-Mantel-Haenszel estimate of the RR and corresponding 2-sided 90% and 95% confidence interval (CI).

Comparison groups	Avastin® (EU-Bevacizumab, Ref.product) arm v MB02 (Bevacizumab biosimilar) arm
Number of subjects included in analysis	627
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Risk ratio (RR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.758
upper limit	1.092

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout the study completion. An average of two years (from the beginning of the study at 06-February-2018 till last patient last visit in 27-February-2020).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	MB02 (Bevacizumab biosimilar) arm

Reporting group description:

MB02 (test; bevacizumab biosimilar drug sourced from mAbxience Spain), administered as an IV infusion at an intended dose of 15 mg/kg on Day 1 of every 3-week treatment cycle in combination with chemotherapy (carboplatin and paclitaxel).

Reporting group title	Avastin® (EU-Bevacizumab, Ref.product) arm

Reporting group description:

Avastin® (reference; sourced from the EU), administered as an IV infusion at an intended dose of 15 mg/kg on Day 1 of every 3-week treatment cycle in combination with chemotherapy (carboplatin and paclitaxel).

Serious adverse events	MB02 (Bevacizumab biosimilar) arm	Avastin® (EU-Bevacizumab, Ref.product) arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	58 / 311 (18.65%)	54 / 310 (17.42%)	
number of deaths (all causes)	91	90	
number of deaths resulting from adverse events	23	24	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			
subjects affected / exposed	1 / 311 (0.32%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			

subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypertension			
subjects affected / exposed	1 / 311 (0.32%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitis			
subjects affected / exposed	0 / 311 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 311 (0.00%)	2 / 310 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Death			
subjects affected / exposed	2 / 311 (0.64%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Disease progression			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Fatigue			
subjects affected / exposed	0 / 311 (0.00%)	2 / 310 (0.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			

subjects affected / exposed	3 / 311 (0.96%)	6 / 310 (1.94%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 8	0 / 11	
Non-cardiac chest pain			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 311 (0.64%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	2 / 311 (0.64%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 311 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 311 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	0 / 311 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Epistaxis			
subjects affected / exposed	0 / 311 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hemoptysis			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 311 (0.32%)	2 / 310 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	0 / 311 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonay embolism			
subjects affected / exposed	6 / 311 (1.93%)	4 / 310 (1.29%)	
occurrences causally related to treatment / all	4 / 6	4 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pulmonary hemorrhage			
subjects affected / exposed	1 / 311 (0.32%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	1 / 1	
Respiratory failure			
subjects affected / exposed	0 / 311 (0.00%)	2 / 310 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase			

increased			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood sodium decreased			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	0 / 311 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Thoracic vertebral fracture			
subjects affected / exposed	0 / 311 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 311 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute myocardial infarction			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Atrial fibrilation			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Arrest			
subjects affected / exposed	0 / 311 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure acute			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiorespiratory arrest			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 311 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			

subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 311 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischemia			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 311 (0.00%)	2 / 310 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysmetria			
subjects affected / exposed	0 / 311 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paralysis			
subjects affected / exposed	0 / 311 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischemic stroke			
subjects affected / exposed	1 / 311 (0.32%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			

subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemorrhage intracranial			
subjects affected / exposed	2 / 311 (0.64%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 311 (0.32%)	2 / 310 (0.65%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	4 / 311 (1.29%)	7 / 310 (2.26%)	
occurrences causally related to treatment / all	5 / 5	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	3 / 311 (0.96%)	6 / 310 (1.94%)	
occurrences causally related to treatment / all	4 / 4	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 311 (0.64%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Vision blurred			
subjects affected / exposed	0 / 311 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	0 / 311 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	0 / 311 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 311 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gastric ulcer			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastric ulcer perforation			
subjects affected / exposed	0 / 311 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemorrhoids			
subjects affected / exposed	0 / 311 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperchlorhydria			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			

subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 311 (0.32%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 311 (0.64%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nephrotic syndrome			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Infections and infestations			
Brain abscess			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
subjects affected / exposed	0 / 311 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	3 / 311 (0.96%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastroenteritis			

