



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 |
| <p>Statistical analysis description:</p> <p>Equivalence analysis was based on the risk ratio (RR) (MB02/EU-approved Avastin) with an equivalence margin predefined [0.73, 1.36].</p> <p>The ORR estimate was stratified using the Cochran-Mantel-Haenszel estimate of the RR and corresponding 2-sided 90% and 95% confidence interval (CI).</p> | |
| 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 | |
| Pulmonary 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 fibrillation 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 occurrences (all) | 20 / 311 (6.43%) 31 | 22 / 310 (7.10%) 26 | |
| Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) | 155 / 311 (49.84%) 193 | 163 / 310 (52.58%) 206 | |
| Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all) | 18 / 311 (5.79%) 33 | 25 / 310 (8.06%) 53 | |
| Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) | 23 / 311 (7.40%) 44 19 / 311 (6.11%) 31 | 30 / 310 (9.68%) 53 20 / 310 (6.45%) 26 | |
| Infections and infestations Respiratory tract infection viral subjects affected / exposed occurrences (all) | 16 / 311 (5.14%) 22 | 16 / 310 (5.16%) 16 | |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 14 / 311 (4.50%) 16 | 20 / 310 (6.45%) 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