subjects affected / exposed	1 / 311 (0.32%)	2 / 310 (0.65%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 311 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	8 / 311 (2.57%)	8 / 310 (2.58%)	
occurrences causally related to treatment / all	4 / 8	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory tract infection viral			
subjects affected / exposed	0 / 311 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 311 (0.64%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 311 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	0 / 311 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 311 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 311 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hypernatremia			
subjects affected / exposed	1 / 311 (0.32%)	0 / 310 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcemia			
subjects affected / exposed	0 / 311 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalemia			
subjects affected / exposed	1 / 311 (0.32%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	0 / 311 (0.00%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatremia			
subjects affected / exposed	1 / 311 (0.32%)	1 / 310 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	MB02 (Bevacizumab biosimilar) arm	Avastin® (EU-Bevacizumab, Ref.product) arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	230 / 311 (73.95%)	234 / 310 (75.48%)	
Investigations			
Weight decreased			
subjects affected / exposed	23 / 311 (7.40%)	27 / 310 (8.71%)	
occurrences (all)	27	36	
Platelet count decreased			
subjects affected / exposed	26 / 311 (8.36%)	19 / 310 (6.13%)	
occurrences (all)	52	34	
Alanine aminotransferase increased			
subjects affected / exposed	15 / 311 (4.82%)	21 / 310 (6.77%)	
occurrences (all)	33	28	
Aspartate aminotransferase increased			
subjects affected / exposed	14 / 311 (4.50%)	22 / 310 (7.10%)	
occurrences (all)	35	26	
Neutrophil count decreased			
subjects affected / exposed	18 / 311 (5.79%)	18 / 310 (5.81%)	
occurrences (all)	32	25	
Vascular disorders			
Hypertension			
subjects affected / exposed	24 / 311 (7.72%)	26 / 310 (8.39%)	
occurrences (all)	32	35	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	38 / 311 (12.22%)	41 / 310 (13.23%)	
occurrences (all)	70	60	
Peripheral sensory neuropathy			
subjects affected / exposed	22 / 311 (7.07%)	23 / 310 (7.42%)	
occurrences (all)	30	36	
Paresthesia			
subjects affected / exposed	21 / 311 (6.75%)	13 / 310 (4.19%)	
occurrences (all)	34	18	

Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	101 / 311 (32.48%)	94 / 310 (30.32%)	
occurrences (all)	193	191	
Leukopenia			
subjects affected / exposed	24 / 311 (7.72%)	18 / 310 (5.81%)	
occurrences (all)	42	34	
Neutropenia			
subjects affected / exposed	34 / 311 (10.93%)	45 / 310 (14.52%)	
occurrences (all)	75	81	
Thrombocytopenia			
subjects affected / exposed	41 / 311 (13.18%)	42 / 310 (13.55%)	
occurrences (all)	95	75	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	39 / 311 (12.54%)	36 / 310 (11.61%)	
occurrences (all)	85	82	
Asthenia			
subjects affected / exposed	39 / 311 (12.54%)	29 / 310 (9.35%)	
occurrences (all)	67	53	
General physical health deterioration			
subjects affected / exposed	23 / 311 (7.40%)	29 / 310 (9.35%)	
occurrences (all)	23	29	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	47 / 311 (15.11%)	44 / 310 (14.19%)	
occurrences (all)	84	81	
Diarrhea			
subjects affected / exposed	29 / 311 (9.32%)	27 / 310 (8.71%)	
occurrences (all)	38	39	
Vomiting			
subjects affected / exposed	22 / 311 (7.07%)	11 / 310 (3.55%)	
occurrences (all)	31	13	
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	20 / 311 (6.43%)	22 / 310 (7.10%)	
occurrences (all)	31	26	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	155 / 311 (49.84%)	163 / 310 (52.58%)	
occurrences (all)	193	206	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	18 / 311 (5.79%)	25 / 310 (8.06%)	
occurrences (all)	33	53	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	23 / 311 (7.40%)	30 / 310 (9.68%)	
occurrences (all)	44	53	
Arthralgia			
subjects affected / exposed	19 / 311 (6.11%)	20 / 310 (6.45%)	
occurrences (all)	31	26	
Infections and infestations			
Respiratory tract infection viral			
subjects affected / exposed	16 / 311 (5.14%)	16 / 310 (5.16%)	
occurrences (all)	22	16	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	14 / 311 (4.50%)	20 / 310 (6.45%)	
occurrences (all)	16	30	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 December 2018	The main reason for the amendment was to implement the FDA recommendations received after the FDA Scientific Advice was provided on 04-October-2018. Other minor updates were also made as a result of recommendations received from the DSMB recommendations and to clarify aspects of the protocol which were unclear in version 1.0.
24 May 2019	The main reason to issue the present amendment was to clarify the procedures applicable to subjects that were responding to treatment at Week 52 and were offered the opportunity to be treated with biosimilar MB02 monotherapy until disease progression, unacceptable toxicity, or death.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported