Protocol Title:	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)
NCT Number:	NCT03296163
Protocol version date:	Version 4.0, 24 May 2019

CLINICAL STUDY PROTOCOL

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)

Protocol Number:	MB02-C-02-17
EudraCT Number:	2017-001769-26
Investigational Product:	Bevacizumab biosimilar drug (MB02)
Phase:	Phase 3
Sponsor:	mAbxience Manuel Pombo Angulo, 28, 3rd Floor Madrid, Spain
Protocol Date:	04 August 2017
Protocol Version:	Version 1.0
Protocol Amendment 1:	03 December 2018 (Version 3.0)
Protocol Amendment 2:	24 May 2019 (Version 4.0)

1 PROTOCOL APPROVAL SIGNATURES

Protocol Title: 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)

Protocol Number: MB02-C-02-17

This study will be conducted in compliance with the clinical study protocol (and amendments), International Conference on Harmonisation guidelines for current Good Clinical Practice and applicable regulatory requirements.

Sponsor Signatory

[redacted]

Medical Advisor
mAbxience Research SL
C/ Manuel Pombo Angulo, 28, 3rd floor
28050 - Madrid
Spain

[redacted]

Clinical Project Manager
mAbxience Research SL
C/ Manuel Pombo Angulo, 28, 3rd floor
28050 - Madrid
Spain

Syneos Health Signatories

[redacted]

Senior Project Manager
Oncology

[redacted]

Safety Physician
Safety &
Pharmacovigilance

[redacted]

2 STUDY PERSONNEL

Sponsor Personnel

Medical Monitor

Name: [redacted]
Title: Medical Advisor
Address: mAbxience Research SL
C/ Manuel Pombo Angulo, 28, 3rd floor
28050 - Madrid
Spain
Telephone No.: [redacted]

Project Manager

Name: [redacted]
Title: Clinical Project Manager
Address: mAbxience Research SL
C/ Manuel Pombo Angulo, 28, 3rd floor 28050 - Madrid
Spain
Telephone No.: [redacted]

Other Personnel

Medical Monitor

Name: [redacted]
Title: Senior Medical Director, Global Oncology & Hematology
Address: INC Research GmbH – a Syneos Health Company
Katzbergstr. 1 | D-40764 Langenfield
Germany
Telephone No.: [redacted]

Project Manager

Name: [redacted]
Title: Senior Project Manager, Oncology
Address: INC Research GmbH – a Syneos Health Company
1 Pinehurst Road
Farnborough, Hants
GU14 7BF
United Kingdom
Telephone No.: [redacted]

3 SYNOPSIS

Protocol Number:

MB02-C-02-17

Title:

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)

Investigational Product:

MB02

Study Centers:

Approximately 150 sites and 19 countries

Phase:

Phase 3

Objectives:

Primary objective: To compare the objective response rates (ORRs) of MB02 and European Union (EU) approved Avastin® when administered in combination with carboplatin and paclitaxel in subjects with Stage IIIB/IV non-squamous NSCLC as assessed according to Response Evaluation Criteria in Solid Tumors (RECIST version 1.1).

Secondary objective(s):

- To evaluate the safety profile of MB02 compared with Avastin® in subjects with Stage IIIB/IV non-squamous NSCLC as per National Cancer Institute-Common-Toxicity Criteria for Adverse Events (NCI-CTCAE; version 4.03).
- To assess the potential immunogenicity of MB02 compared with that of Avastin® assessed through determination of antidrug antibodies (ADA).
- To assess progression-free survival (PFS) and overall survival (OS) at cutoff points at Week 18 and at Week 52 compared with those of Avastin®.

Study Design:

This is a multicenter, multinational, double-blind, 1:1 randomized, parallel-group, equivalence Phase 3 study to compare the efficacy and safety of MB02 plus chemotherapy (carboplatin and paclitaxel) versus Avastin® plus chemotherapy (carboplatin and paclitaxel) in subjects with Stage IIIB/IV non-squamous NSCLC. MB02/Avastin® plus chemotherapy will be repeated every 21 days for 6 cycles unless there is evidence of disease progression or intolerance of the study treatment. After 6 cycles (i.e., at the start of Cycle 7), subjects can continue to receive MB02/Avastin® monotherapy treatment every 3 weeks until evidence of disease progression or until unacceptable toxic effects develop. The study ends at Week 52, after Week 52, all subjects (including those randomized to Avastin® during the study) will be offered the opportunity to continue receiving biosimilar MB02 monotherapy until disease progression, unacceptable toxicity, lost to follow-up, withdrawal of consent, initiation of any new treatment or death. For specific information about post Week 52 procedures refer to Section 8.6.

Subjects eligible for the current study will be randomized centrally in a 1:1 manner and stratified by sex (male/female), smoking status (smoker/nonsmoker), disease diagnosis (newly diagnosed/recurrent disease) and stage (IIIB/IV). For stratification purposes, former smokers will be classified as smokers if they stopped less than 5 years ago and as nonsmokers if they have not smoked for the last 5 years or more or have stopped prior to study and cannot provide information on when they stopped smoking.

Tumor assessments will be performed at intervals of 6 weeks, from Cycle 1 Day 1 until the end of Cycle 6 (i.e., 18 weeks after first study drug administration); after Cycle 6, tumor assessments will be performed at intervals of 9 weeks until evidence of disease progression and/or the start of new antitumor treatment, death, or Week 52 (End-of-Study Visit), whichever occurs first.

Subjects who withdraw for any reason other than progression of disease (PD) or withdrawal of consent will be followed up every 9 weeks with tumor assessment until PD and/or the start of new antitumor treatment, subject decision, death, or Week 52 (End-of-Study Visit), whichever occurs first. Subjects who withdraw because of PD and/or initiate new antitumor therapy or those who progress during the Follow-up period will then be followed up for survival at intervals of 12 weeks until death or Week 52 (End-of-Study Visit), whichever occurs first. No further tumor assessment will be required.

An independent radiology review committee will assess the primary efficacy endpoint (observed response rate at Week 18) using computed tomography (CT) and/or magnetic resonance imaging (MRI) according to RECIST version 1.1 criteria. A Data Safety Monitoring Board (DSMB) will assess the safety data periodically and will recommend to the Sponsor whether to continue, modify, or stop the trial. This decision will be based on benefit risk evaluation.

Number of Subjects:

Based on recommendation of two different agencies, two different analyses will be performed: one based on Risk Ratio (United States [US] Food and Drug Administration [FDA]) and one based on Risk Difference (RD; European Medicines Agency [EMA]). Hence, the sample size calculation should ensure that sufficient power is retained on both analyses. No multiplicity correction will be applied.

The determination of equivalence will be based on the Intent-to-Treat (ITT) population. The per protocol population will be used as a supportive population for evaluating sensitivity of main analysis.

Risk Ratio

The US FDA requires a primary endpoint of risk ratio (RR) based on ORR, with an equivalence margin of [0.73, 1.36]. In order to gain an understanding of the clinical effect of the reference treatment, Avastin®, a meta-analysis has been conducted to ascertain the expected ORR for the reference arm, including the following references: Sandler et al. (N Engl J Med 2006;533:2542-50), Johnson et al. (J Clin Oncol 2004;22:2184-91), Niho et al. (Lung Cancer 2012;76:362-7), Reck et al. (Ann Oncol 2010;21:1804-9), and Zhou et al. (J Clin Oncol 2015;33:2197-204). The results of this meta-analysis, conducted using StatsDirect 3 software, are as follows:

Study	Responders	N	ORR	95% CI	Weight (%)
Sandler et al.	133	381	0.349	(0.301, 0.399)	22.2%
Johnson et al.	11	34	0.324	(0.174, 0.505)	15.2%
Niho et al.	71	117	0.607	(0.512, 0.696)	20.1%
Reck et al.	114	351	0.325	(0.276, 0.377)	22.0%
Zhou et al.	74	138	0.536	(0.449, 0.621)	20.5%
Total*	403	1021	0.429	(0.322, 0.539)	100%

Abbreviations: CI = confidence interval; ORR = objective response rate
*The random effects meta-analysis uses response rates for the reference product, Avastin® based on intent-to-treat population for all 5 studies. Weights are provided based on the random effects analysis. The corresponding fixed effects analysis provides a pooled proportion = 0.394.

The pooled ORR for the reference product was estimated to be 0.429 (42.9%), using a random effects model for the meta-analysis (i.e., individual proportion was weighted by the corresponding study size, accounting for random effects); a random effects meta-analysis is chosen in this case due to a high chance of heterogeneity (Cochran Q = 43.8, $P < 0.0001$, $I^2 = 90.9\%$).

Utilizing a 2-sided 90% confidence interval (CI) for the RR, a reference proportion of 42.9% for Avastin® and an equivalence margin of (0.73, 1.36), a sample size of 300 subjects per arm (600 total) provides approximately 89% power to show equivalence of MB02 plus chemotherapy with Avastin® plus chemotherapy on a primary endpoint of RR. In addition, approximately 81% power is achieved under the same conditions when a 95% CI is used.

Any subjects who discontinue study treatment prior to the 18-week time point with no Week 18 tumor response assessment will be classed as non-responders in the final analysis of the primary efficacy endpoint.

Risk difference

The EMA requested that the risk difference (RD) in ORRs is used as the primary efficacy analysis, using an equivalence margin of (-12%, +12%). Utilizing a 2-sided 90% CI for the RD, 300 subjects per arm are sufficient to show equivalence of MB02 plus chemotherapy with Avastin® plus chemotherapy on RD with approximately 82% power.

All sample size calculations are conducted using PASS13 software.

Treatment:

The investigational products will be as follows:

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

Combination chemotherapy treatment (from Cycle 1 to Cycle 6) will be as follows:

- Paclitaxel: to be administered as an IV infusion at an intended dose of 200 mg/m^2 on Day 1 of every 3-week treatment cycle

- Carboplatin: to achieve an area under the plasma concentration-time curve of 6 mg/mL × min (AUC6) as an IV infusion on Day 1 of every 3-week treatment cycle

For up to the first 6 cycles, the study treatment will consist of an initial administration of paclitaxel 200 mg/m^2 IV over 3 hours, followed by carboplatin AUC6 IV over 15 to 60 minutes and then, immediately afterward either MB02 or Avastin® 15 mg/kg. MB02 and Avastin® will be administered IV. From Cycle 7 onwards, the study treatment will consist of either MB02 or Avastin® 15 mg/kg. MB02 and Avastin® monotherapy will be administered IV. A window of 30 minutes is allowed between the administration of the 2 chemotherapy drugs and/or between the administration of either chemotherapy drug and either study drug (MB02 or Avastin®).

The first MB02 or Avastin® treatment will be administered as a 90-minute infusion. If the study drug is well tolerated, the next infusion will be given over a 60-minute period. Thereafter, the drug will be given as a 30-minute IV infusion. If the study drug is not well tolerated, the instructions from Avastin® Summary of Product Characteristics (SmPC) should be followed.

Retreatment Criteria:

Further treatment cycles (i.e., Cycle 2 or subsequent) will be administered if the subject fulfils all the following retreatment criteria: Absolute neutrophil count > 1.5 × 10^9/L; platelets counts >100,000/μL, hemoglobin level > 9 g/dL, controlled hypertension and proteinuria
< 2+ and all other non-hematological related toxicities have resolved to ≤ grade 1 (except alopecia, anorexia, constipation, not optimally treated nausea and/or vomiting and non-clinically relevant isolated biochemical abnormalities) or to the subject's baseline condition.

Dose Adjustment of MB02/Avastin®:

Until the Week 18 assessment, any reduction in MB02/Avastin® dose will not be permitted. Treatment (both MB02/Avastin® and chemotherapy) should be put on hold in the event of toxicities ≥ grade 3, that the investigator considers to be clinically significant and related to study treatment. The maximum permitted length of treatment hold is 14 days, equivalent to 5 weeks from the last treatment dose. Treatment can be restarted when retreatment criteria are met. An MB02/Avastin® dose adjustment to weight change may or may not be implemented (under investigator's discretion) if the subject's body weight changes less than 10% from Baseline or from the weight at the last dose adjustment, and must be compulsorily done if the subject's body weight changes by 10% or more from Baseline or from the weight at the last dose adjustment. After Week 18, intended dose reduction of MB02/Avastin® is allowed if clinically necessary to a dose level of 7.5 mg/kg. No further dose reduction of MB02/Avastin® is allowed.

If a subject discontinues MB02/Avastin® treatment before completing 6 cycles of therapy and before the primary endpoint at Week 18, the subject must discontinue study treatment and proceed to the End-of-Treatment Visit.

Toxicities should be managed according to the relevant Avastin® SmPCs. If grade 3 toxicity recurs upon reintroduction of MB02/Avastin®, the investigator should consider the individual benefit versus the risk of continuing therapy. If the event occurs again upon a second reintroduction of MB02/Avastin®, treatment should be permanently discontinued.

The main toxicities anticipated for MB02/Avastin® (on the basis of the product label for EU-approved Avastin®) in this study are as follows:

- Gastrointestinal (GI) perforations (GI perforations, fistula formation in the GI tract, intra-abdominal abscess), fistula formation involving an internal organ.
- Wound dehiscence and wound healing complications requiring medical intervention.
- Serious hemorrhage (i.e., requiring medical intervention).
- Severe arterial thromboembolic events.
- Life-threatening (grade 4) venous thromboembolic events, including pulmonary embolism.
- Hypertensive crisis or hypertensive encephalopathy.
- Posterior reversible encephalopathy syndrome.
- Nephrotic syndrome.
- Severe hypertension not controlled with medical management.
- Moderate to severe proteinuria.
- Severe infusion reactions.

As osteonecrosis of the jaw has been reported for subjects on bevacizumab and invasive dental procedures are an identified risk factor, a dental examination and appropriate preventive dentistry should be considered before the start of treatment, if clinically indicated. Procedures that involve direct osseous injury and placement of dental implants should be avoided if not strictly necessary. Caution should be exercised for subjects receiving intravenous bisphosphonates.

Dose modification of chemotherapy

For the chemotherapy agents paclitaxel/carboplatin, dose adjustments and toxicities will be managed according to specific SmPC.

If a subject discontinues paclitaxel and carboplatin before completing 6 cycles of therapy and before the primary endpoint at Week 18, the continuation of bevacizumab (MB02 or Avastin®, as allocated) as monotherapy should be justified and discussed with the Sponsor prior to such a change in schedule.

For additional information please refer to SmPCs for Avastin®, carboplatin, and paclitaxel.

Study Population:

Inclusion Criteria

To be eligible for study entry, subjects must satisfy all of the following criteria:

1. Males and female subjects aged ≥18 years to ≤80 years.

2. Signed informed consent must be obtained before initiation of any study-specific procedures or treatment as confirmation of the subject's awareness and willingness to comply with the study requirements.

3. Subjects should have newly diagnosed or recurrent Stage IIIB/IV (defined by seventh edition of the TNM classification for Lung Cancer, 2010) non-squamous NSCLC not amenable to curative intent surgery, and not have received any systemic therapy for advanced disease (exclusion criteria 3 and 4). For subjects with recurrent disease, at least 6 months must have elapsed before randomization from previous adjuvant treatment. For Stage IV disease, malignant pleural or pericardial effusion must be

confirmed by cytological examination if the effusion is the only lesion that confirms Stage IV of the disease. In all other cases, the cytological confirmation of effusion is not mandatory.

4. Previous radiation therapy if completed >4 weeks before randomization. Palliative radiotherapy to bone lesions is allowed if completed >2 weeks of randomization.

5. Subjects must have at least 1 unidimensional measurable lesion per RECIST version 1.1 (assessed locally).

6. Subjects must have an ECOG performance status ≤1 at Screening.

7. Subjects must have adequate hepatic, renal and hematologic function defined as:

   - Hepatic function: bilirubin level <1.5 × ULN, ALT and AST levels<2.5×ULN.
   - Renal function: serum creatinine level <1.5 × ULN, calculated creatinine clearance (CrCl) >50 mL/min (Cockroft-Gault formula), urine protein to creatinine ratio <1. Subjects with urine protein-to-creatinine ratio ≥1 may be enrolled if they have <1 g of protein in 24-hour urine collection.
   - Hematological function: Absolute neutrophil count >1.5 × 10^9 /L; platelets >100 × 10^9 /L, hemoglobin (Hb) >9 g/dL.
   - Adequate coagulation parameters such as: INR ≤ 2.0 and aPTT ≤ 1.5 × ULN within 7 days prior to randomization for patients not receiving anticoagulation therapy.

8. Eligible subjects must have a systolic blood pressure of ≤ 140 mm Hg and a diastolic blood pressure of ≤ 90 mm Hg at screening.

9. Women of childbearing potential, and their partners, must agree to adhere to pregnancy prevention methods throughout the duration of the study (including the Follow-up visits, where applicable). Women of childbearing potential are defined as those who are not surgically sterile (did not underwent bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) and not postmenopausal.

   Subjects and their partners must agree to use a highly effective method of contraception, to avoid women becoming pregnant throughout the course of the study. Medically acceptable forms of birth control can include the following, with approval of the treating physician:

   - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, sexual abstinence.

10. Non fertile women can be included, that is, those who are physiologically incapable of becoming pregnant, because of:

    - Hysterectomy.
    - Bilateral oophorectomy (ovariectomy).
    - Bilateral tubal ligation or,

- Postmenopausal women defined as:

Subjects not using HRT and who have experienced total cessation of menses for ≥1 year and be greater than 45 years of age, OR, in questionable cases, have a follicle stimulating hormone >40 mIU/mL and an estradiol value <40 pg/mL (<140 pmol/L).

Subjects must discontinue HRT before study enrolment because of the potential for inhibition of cytochrome enzymes that metabolize estrogens and progestins. For most forms of HRT, at least 2 to 4 weeks must elapse between the cessation of HRT and determination of menopausal status; the length of this interval depends on the type and dosage of HRT.

If a female subject is determined not to be postmenopausal, that subject must use adequate contraception, as defined immediately above (inclusion 8).

Exclusion Criteria

Subjects will be excluded from the study if 1 or more of the following criteria are applicable:

1. Inability to comply with protocol procedures.

2. Participation in another clinical trial or treatment with another investigational agent within 4 weeks or 5 half-lives of investigational agent before randomization, whichever is longer.

3. Subjects previously treated with monoclonal antibodies or small molecule inhibitors against VEGF or VEGF receptors, including Avastin®.

4. Subjects who have received previous chemotherapy, immunotherapy, targeted therapy, or biological therapy for their lung cancer. Note: Adjuvant and neo-adjuvant therapy are permitted (see: inclusion criterion 3).

5. Subjects who have known malignant central nervous system disease, with the exception of subjects with treated brain metastases who have completed treatment (radiation, surgery or stereotactic surgery) and have not received steroids for at least 4 weeks before randomization. Subjects with central nervous system metastases treated by neurosurgical resection or brain biopsy performed within 8 weeks before randomization will be excluded. Subjects with known or history of brain metastases must undergo brain imaging during screening.

6. Current or recent (within 10 days of the first dose of study treatment) use of aspirin (at least 325 mg/day) or other nonsteroidal anti-inflammatory drugs with antiplatelet activity or treatment with dipyridamole (Persantine®), ticlopidine (Ticlid®), clopidogrel (Plavix®), or cilostazol (Pletal®).

7. Current or recent (within 5 days) use of therapeutic anticoagulation or use of thrombolytic agent. Prophylactic use of low molecular weight heparin is allowed.

8. Subjects with an INR >2, unless receiving active anticoagulation treatment, will be excluded.

9. Subjects who have a diagnosis of small cell carcinoma of the lung or squamous cell carcinoma of the lung. Mixed tumors should be categorized according to the predominant histology. If small cell elements are present, the subject will be excluded.

10. Subjects with known tumors that harbor activating epidermal growth factor receptor and anaplastic lymphoma receptor tyrosine kinase (assessed locally).

11. Subjects who have a history of hypersensitivity to the active substance (bevacizumab, carboplatin, and/or paclitaxel) or any of the excipients (such as trehalose dehydrate, sodium phosphate, or polysorbate 20).

12. Subjects with known active viral infection, including but not limited to: hepatitis B, hepatitis C, or HIV.

13. Subjects who are pregnant or breastfeeding. Women of child-bearing potential must have a negative pregnancy test at Screening.

14. Subjects with previous major surgery, open biopsy, open pleurodesis, or significant traumatic injury within 4 weeks before randomization or those anticipated to require major surgery during the study.

15. Subjects who have had a core biopsy taken or have had another minor surgical procedure, excluding placement of vascular access device, closed pleurodesis, thoracentesis, and mediastinoscopy, within 1 week of randomization.

16. Subjects with a history of abdominal fistula, GI perforation, intra-abdominal abscess within 6 months of randomization.

17. Subjects with a nonhealing wound, active ulcer, or untreated bone fracture.

18. Subjects with previous history of hypertensive crisis or hypertensive encephalopathy.

19. Subjects with New York Heart Association Grade II or greater congestive heart failure, or angina, myocardial infarction within 6 months before randomization; symptomatic arrhythmia or serious cardiac arrhythmia requiring medication; abnormal left ventricular ejection fraction < 50% assessed by ultrasound or multigated acquisition scan.

20. Subjects with a previous malignancy within 3 years of randomization (other than superficial basal cell and superficial squamous (skin) cell carcinoma, or carcinoma *in situ* of the uterine cervix, bladder, or prostate).

21. Subjects with history of a significant vascular event within 6 months before randomization (including, but not limited to myocardial infarction and stroke or transient ischemic attack).

22. Subjects with known bleeding diathesis or significant coagulopathy defined as a bleeding event grade ≥ 2 within 3 months before randomization.

23. Subjects with history of grade ≥2 hemoptysis within 6 months before randomization (≥0.5 teaspoons of bright red blood per event).

24. Subjects with a tumor(s) invading or compressing major blood vessels.

Discontinuation from Treatment:

A subject should be withdrawn from study treatment if, in the opinion of the investigator, it is medically necessary, or if it is the wish of the subject. Subjects will be withdrawn from treatment for any of the following reasons:

- Progression of disease.
- Unacceptable toxicity.
- Withdrawal of consent.
- Subject decision (may continue in the study for the follow-up visits).
- Lost to Follow-up.
- Protocol violation.
- Death.
- Investigator decision.
- Subject becomes pregnant.

The SmPC for Avastin® specifies the following reasons for discontinuation:

- Necrotizing fasciitis.
- Medically significant hypertension that cannot be adequately controlled with antihypertensive therapy.
- Nephrotic syndrome, grade 4 proteinuria.
- Arterial thromboembolic reactions.
- Grade 3 or 4 bleeding.
- Intracranial bleeding.

If a subject discontinues MB02/Avastin® treatment before completing 6 cycles of therapy and before the primary endpoint at Week 18, the subject must discontinue study treatment and proceed to the End-of-Treatment Visit.

If a subject discontinues paclitaxel and carboplatin before completing 6 cycles of therapy and before the primary endpoint at Week 18, the continuation of bevacizumab (MB02 or Avastin®, as allocated) as monotherapy should be justified and discussed with the Sponsor prior to such a change in schedule.

Every attempt will be made to conduct follow-up visits until the End-of-Study at Week 52 for any subject who discontinues treatment before Week 52.

Discontinuation from Study:

Subjects can be discontinued from the study for any of the following reasons:

- Withdrawal of consent.
- Death.
- Lost to Follow-up.
- Protocol violation.
- Termination of the study by the Sponsor.
- Subject becomes pregnant.

Re-screening is not allowed.

Subjects who discontinue from the study prematurely after randomization will not be replaced. Subjects are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason(s) for withdrawal will be documented in the electronic case report form (eCRF).

Every attempt will be made to conduct the assessments scheduled for the End-of-Study Visit in any subject who discontinues from the study. The aim is to record data in the same way for discontinued subjects as for subjects who completed the study.

Concomitant medications allowed:

- Antihypertensive: No limitations in type of medication according to the investigators discretion.
- Antiemetic premedication may be used for nausea; paclitaxel premedication by anti-histamine receptor (H1 and H2) steroids is allowed.
- Low molecular weight heparins may be used for the treatment of deep vein thrombosis or pulmonary embolism, if they occur.
- Antidiarrheals: Used as needed per investigator's discretion.
- Analgesics: Used as needed per investigator's discretion.
- Corticosteroids and/or bisphosphonates for the treatment of bone metastases.
- Megestrol acetate, when prescribed for appetite stimulation.
- Primary and secondary prophylaxis with granulocyte colony-stimulating factor, according to the investigator's judgement.
- Erythropoietin.

Additional details are provided in protocol Section 7.4.8.

Primary Endpoint:

Objective Response Rate: Objective response (OR) will be assigned for a subject if the subject displays either complete response (CR) or partial response (PR) per RECIST version 1.1 at Week 18 as assessed by independent review.

Secondary Efficacy Endpoints:

Progression Free Survival: PFS will be defined as the time from randomization to subsequent confirmed progression per RECIST version 1.1, measured in weeks and will be analyzed for all subject data at cutoff points at Week 18 and at Week 52.

Overall Survival: OS will be defined as the time from randomization to subsequent death, measured in weeks and will be analyzed for all subject data at cutoff points at Week 18 and at Week 52.

Efficacy:

Tumor assessments will be performed at intervals of 6 weeks, from Cycle 1 Day 1 until the end of Cycle 6 (i.e., 18 weeks after first study drug administration); after Cycle 6, tumor assessments will be performed at intervals of 9 weeks until evidence of disease progression and/or the start of new antitumor treatment, death, or Week 52 (End-of-Study Visit), whichever occurs first. Tumor assessment schedule is not linked to the treatment schedule: in case of treatment delays, tumor assessment should be continued according to the initial schedule.

Subjects who withdraw for any reason other than PD or withdrawal of consent will be followed up every 9 weeks with tumor assessment until PD and/or the start of new antitumor treatment, subject decision, death, or Week 52 (End-of-Study Visit) whichever occurs first. Subjects who withdraw because of PD and/or initiate new antitumor therapy or those who progress during the Follow-up period will then be followed up for survival at intervals of 12 weeks until death or Week 52 (End-of-Study Visit) whichever occurs first. No further tumor assessment will be required.

Immunogenicity:

Blood samples will be taken to determine serum biomarkers (antidrug antibodies) through 52 weeks after first study drug administration. Analysis of immunogenicity endpoints will be conducted by an external provider.

Safety:

Safety will be monitored by: incidence, nature, and severity of adverse events (AEs), including adverse drug reactions graded according to NCI-CTCAE (version 4.03); incidence of clinical laboratory value abnormalities (hematology, clinical chemistry, and urinalysis); physical examination; ECOG performance status; 12-lead electrocardiogram (ECG), vital sign assessment and brain CT (in subjects with history of brain metastases only).

Statistical Analysis:

The statistical analysis will aim to demonstrate equivalence in terms of ORR between MB02 and Avastin®.

The ITT analysis set will consist of all randomized subjects (subjects will be analyzed under randomized treatment); the per protocol set (PPS) with regards to the primary endpoint will consist of all subjects in the ITT population who complete at least the first 6 cycles of treatment and for whom no major protocol deviations affecting efficacy occur until Week 18 (subjects will be analyzed under randomized treatment); the safety analysis set (SAF) will consist of all randomized subjects who received at least 1 administration of study drug. On the SAF, all subjects will be analyzed under the actual treatment received.

For RR (FDA recommendations) equivalence on the primary endpoint will be declared if the 2-sided 90% CI of the strata adjusted using the Cochran- Mantel-Haenszel estimate of the RR lies entirely within the range 0.73 (excluded) to 1.36 (excluded). This primary analysis will be conducted in the ITT population.

For RD (EMA recommendation), equivalence on the primary endpoint will be declared if the 2-sided 90% CI of the strata adjusted Cochran- Mantel-Haenszel estimate of the RD lies within the range -12% (excluded) to +12% (excluded). This primary analysis will be conducted in the ITT population.

For additional equivalence criteria on the primary endpoint required by regulatory bodies (i.e., Pharmaceuticals and Medical Devices Agency, [PMDA]), 90% and 95% for RR and RD will also be provided in the ITT population.

Progression-free survival will be presented using Kaplan-Meier figures and estimates and estimated median (95% CI) (if available), along with the log-rank test to compare the survival distributions; a Cox proportional hazards model will be used to estimate the hazard ratio (90% CI) of MB02 compared with Avastin® at cutoff points at Week 18 and Week 52.
Overall survival will be analyzed in the same way. For both assessments, all subject data will be included as accrued up to the cutoff time point. For example, if a subject has survival data after Week 18, it will be included for the time-to-event analysis at the Week 18 cutoff.

Descriptive analysis of safety variables will be performed on the SAF. Further information will be provided in the Statistical Analysis Plan (SAP).

4 TABLE OF CONTENTS

List of Tables:

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine transaminase
aPTT	activated partial prothrombin time
AST	aspartate transaminase
AUC6	area under the plasma concentration time curve of 6 mg/mL × min
CI	confidence interval
CR	complete response
CT	computed tomography
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	Identifier
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IRC	independent radiology review committee
ITT	Intention-to-treat
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival
PD	progression of disease
PET	positron emission tomography
PFS	progression free survival
PK	Pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	per protocol set
PR	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
RD	risk difference
RR	risk ratio
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SD	stable disease
SmPC	summary of product characteristics
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal

US	United States
VEGF	vascular endothelial growth factor
WHO	World Health Organization

5 INTRODUCTION

5.1 Background: Non-Small Cell Lung Cancer

Global cancer statistics show that deaths from lung cancer exceed those from any other malignancy; primary lung cancer is the second-most common malignancy.[1] Non-small cell lung cancers (NSCLCs) account for 85%–90% of lung cancers[1] and there are 3 main subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. The distribution of histological types of NSCLC has changed over the last 25 years. In the United States, the incidence of squamous cell carcinoma has decreased, although adenocarcinoma has increased for both men and women. In Europe, similar trends have occurred in men; however, in women, incidence of both squamous cell carcinoma and adenocarcinoma have increased.[2]

Platinum-based chemotherapy regimens can improve survival time and the quality of life for subjects with newly diagnosed, advanced NSCLC; however, most subjects still develop progressive disease in the first 6 months of treatment. Therefore, newer therapies that disrupt critical growth factor/receptor signaling pathways involved in tumor angiogenesis and lymphangiogenesis are required. One potential treatment target is vascular endothelial growth factor (VEGF), which induces the proliferation, migration, and survival of vascular endothelial cells and stimulates the recruitment of bone marrow-derived endothelial progenitor cells to new blood vessels serving the tumor. High expression levels of VEGF in the tumor microenvironment have been correlated with increased tumor vascular density, invasive behavior, and metastasis in NSCLC and other tumor types.

5.2 Reference Therapy (Bevacizumab; Avastin®)

Bevacizumab, the active component of Avastin®, is a recombinant humanized monoclonal immunoglobulin G1 antibody (93% human, 7% murine sequences, molecular weight 149 kDa) that selectively binds with high affinity to all isoforms of human VEGF and neutralizes VEGF's biologic activity through steric blocking of the binding of VEGF to its receptors on the surface of endothelial cells. Because there is very low or undetectable expression of VEGF receptors in most normal tissues but significant up-regulation in the vasculature of many tumors, neutralization of VEGF by bevacizumab is thought to inhibit tumor growth and block metastasis.[3,4]

Avastin® has been approved by the US Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) as first-line treatment for a range of solid tumors in combination with other chemotherapeutic agents including: non-squamous NSCLC; metastatic renal cell cancer; metastatic carcinoma of the colon or rectum; metastatic breast cancer; epithelial ovarian, fallopian tube and primary peritoneal cancer; and cervical cancer.[5]

According to the Avastin® Summary of Product Characteristics (SmPC), the elimination half-life is 18 days for a typical female subject and 20 days for a typical male subject. [5]

The main toxicities anticipated (on the basis of the product label for European Union [EU-] approved Avastin®) in this study are as follows:

- Gastrointestinal perforations (GI perforations, fistula formation in the GI tract, intra-abdominal abscess), fistula formation involving an internal organ.
- Wound dehiscence and wound healing complications requiring medical intervention.

- Serious hemorrhage (i.e., requiring medical intervention).
- Severe arterial thromboembolic events.
- Life-threatening (grade 4) venous thromboembolic events, including pulmonary embolism.
- Hypertensive crisis or hypertensive encephalopathy.
- Posterior reversible encephalopathy syndrome.
- Nephrotic syndrome.
- Severe hypertension not controlled with medical management.
- Moderate to severe proteinuria.
- Severe infusion reactions.

5.3 Investigational Product (MB02; Bevacizumab biosimilar)

5.3.1 Nonclinical Data

MB02 was shown to have the same characteristics as the reference product Avastin® in a series of in vitro assays, selected according to the current EMA guideline on biosimilars (EMA/CHMP/BMWP/403543/2010).

The results of these assays are presented in detail in the MB02 Investigator's Brochure (version 5.0, dated May 2017).[6] In summary:

- MB02 and Avastin® have a similar molecular mass.
- MB02 and Avastin® have the same amino acid sequence (100% sequence match); no chemical modification was observed on any of the amino acids.
- MB02 and Avastin® have the same glycan attachment site.
- MB02 and Avastin® have a similar protein conformation.
- The distribution of glycans is similar in MB02 and Avastin®.
- MB02 and Avastin® have a similar charge variants profile as confirmed by the capillary isoelectric focusing and ion-exchange analysis.
- MB02 and Avastin® have similar purity in sodium dodecyl sulfate polyacrylamide gel electrophoresis, size-exclusion high performance liquid chromatography and area under the curve analysis.
- The values found in the aggregation kinetics study for the conformational and colloidal stability (unfolding transition temperature, aggregation onset temperatures [T_{agg}; 266 nm and T_{agg}; 473 nm]) show extreme similarity in both colloidal and conformational stability between MB02 and Avastin®. This indicates that both products behave similarly in stress conditions, an observation indicative of a similar stability profile.
- MB02 and Avastin® have similar affinity for VEGF as determined by 2 independent techniques.
- MB02 and Avastin® have similar potency as evidenced by human umbilical vein endothelial cell assay activity.
- MB02 and Avastin® have similar neonatal Fc receptor binding, which is predictive of similar pharmacokinetic (PK) profiles for the 2 products.

In addition, a repeat-dose (twice weekly for 28 days) toxicokinetic study in monkeys showed that:

- Maximum serum concentrations were attained generally at or near to the end of infusion. The degree of accumulation observed on Day 25 of repeat dosing was similar for MB02 and Avastin®, with mean accumulation ratios ranging from 3.7 to 4.2 and 3.0 to 3.1, respectively.
- According to the area under the plasma concentration-time curve from time zero to 72 hours and maximum plasma concentration after single and repeat dosing, there were no appreciable (>2-fold) sex-related differences in exposure to MB02 and Avastin®.
- Systemic exposure to MB02 was similar to that of Avastin® on Days 1 and 25 (relative bioavailability estimates ranged from 88% to 107% in male monkeys and 89% to 128% in female monkeys).

Moreover, MB02 and Avastin® were well tolerated with no clear differences between them. Microscopic findings of physeal thickening in the femur, adrenal cortical eosinophilia, and reduced glands in the uterus were similar for both products.

5.3.2 Clinical Data

A multicenter, open label, randomized, parallel group bioequivalence study of MB02 (bevacizumab biosimilar) and Avastin® was conducted to compare the PK efficacy and safety of MB02 and Avastin® in combination with FOLFOX or FOLFIRI chemotherapy as first-line treatment in subjects with metastatic colorectal cancer (Protocol number: BEVZ92-A-01-13; ClinicalTrials.gov identifier: NCT02069704).

There were no new findings related to the safety of MB02/Avastin®. Overall, the safety comparability exercise showed no signals of concern regarding previous experience with bevacizumab, and no obvious differential effects between the biosimilar and the reference medicinal product. This pivotal study indicated no new safety signals, raised no concerns about immunogenicity and did not suggest an increase in risk of bleeding. The analysis of the number of subjects with treatment-emergent AEs in the 2 treatment arms suggested that the safety profile in terms of nature, frequency and severity of AEs was similar to that of the reference medicinal product and according to what is expected given the underlying disease and concurrent use of chemotherapy. Moreover, no new events were reported in any treatment arm in relation to the current SmPC for Avastin.[5]

The pattern of AEs and serious AEs (SAEs) in subjects treated with MB02 was consistent with the profile of subjects undergoing Avastin® therapy for the treatment of metastatic colorectal cancer.

Data from the BEVZ92-A-01-13 study showed MB02 and Avastin® to have equivalent PK in terms of AUC and similar efficacy in terms of tumor response in the sensitive population of metastatic colorectal subjects. It was concluded that MB02 was biosimilar to Avastin®. When MB02 is used in the same way as Avastin®, following the same warnings and precautions, it is anticipated that MB02 will provide the same benefit with no difference in risk.

5.4 Rationale for Current Study

Non-small cell lung cancer is the most common type of lung cancer, is among the leading causes of death worldwide and contributes significantly to growing health care costs.

Avastin® has been approved for use in many cancer indications and settings, including first-line treatment of NSCLC in combination with other chemotherapeutic agents.

MB02 is currently being developed as a treatment biosimilar to Avastin®. In order to support the similarity of MB02 already demonstrated in preclinical development, according to guidelines issued by the US FDA, EMA and World Health Organization (WHO) a properly conducted comparative clinical trial demonstrating comparable efficacy is necessary.[7,8,9] The current study is part of the stepwise development of MB02 and has been requested and validated by the EMA as an equivalence trial.

5.5 Additional Information on Non-Investigational Medicinal Products

For additional information on the non-investigational medicinal products in this study, please refer to SmPCs for Avastin®[5], carboplatin[10,11,12], and paclitaxel[13,14,15].

6 STUDY OBJECTIVES

6.1 Primary Objective

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 (version 1.1).[16]

6.2 Secondary Objectives

The secondary objectives of the study are as follows:

- To evaluate the safety profile of MB02 compared with Avastin® in subjects with Stage IIIB/IV non-squamous NSCLC as per NCI-CTCAE (v4.03).
- To assess the potential immunogenicity of MB02 compared with Avastin® assessed through determination of antidrug antibodies (ADA).
- To assess PFS and OS at cutoff points at Week 18 and at Week 52 compared with those of Avastin®.

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan: Description

This is a multicenter, multinational, double-blind, 1:1 randomized, parallel-group, equivalence Phase III study to compare the efficacy and safety of MB02 plus chemotherapy (carboplatin and paclitaxel) versus Avastin® plus chemotherapy (carboplatin and paclitaxel) in 600 subjects with Stage IIIB/IV non-squamous NSCLC. MB02/Avastin® plus chemotherapy will be repeated every 21 days for 6 cycles unless there is evidence of disease progression or intolerance of the study treatment. After 6 cycles, (i.e., at the start of Cycle 7), subjects can continue to receive MB02/Avastin® monotherapy treatment every 3 weeks until evidence of disease progression or until unacceptable toxic effects develop.

The study ends at Week 52, after Week 52, all subjects (including those randomized to Avastin® during the study) will be offered the opportunity to continue receiving biosimilar MB02 monotherapy until disease progression, unacceptable toxicity, lost to follow-up, withdrawal of consent, initiation of any new treatment or death. For specific information about post Week 52 procedures refer to Section 8.6.

Subjects eligible for the current study will be randomized centrally in a 1:1 manner and stratified by sex (male/female), smoking status (smoker/nonsmoker), disease diagnosis (newly diagnosed/recurrent disease) and stage (IIIB/IV). A rationale for the study design is presented in Section 7.2.

Tumor assessments will be performed at intervals of 6 weeks, from Cycle 1 Day 1 until the end of Cycle 6 (i.e., 18 weeks after first study drug administration); after Cycle 6, tumor assessments will be performed at intervals of 9 weeks until evidence of disease progression and/or the start of new antitumor treatment, death, or Week 52 (End-of-Study Visit), whichever occurs first.

Subjects who withdraw for any reason other than progression of disease (PD) or withdrawal of consent will be followed up every 9 weeks with tumor assessment until PD and/or the start of new antitumor treatment, subject decision, death, or Week 52 (End-of-Study Visit) whichever occurs first. Subjects who withdraw because of PD and/or initiate new antitumor therapy or those who progress during the Follow-up Period will then be followed up for survival at intervals of 12 weeks until death or Week 52 (End-of-Study Visit), whichever occurs first. No further tumor assessment will be required.

The primary endpoint is ORR (i.e., complete response [CR] or partial response [PR] per RECIST version 1.1) at Week 18; an independent radiology review committee (IRC) will assess the primary efficacy endpoint using computed tomography (CT) and/or magnetic resonance imaging (MRI) according to RECIST version 1.1 criteria.

A Data Safety Monitoring Board (DSMB) will assess the safety data periodically and will recommend to the Sponsor whether to continue, modify or stop the trial. This decision will be based on benefit risk evaluation. Further details of the DSMB are provided in Section 9.2.

If a subject discontinues treatment before Week 52 from first study drug administration, he/she will be requested to attend follow-up visits. The following assessments will be made:

- Subjects with no radiological disease progression will be assessed for: tumor evaluation, initiation of other treatments, physical examination, Eastern Cooperative

Oncology Group (ECOG) performance status, supine vital signs, concomitant medications, surgeries, procedures, AEs/SAEs , concomitant diseases and immunogenicity will be recorded in the electronic case report form (eCRF) at follow-up visits at intervals of 9 weeks up to disease progression and/or the start of new antitumor treatment, death, or Week 52 (End-of-Study Visit).

- Subjects that discontinue treatment with radiological progression and/ or initiate new antitumor therapy will be assessed for: initiation of other treatments, concomitant medications, surgeries, procedures, AEs/SAEs (ongoing and/or related to drug study) and concomitant diseases, all of which will be recorded in the eCRF. Subjects will be followed up for survival at intervals of 3 months (±14 days) until death or Week 52 End-of-Study Visit (documented phone call is acceptable), but no further tumor assessment will be required.

After Week 52, all subjects (including those randomized to Avastin® during the study) will be offered to continue receiving biosimilar MB02 monotherapy until disease progression, unacceptable toxicity, lost to follow-up, withdrawal of consent, initiation of any new treatment or death. For specific information about post Week 52 procedures refer to Section 8.6.

If a subject discontinues MB02/Avastin® treatment before completing 6 cycles of therapy and before the primary endpoint at Week 18, the subject must discontinue study treatment and proceed to the End-of-Treatment Visit.

If a subject discontinues paclitaxel and carboplatin before completing 6 cycles of therapy and before the primary endpoint at Week 18, the continuation of bevacizumab (MB02 or Avastin®, as allocated) as monotherapy should be justified and discussed with the Sponsor prior to such a change in schedule.

7.1.1 Schedule of Assessments

Tests & Procedures	**Screening period**	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**Additional Cycles[b]**	**End of Treatment**	**Additional Follow -up Visits (no disease progression)**	**Additional Follow-up (disease progression)**	**Week 52 End-of-Study Visit**	**Post Week 52Period[q]**
Week (Day)[a]	**Days -28 to -1**	**1 (1)**	**4 (22)**	**7 (43)**	**10 (64)**	**13 (85)**	**16 (106)**	**19 (127) then every 3 weeks**	**Within 3 weeks of last cycle**	**Every 9 weeks**	**Every 3 months**	**52**	
Window (Days)		**-1/+3**	**-1/+3**	**-1/+3**	**-1/+3**	**-1/+3**	**-1/+3**	**-1/+3**	**± 5**	**± 7**	**± 14**	**± 7**	
Written Informed Consent[c]	Before any study procedure: -28 to -1												
Informed Consent accepting the risk of potential treatment switch[q]													X
Eligibility (inclusion/exclusion criteria)	-7 to -1												
Demography data	-28 to -1												
Medical history / baseline conditions	-28 to -1												
NSCLC History	-28 to -1												
Randomization[d]	-1 to 1												
Physical examination	-14 to -1	X	X	X	X	X	X	X	X	X		X	
ECOG/ performance status	-14 to -1	X	X	X	X	X	X	X	X	X		X	
Vital signs, weight and height[e]	-14 to -1	X	X	X	X	X	X	X	X	X		X	
Hematology[f]	-7 to -1	X[f]	X	X	X	X	X	X	X				
Blood chemistry[f]	-7 to -1	X[f]	X	X	X	X	X	X	X				
Coagulation[f]	-7 to -1	X[f]	X	X	X	X	X	X	X				

Tests & Procedures	Screening period	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Additional Cycles[b]	End of Treatment	Additional Follow -up Visits (no disease progression)	Additional Follow-up (disease progression)	Week 52 End-of-Study Visit	Post Week 52Period[q]
Week (Day)[a]	**Days -28 to -1**	**1 (1)**	**4 (22)**	**7 (43)**	**10 (64)**	**13 (85)**	**16 (106)**	**19 (127) then every 3 weeks**	**Within 3 weeks of last cycle**	**Every 9 weeks**	**Every 3 months**	**52**	
Window (Days)		**-1/+3**	**-1/+3**	**-1/+3**	**-1/+3**	**-1/+3**	**-1/+3**	**-1/+3**	**± 5**	**± 7**	**± 14**	**± 7**	
Urinalysis[f]	-14 to -1	X[f]	X	X	X	X	X	X	X				
Virology[g]	-14 to -1												
Pregnancy test[h]	-14 to -1	X	X	X	X	X	X	X	X				
12-lead electrocardiogram[i]	-28 to -1			X		X	X		X			X	
LVEF measurement[p]	-28 to -1								X				
Brain CT[j]	-28 to -1	If clinically indicated											
Tumor assessment[k]	-28 to -1		X		X		X	X[k]	X	X[k]		X[k]	
Serum biomarkers (ADA)[l]		X	X		X			X[l]	X	X[l]		X	
Prior and Concomitant medications[m]	-14 to -1	X	X	X	X	X	X	X	X	X	X	X	
Prior and Concomitant Surgeries and Procedures[m]	-14 to -1	X	X	X	X	X	X	X	X	X	X	X	
Adverse events[n]	-28 to -1	X	X	X	X	X	X	X	X	X	X	X	X
Drug administration		X	X	X	X	X	X	X					X (Not to be captured in eCRF, source documents only)
Initiation of new antitumor therapy recorded[o]										X	X	X	
Survival Status[o]		X	X	X	X	X	X	X	X	X	X	X	

Abbreviations: ADA = antidrug antibodies; CT = computed tomography, ECOG = Eastern Cooperative Oncology Group; HIV = human immunodeficiency virus; LVEF=left ventricular ejection fraction; NSCLC = non-small cell lung cancer; PD=progression of disease; WOCBP=women of childbearing potential;

[a] Calculated using the first day of assigned treatment as Day 1 and unless otherwise specified in other footnotes for a specific activity

[b] Treatment in additional cycles should continue until: PD, unacceptable toxicity, withdrawal of consent, subject decision, lost to follow-up, protocol violation, death, investigator decision, or subject becomes pregnant

[c] Must have been obtained before any study-related procedures are performed

[d] Randomization of subjects will take place on the same day (Day 1) or the day before the planned treatment dose administration (Day -1); should an unintended delay occur, the initial cycle of MB02 must start within 4 (-1/+3) days of randomization

e Supine Vital signs including blood pressure, pulse rate, respiratory rate and body temperature Height will be measured at Screening only

[f] Laboratory assessments will be conducted by a **central laboratory** and will include hematology (complete blood count including hemoglobin, hematocrit, white blood cell count with 5-part differential, red blood cell count and platelet count), blood chemistry (bicarbonate, calcium, phosphorus, magnesium, albumin, glucose, serum creatinine, total protein, and blood urea nitrogen), liver function tests (aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, and total and direct bilirubin), coagulation analysis (international normalized ratio, prothrombin time, partial thromboplastin time and fibrinogen), and urinalysis (microscopy including protein, protein-to-creatinine ratio (Screening only), specific gravity, glucose, and blood) If protein-to creatinine ratio is ≥ 1 at Screening, then 24-hour urine must demonstrate < 1 g of protein in 24 hours For routine on-study urinalysis assessments, dipstick is sufficient as long as the urine protein result is less than 2+ (urinalysis also acceptable) If dipstick urine protein result is ≥ 2+, 24-hour urine must demonstrate < 1 g of protein in 24 hours *A window timeframe of -5/+3 days will be allowed for laboratory assessments.* If screening laboratory assessments are done within 7 days of Cycle 1 Day 1 (first dose), they do not need to be repeated on Day 1 For retreatment (Cycle 2 and on) purposes, local laboratories may be utilized, **in addition to the central laboratory**

[g] Testing for viral infection is not required at screening only to assess whether the status of viral infection (including but not limited to hepatitis B, hepatitis C, and HIV) is known

[h] Urine or serum as per local requirements; WOCBP only

[i] Electrocardiogram will be performed at Screening, at Cycle 3 (before dosing), Cycle 5 (before dosing), Cycle 6 (Week 18 [± 1 week]), End of Treatment Visit, at Week 52 (Cycle 18 predose) and any time if clinically indicated

[j] Brain CT will be performed only in subjects with known or history of brain metastases or if clinically indicated

[k] Perform a CT and/or MRI of the chest, upper abdomen, and any other involved regions Disease status and tumor response will be assessed per RECIST version 1 1 criteria at Screening (within 4 weeks before the first scheduled dose of study drug) and then every 6 weeks (±3 days) from Cycle 1 Day 1 until end of Cycle 6 (Week 18) and, thereafter every 9 weeks (±5 days) until Week 52, PD, start of new treatment, subject decision, or death, whichever occurs first Week 18 tumor assessments have a 1 week window (±1 week) In addition, tumor assessment should be performed at any time if clinically indicated Tumor measurement will also be performed during the End-of-Treatment Visit if it was not done within the previous 4 weeks Every effort will be made to ensure that the same method of assessment used at Screening is used at all subsequent time points For those subjects who discontinue treatment without radiological disease progression, tumor assessment should be performed every 9 weeks (±5 days) until Week 52, PD, start of new treatment, subject decision, or death, whichever occurs first Once radiological disease progression is documented, subjects are no longer required to undergo additional tumor assessment

[l] Blood sample for Serum Biomarkers (ADA) determination will be collected at Week 1 (Cycle 1 Predose), at Week 4 (Cycle 2 Predose), at Week 10 (Cycle 4 Predose), at Week 19 (Cycle 7 Predose), at Week 34 (Cycle 12 Predose) and at Week 52 and, at the End of Treatment Visit if an ADA sample has not been collected within the previous 3 weeks If study treatment should be delayed, ADA sample should also be delayed accordingly Once subject discontinues treatment, ADA sample will follow specified weeks as scheduled

[m] Concomitant medications, surgeries and procedures will be collected/reported from signing of informed consent form until 30 days after last cycle administration Beyond this date, only concomitant medications, surgeries and procedures administered for an AE or SAE considered related to study drugs will be collected/reported

[n] All AEs and SAEs will be collected/reported from signing of informed consent form until 30 days after last cycle administration Beyond this date, only AEs and SAEs considered related to study drugs will be collected/reported

[o] Subjects who discontinue treatment due to disease progression will be followed up every 3 months (±14 days) until start of new antitumor therapy, death, or week 52, whichever occurs first This follow-up may be performed through a documented phone call No further tumor assessments will be required

[p] Left ventricular ejection fraction to be measured by cardiac ultrasound or multigated acquisition scan at Screening Visit and End of Treatment Visit (if not done in previous 6 weeks); left ventricular ejection can also be measured during any treatment cycle, if clinically indicated

[q] Subjects will be asked to reconsent for the potential risk of switching treatment to MB02 in case they have been randomized to Avastin ® treatment Subjects will remain blinded

7.2 Discussion of Study Design

This is a double-blind study, i.e., all those involved in study conduct including investigators and the subjects are unaware of who will receive each of the 2 treatments. The double-blind design reduces the potential for bias, particularly in the assessment of AEs. Most of the other assessments in the current study are objective in nature and, therefore, less prone to bias. A DSMB will assess safety data periodically and, on benefit/risk evaluation, will recommend to the Sponsor any required change in study conduct.

This is a comparator-controlled study in which the test product, the bevacizumab biosimilar MB02, will be compared with the EU-approved bevacizumab product, Avastin®. Use of a placebo in the planned subject population would provide no potential for benefit and therefore is not considered appropriate. The primary objective is to compare the ORR of MB02 and Avastin®. During their participation in the study, each subject will be exposed to 1 of the 2 treatments. A parallel-group study is preferred to a crossover design for its shorter duration and for continuity of treatment in this population with advanced disease. Should subjects complete 6 cycles, and they wish to and are eligible to continue to receive treatment, they can receive MB02 or Avastin® monotherapy to be administered every 3 weeks until treatment withdrawal (see Sections 7.1.1 and 7.3.4.1).

The study population will comprise subjects with Stage IIIB/IV non-squamous NSCLC not amenable to curative intent surgery and, who have not received any systemic therapy for advanced disease. There is a potential for this population to benefit from either treatment.

7.3 Selection of Study Population

7.3.1 Number of Planned Subjects

The sample size calculation found that 600 subjects (300 subjects per group) are required to complete the study for determination of equivalence. Sufficient subjects will be screened to enable 600 subjects to be randomized.

7.3.2 Inclusion Criteria

To be eligible for study entry, subjects must satisfy all of the following criteria:

1. Males and female subjects aged ≥18 years to ≤80 years.

2. Signed informed consent must be obtained before initiation of any study-specific procedures or treatment as confirmation of the subject's awareness and willingness to comply with the study requirements.

3. Subjects should have newly diagnosed or recurrent Stage IIIB/IV (defined by seventh edition of the TNM classification for Lung Cancer, 2010) non-squamous NSCLC not amenable to curative intent surgery, and not have received any systemic therapy for advanced disease (exclusion criteria 3 and 4) (Section 16.3). For subjects with recurrent disease, at least 6 months must have elapsed before randomization from previous adjuvant treatment. For Stage IV disease, malignant pleural or pericardial effusion must be confirmed by cytological examination if the effusion is the only lesion that confirms Stage IV of the disease. In all other cases, the cytological confirmation of effusion is not mandatory.

4. Previous radiation therapy if completed >4 weeks before randomization. Palliative radiotherapy to bone lesions is allowed if completed >2 weeks of randomization.

5. Subjects must have at least 1 unidimensional measurable lesion per RECIST version 1.1 (assessed locally).

6. Subjects must have an ECOG performance status ≤1 at Screening.

7. Subjects must have adequate hepatic, renal and hematologic function defined as:

   - Hepatic function: bilirubin level <1.5 ULN, ALT and AST levels<2.5×ULN.
   - Renal function: serum creatinine level <1.5×ULN, calculated creatinine clearance (CrCl) >50 mL/min (Cockroft-Gault formula), urine protein to creatinine ratio <1. Subjects with urine protein-to-creatinine ratio ≥1 may be enrolled if they have <1 g of protein in 24-hour urine collection.
   - Hematological function: Absolute neutrophil count >1.5×10^9 /L; platelets >100×10^9 /L, hemoglobin (Hb) >9 g/dL.
   - Adequate coagulation parameters such as: INR ≤ 2.0 and aPTT ≤ 1.5 × ULN within 7 days prior to randomization for patients not receiving anticoagulation therapy.

8. Eligible subjects must have a systolic blood pressure of ≤ 140 mm Hg and a diastolic blood pressure of ≤ 90 mm Hg at screening.

9. Women of childbearing potential, and their partners, must agree to adhere to pregnancy prevention methods throughout the duration of the study (including the Follow-up visits, where applicable). Women of childbearing potential are defined as those who are not surgically sterile (did not underwent bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) and not postmenopausal.

Subjects and their partners must agree to use a highly effective method of contraception, to avoid women becoming pregnant throughout the course of the study. Medically acceptable forms of birth control can include the following, with approval of the treating physician:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, sexual abstinence.

10. Non fertile women can be included, that is, those who are physiologically incapable of becoming pregnant, because of:

    - Hysterectomy.
    - Bilateral oophorectomy (ovariectomy).
    - Bilateral tubal ligation or,
    - Postmenopausal women defined as:

    Subjects not using HRT and who have experienced total cessation of menses for ≥1 year and be greater than 45 years of age, OR, in questionable cases, have a follicle stimulating hormone >40 mIU/mL and an estradiol value <40 pg/mL (<140 pmol/L).

    Subjects must discontinue HRT before study enrolment because of the potential for inhibition of cytochrome enzymes that metabolize estrogens and progestins. For most forms of HRT, at least 2 to 4 weeks must elapse between the cessation of HRT and determination of menopausal status; the length of this interval depends on the type and dosage of HRT.

    If a female subject is determined not to be postmenopausal, that subject must use adequate contraception, as defined immediately above (inclusion 8).

7.3.3 Exclusion Criteria

Subjects will be excluded from the study if 1 or more of the following criteria are applicable:

1. Inability to comply with protocol procedures.

2. Participation in another clinical trial or treatment with another investigational agent within 4 weeks or 5 half-lives of investigational agent before randomization, whichever is longer.

3. Subjects previously treated with monoclonal antibodies or small molecule inhibitors against VEGF or VEGF receptors, including Avastin®.

4. Subjects who have received previous chemotherapy, immunotherapy, targeted therapy, or biological therapy for their lung cancer. Note: Adjuvant and neo-adjuvant therapy are permitted (see: inclusion criterion 3).

5. Subjects who have known malignant central nervous system disease, with the exception of subjects with treated brain metastases who have completed treatment (radiation, surgery or stereotactic surgery) and have not received steroids for at least 4 weeks before randomization. Subjects with central nervous system metastases treated by neurosurgical resection or brain biopsy performed within 8 weeks before randomization will be excluded. Subjects with known or history of brain metastases must undergo brain imaging during screening.

6. Current or recent (within 10 days of the first dose of study treatment) use of aspirin (at least 325 mg/day) or other nonsteroidal anti-inflammatory drugs with antiplatelet activity or treatment with dipyridamole (Persantine®), ticlopidine (Ticlid®), clopidogrel (Plavix®), or cilostazol (Pletal®).

7. Current or recent (within 5 days) use of therapeutic anticoagulation or use of thrombolytic agent. Prophylactic use of low molecular weight heparin is allowed.

8. Subjects with an INR >2, unless receiving active anticoagulation treatment, will be excluded.

9. Subjects who have a diagnosis of small cell carcinoma of the lung or squamous cell carcinoma of the lung. Mixed tumors should be categorized according to the predominant histology. If small cell elements are present, the subject will be excluded.

10. Subjects with known tumors that harbor activating epidermal growth factor receptor and anaplastic lymphoma receptor tyrosine kinase (assessed locally).

11. Subjects who have a history of hypersensitivity to the active substance (bevacizumab, carboplatin, and/or paclitaxel) or any of the excipients (such as trehalose dehydrate, sodium phosphate, or polysorbate 20).

12. Subjects with known active viral infection, including but not limited to: hepatitis B, hepatitis C, or HIV.

13. Subjects who are pregnant or breastfeeding. Women of child-bearing potential must have a negative pregnancy test at Screening.

14. Subjects with previous major surgery, open biopsy, open pleurodesis, or significant traumatic injury within 4 weeks before randomization or those anticipated to require major surgery during the study.

15. Subjects who have had a core biopsy taken or have had another minor surgical procedure, excluding placement of vascular access device, closed pleurodesis, thoracentesis, and mediastinoscopy, within 1 week of randomization.

16. Subjects with a history of abdominal fistula, GI perforation, intra-abdominal abscess within 6 months of randomization.

17. Subjects with a nonhealing wound, active ulcer, or untreated bone fracture.

18. Subjects with previous history of hypertensive crisis or hypertensive encephalopathy.

19. Subjects with New York Heart Association[17] Grade II or greater congestive heart failure, or angina, myocardial infarction within 6 months before randomization; symptomatic arrhythmia or serious cardiac arrhythmia requiring medication; abnormal left ventricular ejection fraction < 50% assessed by ultrasound or multigated acquisition scan.

20. Subjects with a previous malignancy within 3 years of randomization (other than superficial basal cell and superficial squamous (skin) cell carcinoma, or carcinoma *in situ* of the uterine cervix, bladder, or prostate).

21. Subjects with history of a significant vascular event within 6 months before randomization (including, but not limited to myocardial infarction and stroke or transient ischemic attack).

22. Subjects with known bleeding diathesis or significant coagulopathy defined as a bleeding event grade ≥ 2 within 3 months before randomization.

23. Subjects with history of grade ≥2 hemoptysis within 6 months before randomization (≥0.5 teaspoons of bright red blood per event).

24. Subjects with a tumor(s) invading or compressing major blood vessels.

7.3.4 Removal of Subjects from Therapy or Assessments

7.3.4.1 Removal of Subjects From Treatment

A subject should be withdrawn from study treatment if in the opinion of the investigator, it is medically necessary or if it is the wish of the subject. Subjects will be withdrawn from treatment for any of the following reasons:

- Progression of disease.
- Unacceptable toxicity.
- Withdrawal of consent.
- Subject decision (may continue in the study for the follow-up visits).
- Lost to follow-up.
- Protocol violation.
- Death.
- Investigator decision.
- Subject becomes pregnant.

The SmPC for Avastin® specifies the following reasons for discontinuation:

- Necrotizing fasciitis.
- Medically significant hypertension cannot be adequately controlled with antihypertensive therapy.
- Nephrotic syndrome, grade 4 proteinuria.
- Arterial thromboembolic reactions.
- Grade 3 or 4 bleeding.
- Intracranial bleeding.

If a subject discontinues MB02/Avastin® treatment before completing 6 cycles of therapy and before the primary endpoint at Week 18, the subject must discontinue study treatment and proceed to the End-of-Treatment Visit.

If a subject discontinues paclitaxel and carboplatin before completing 6 cycles of therapy and before the primary endpoint at Week 18, the continuation of bevacizumab (MB02 or Avastin®, as allocated) as monotherapy should be justified and discussed with the Sponsor prior to such a change in schedule.

Every attempt will be made to conduct follow-up visits every 9 weeks until Week 52 as well as the End-of-Study Visit in any subject who discontinues treatment before Week 52.

7.3.4.2 Removal of Subjects from Study

Subjects can be discontinued from the study for any of the following reasons:

- Withdrawal of consent.
- Death.
- Lost to follow-up.
- Protocol violation.
- Termination of the study by the Sponsor.
- Subject becomes pregnant.

Rescreening is not allowed.

Subjects who discontinue the study prematurely after randomization will not be replaced. Subjects are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason(s) for withdrawal will be documented in the eCRF.

Every attempt will be made to conduct the assessments scheduled for the End-of-Study Visit in any subject that discontinues from the study. The aim is to record data in the same way for discontinued subjects as for subjects who completed the study.

Reasonable efforts will be made to contact subjects who are lost to follow-up. These efforts must be documented in the subject's file.

The Sponsor has the right to terminate the study at any time in case of SAEs or if special circumstances concerning MB02 or the company itself occur, making further treatment of subjects impossible. In this event, the investigator(s) will be informed of the reason for study termination.

Pregnancy and breast feeding

Subjects will be instructed that known or suspected pregnancy occurring during the study, in subjects or in female partners of male subjects, should be confirmed and reported to the investigator, who will then withdraw the subject from treatment without delay. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a female subject is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed up to term, and the status of mother and child will be reported to the Sponsor after delivery. Female partners of male subjects who become pregnant will be followed up in the same way.

It is not known whether Avastin® is excreted in human milk. Because maternal immunoglobulin G is excreted in milk and Avastin® could harm infant growth and development, women must discontinue breastfeeding during therapy and not breastfeed for at least 6 months after the last dose of Avastin®. Breastfeeding is listed as an exclusion criterion for this study.

Full details will be recorded on the withdrawal page of the eCRF. A pregnancy form should be sent within 24 hours of investigator´s knowledge of the pregnancy or breastfeeding (see Section 9.1.3.2).

7.4 Investigational Products

7.4.1 Investigational Products Administered

The investigational products will be as follows:

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

The investigational product (MB02 or Avastin®) will be given in combination with paclitaxel and carboplatin (both to be sourced centrally).

Combination chemotherapy treatment (from Cycle 1 to Cycle 6) will be as follows:

- Paclitaxel: to be administered as an IV infusion at an intended dose of 200 mg/m^2 on Day 1 of every 3 week treatment cycle
- Carboplatin: to achieve an AUC6 as an IV infusion on Day 1 of every 3 week treatment cycle

For up to the first 6 cycles, the study treatment will consist of an initial administration of paclitaxel 200 mg/m^2 IV over 3 hours, followed by carboplatin AUC6 IV over 15 to 60 minutes and then, immediately afterward either MB02 or Avastin® 15 mg/kg. MB02 and Avastin® will be administered IV. A window of 30 minutes is allowed between the administration of the 2 chemotherapy drugs and/or between the administration of either chemotherapy drug and either study drug (MB02 or Avastin®).

The first MB02 or Avastin® treatment will be administered as a 90-minute infusion. If the study drug is well tolerated, the next infusion will be given over a 60-minute period. Thereafter, the drug will be given as a 30-minute IV infusion.

Subjects who complete 6 cycles of the combination treatment (MB02 or Avastin® in combination with paclitaxel and carboplatin) can continue to receive monotherapy treatment every 3 weeks until PD, unacceptable toxicity, death, or withdrawal.

7.4.2 Identity of Investigational Products

MB02 and Avastin® will be presented in single-use vials as follows:

- 100 mg of MB02 or Avastin® in a 4-mL volume. Each 100-mg (25 mg/mL) glass vial product is formulated in 240 mg α,α-trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and water for injection.
- 400 mg of MB02 or Avastin® in a 16-mL volume. Each 400-mg (25 mg/mL) glass vial product is formulated in 960 mg α,α-trehalose dihydrate, 92.8 mg sodium phosphate (monobasic, monohydrate), 19.2 mg sodium phosphate (dibasic, anhydrous), 6.4 mg polysorbate 20, and water for injection.

Combination Chemotherapy treatment will be presented in single use vials as follows:

- Paclitaxel vials of 300 mg (6 mg/mL) and 100 mg (6 mg/mL).
- Carboplatin vials of 450 mg (10 mg/mL) and 150 mg (10 mg/mL).

All study drugs will be manufactured and imported according to relevant regulatory requirements. MB02/ Avastin® vials must be stored in a refrigerator at 2°C to 8°C (36 ºF to 46ºF) in their outer carton to protect from light. Once prepared, infusion solutions of MB02 or Avastin® in polyvinylchloride or polyethylene bags containing 0.9% sodium chloride injection (United States Pharmacopeia, USP), should be stored at 2°C to 8ºC (36–46ºF) for no more than 24 hours before use. Paclitaxel/carboplatin will be stored and prepared according to SmPCs.

7.4.3 Packaging and Labeling

Study packaging will be performed by Clinical Supplies Management (CSM) Europe SA, Mont-Saint-Guibert, Belgium. All packaging and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products and local regulatory requirements. MB02 and Avastin® are supplied as a concentrate for solution for infusion. They are provided in sterile, preservative-free, nonpyrogenic, type I glass vials with a rubber stopper.

MB02 and Avastin® will be labeled with information in the same format and as required by the relevant regulatory and national requirements. Labeling will be performed according to Annex 13 of the Good Manufacturing Practice (GMP) guidelines of the European Commission, International Conference on Harmonisation (ICH), Good Clinical Practice (GCP) guidelines, and local law.

Paclitaxel and Carboplatin will be supplied with their commercial packaging to which will be attached a study specification label and stamped.

7.4.4 Method of Assigning Subjects to Treatment Groups

Subjects (i.e., the unique subject identifier [ID] consisting of center ID and subject ID) will be randomly allocated (1:1 ratio) to treatment according to a prespecified blocked randomization scheme. Randomization will be stratified by sex (male/female), smoking status (smoker/nonsmoker), disease diagnosis (newly diagnosed/recurrent disease) and stage (Stage IIIB/Stage IV). For stratification purposes, former smokers will be classified as smokers if they stopped less than 5 years ago and as nonsmokers if they have not smoked for the last 5 years or more, or have stopped prior to study and cannot provide information on when they stopped smoking.

The randomization list will be prepared by INC Research by an independent unblinded randomization statistician. The randomization will be performed using a centralized Interactive Web Response System, Endpoint®.

7.4.5 Selection of Doses in the Study

The dose and infusion rates of test (MB02) and reference (Avastin®) medications that have been selected are the same as those approved for bevacizumab in the SmPC for first-line treatment of non-squamous NSCLC, i.e., 15 mg/kg given every 3 weeks as an IV infusion, which is the standard of care and posology for the disease under study.

7.4.6 Selection and Timing of Dose for Each Subject

Randomization of subjects will take place on the same day (Day 1) or the day before the planned treatment dose administration (Day -1); should an unintended delay occur, the initial cycle of MB02 must start within 4 (-1/+3) days of randomization. Beyond this period, the imaging and laboratory tests must be repeated. Subsequent bevacizumab doses will be administered at 21 day intervals (-1/+3 days) due to holidays, etc.

Further treatment cycles (i.e., Cycle 2 or subsequent) will be administered if the subject fulfils all of the following retreatment criteria: absolute neutrophil count more than 1.5×10^9 /L; platelet count more than 100,000/μL, hemoglobin level (Hb) more than 9 g/dL, controlled hypertension and proteinuria less than 2+ or if all other nonhematological related toxicities have resolved to ≤ grade 1 (except alopecia, anorexia, constipation, not optimally treated nausea and/or vomiting and non-clinically relevant isolated biochemical abnormalities) or to the subject's baseline condition.

Until the Week 18 assessment, reduction in MB02/Avastin® dose will not be permitted. Treatment (both MB02/Avastin® and chemotherapy) should be put on hold in the event of toxicities ≥ grade 3, that the investigator considers to be clinically significant and related to study treatment. The maximum permitted length of treatment hold is 14 days, equivalent to 5 weeks from last treatment dose. Treatment can be restarted when retreatment criteria are met. An MB02/Avastin® dose adjustment to weight change may or may not be implemented (under investigator's discretion) if the subject's body weight changes less than 10% from Baseline or from the weight of last dose adjustment, and must be compulsorily done if the subject's body weight changes by 10% or more from Baseline or from the weight at the last dose adjustment. After Week 18, intended dose reduction of MB02/Avastin® is allowed if clinically necessary to a dose level of 7.5 mg/kg. No further dose reduction of MB02/Avastin® is allowed.

If a subject discontinues MB02/Avastin® treatment before completing 6 cycles of therapy and before the primary endpoint at Week 18, the subject must discontinue study treatment and proceed to End-of-Treatment Visit.

Toxicities should be managed according to the relevant Avastin® SmPC. If grade 3 toxicity recurs upon reintroduction of MB02/Avastin®, the investigator should consider the individual benefit versus the risk of continuing therapy. If the event occurs again upon a second reintroduction of MB02/Avastin®, treatment should be permanently discontinued.

Additional information of dose levels is summarized in Section 7.4.1.

7.4.7 Blinding

This is a randomized, double-blind study up to Week 52.

The pharmacist at each study site and a specific clinical team from INC Research and the Sponsor will be unblinded to treatment assigned. Subjects as well as investigators, all other study staff, laboratories and the rest of the INC Research and Sponsor team will remain blinded to treatment assignment up to Week 52. The blind for a specific subject can be broken by the investigator (emergency code breaking) only if the investigator considers the information indispensable to the safety of the subject.

All subjects whose treatment is unblinded by the investigator (break blind option, emergency code breaking) while on the study will be withdrawn at the moment of unblinding, with the reason for unblinding given as the reason for discontinuation from the study.

7.4.8 Previous and Concomitant Therapy

7.4.8.1 Prohibited Medication/Therapy

Any concomitant medications contraindicated according to the SmPC of any of the study drugs (Avastin®/MB02 or chemotherapy -Paclitaxel and Carboplatin-) are considered prohibited in this trial.

As osteonecrosis of the jaw has been reported for subjects on bevacizumab and invasive dental procedures are an identified risk factor, a dental examination and appropriate preventive dentistry should be considered before the start of treatment, if clinically indicated. Procedures that involve direct osseous injury and placement of dental implants should be avoided if not strictly necessary. Caution should be exercised for subjects on intravenous bisphosphonates.

7.4.8.2 Permitted Medication

Antihypertensive medications, antidiarrheal medications, and analgesics can be administered as required, according to the investigator's discretion.

Low molecular weight heparins are allowed and may be used for the treatment of deep vein thrombosis or pulmonary embolism, if they occur.

Antiemetic premedication may be used for nausea and granulocyte colony-stimulating factor (G-CSF) according to the investigator's judgement; corticosteroids and/or bisphosphonates are permitted for treatment of bone metastases. Megestrol acetate can be used for appetite stimulation. Erythropoietin is permitted, as are primary and secondary prophylaxis with granulocyte colony-stimulating factor.

As per paclitaxel SmPC, premedication with anti-histaminic drugs (H1 and H2) and steroids is recommended.

7.4.9 Treatment Compliance

The investigator is ultimately responsible for supervising compliance with the instructions described in this study protocol.

8 TIMING OF STUDY PROCEDURES

Subjects will provide written informed consent up to 28 days before first study drug administration and before any study-related procedures are performed.

The planned study assessments are presented in Section 7.1.1.

8.1 Pretreatment

8.1.1 Screening Visit (Days -28 to -1; Visit 1)

The following screening assessments will be made within the time periods specified:

Up to 28 days before first study drug administration:

- Written informed consent.
- Record demographic data, such as ethnic origin, date of birth, and sex.
- Collect full medical history and baseline conditions.
- Collect full NSCLC history including prior antitumor therapies, as applicable.
- Perform a standard 12-lead electrocardiogram (ECG).
- Measure left ventricular ejection fraction by cardiac ultrasound or multigated acquisition scan.
- Conduct brain CT (only in subjects with known or history of brain metastases).
- Conduct tumor assessment using CT and/or MRI of chest, upper abdomen, and any other involved regions. Disease status and tumor response will be assessed per RECIST version 1.1 criteria.
- Recording of AEs and recording/reporting of SAEs from signature of informed consent.

Up to 14 days before first study drug administration

- Perform a physical examination.
- Determine ECOG/performance status.
- Record supine vital signs (including blood pressure, pulse rate, respiratory rate and body temperature), weight and height (measured at screening only).
- Collection of samples for urinalysis. If the urine protein-to-creatinine ratio ≥ 1, then a 24-hour urine test is to be conducted by a central laboratory.

- Determine status of known active viral infection, including but not limited to: hepatitis B, hepatitis C, or HIV.
- Urine or serum pregnancy test (according to local requirements, female subjects of childbearing potential only).
- Record concomitant medications taken up to 28 days before the planned date of the first dose of study drug.
- Record surgeries and/or procedures (not study related) undergone up to 28 days before the planned date of the first dose of study drug.

Up to 7 days before first study drug administration

- Assess for eligibility against the inclusion and exclusion criteria.
- Collection of samples for hematology, blood chemistry, and coagulation.

Before the start of treatment a complete dental examination is mandatory in order to identify any invasive dental procedure. It is considered a risk factor for osteonecrosis of the jaw, reported for subjects on bevacizumab. Appropriate preventive dentistry should be considered, if clinically indicated (Section 7.4.8.1).

8.2 Treatment Period

8.2.1 Cycle 1 (-1/+3 Days)

Randomization of subjects will take place on the same day or the day before the planned treatment dose administration (Day 1 or Day -1); should an unintended delay occur, the initial cycle of MB02 must start within 4 days (-1/+3 days) of randomization.

The following procedures will be performed prior to dosing:

- Physical examination.
- Determination of ECOG performance status.
- Recording of supine vital signs (including blood pressure, pulse rate, respiratory rate and body temperature) and weight.
- Collection of samples for hematology, blood chemistry, coagulation, and urinalysis tests. (If screening laboratory assessments are done within 7 days of Cycle 1 Day 1 [first dose], they do not need to be repeated on Day 1.)
- Urine or serum pregnancy test (according to local requirements; female subjects of childbearing potential only).
- Collection of a sample for serum biomarkers (antidrug antibodies).
- Review and recording of concomitant medications, procedures and/ or surgeries.
- Review and recording of AEs and concomitant diseases. Recording/reporting of SAEs.

Once all procedures have been performed and, if everything is correct and adequate, chemotherapy will be administered followed by MB02 or Avastin® (15 mg/kg IV infusion) according to the randomization schedule which will be recorded in the eCRF.

In addition to this, a Brain CT and/or CT Scan/MRI will be performed any time throughout the cycle if PD is suspected or if clinically indicated. Standard 12-lead ECG and left ventricular ejection fraction may also be measured by cardiac ultrasound or multigated acquisition scan, if clinically indicated.

If the subject has died, this will be recorded in the eCRF. If the death has occurred because of an SAE, this will be reported as per Section 9.1.3.2.

8.2.2 Cycle 2 (-1/+3 Days)

Cycle 2 will take place 21 days (-1/+3 days) after first administration of study drug.

The following procedures will be performed prior to dosing:

- Physical examination.
- Determination of ECOG performance status.
- Recording of supine vital signs (including blood pressure, pulse rate, respiratory rate and body temperature) and weight.
- Collection of samples for hematology, blood chemistry, coagulation, and urinalysis tests to be conducted by a central laboratory.
- Urine or serum pregnancy test (according to local requirements; female subjects of childbearing potential only).
- Collection of a sample for serum biomarkers (antidrug antibodies).
- Review and recording of concomitant medications, procedures and/ or surgeries.
- Review and recording of AEs and concomitant diseases. Recording/reporting of SAEs.

Once all procedures have been performed and, if everything is correct and adequate, chemotherapy will be administered followed by MB02 or Avastin® (15 mg/kg IV infusion) according to the randomization schedule which will be recorded in the eCRF.

At Week 6 (±3 days) from Cycle 1 Day 1 and/or any time throughout the cycle if clinically indicated, a CT Scan/ MRI of chest, upper abdomen and any other involved regions should be conducted. Disease status and tumor response will be assessed per RECIST version 1.1 criteria.

In addition to this, a Brain CT and/or CT Scan/ MRI will be performed any time throughout the cycle if PD is suspected or if clinically indicated. Standard 12-lead ECG and left ventricular ejection fraction may also be measured by cardiac ultrasound or multigated acquisition scan, if clinically indicated.

If the subject has died, this will be recorded in the eCRF. If the death has occurred because of an SAE, this will be reported as per Section 9.1.3.2.

8.2.3 Cycle 3 (-1/+3 Days)

Cycle 3 visit will take place 21 days (-1/+3 days) after second administration of study drug.

The following procedures will be performed prior to dosing:

- Physical examination.
- Determination of ECOG performance status.
- Recording of supine vital signs (including blood pressure, pulse rate, respiratory rate and body temperature) and weight.
- Collection of samples for hematology, blood chemistry, coagulation, and urinalysis tests to be conducted by a central laboratory.
- Urine or serum pregnancy test (according to local requirements; female subjects of childbearing potential only).
- Standard 12-lead ECG.
- Review and recording of concomitant medications, procedures and/ or surgeries.
- Review and recording of AEs and concomitant diseases. Recording/reporting of SAEs.

Once all procedures have been performed and, if everything is correct and adequate, chemotherapy will be administered followed by MB02 or Avastin® (15 mg/kg IV infusion) according to the randomization schedule which will be recorded in the eCRF.

In addition to this, a Brain CT and/or CT Scan/MRI will be performed any time throughout the cycle if PD is suspected or if clinically indicated. Standard 12-lead ECG and left ventricular ejection fraction may also be measured by cardiac ultrasound or multigated acquisition scan, if clinically indicated.

If the subject has died, this will be recorded in the eCRF. If the death has occurred because of an SAE, this will be reported as per Section 9.1.3.2.

8.2.4 Cycle 4 (-1/+3 Days)

Cycle 4 visit will take place 21 days (-1/+3 days) after third administration of study drug.

The following procedures will be performed prior to dosing:

- Physical examination.
- Determination of ECOG performance status.

- Recording of supine vital signs (including blood pressure, pulse rate, respiratory rate and body temperature) and weight.
- Collection of samples for hematology, blood chemistry, coagulation, and urinalysis tests to be conducted by a central laboratory.
- Urine or serum pregnancy test (according to local requirements; female subjects of childbearing potential only).
- Collection of a sample for serum biomarkers (antidrug antibodies).
- Review and recording of concomitant medications, procedures and/ or surgeries.
- Review and recording of AEs and concomitant diseases. Recording/reporting of SAEs.

Once all procedures have been performed and, if everything is correct and adequate, chemotherapy will be administered followed by MB02 or Avastin® (15 mg/kg IV infusion) according to the randomization schedule which will be recorded in the eCRF.

At Week 12 (±3 days) from Cycle 1 Day 1 and/or any time throughout the cycle if clinically indicated, a CT Scan/ MRI of chest, upper abdomen and any other involved regions should be conducted. Disease status and tumor response will be assessed per RECIST version 1.1 criteria.

In addition to this, a Brain CT will be performed any time throughout the cycle if PD is suspected or if clinically indicated. Standard 12-lead ECG and left ventricular ejection fraction may also be measured by cardiac ultrasound or multigated acquisition scan, if clinically indicated.

If the subject has died, this will be recorded in the eCRF. If the death has occurred because of an SAE, this will be reported as per Section 9.1.3.2.

8.2.5 Cycle 5 (-1/+3 Days)

Cycle 5 visit will take place 21 days (-1/+3 days) after fourth administration of study drug.

The following procedures will be performed prior to dosing:

- Physical examination.
- Determination of ECOG performance status.
- Recording of supine vital signs (including blood pressure, pulse rate, respiratory rate and body temperature) and weight.
- Collection of samples for hematology, blood chemistry, coagulation, and urinalysis tests to be conducted by a central laboratory.
- Urine or serum pregnancy test (according to local requirements; female subjects of childbearing potential only).
- Standard 12-lead ECG.

- Review and recording of concomitant medications, procedures and/ or surgeries.
- Review and recording of AEs and concomitant diseases. Recording/reporting of SAEs.

Once all procedures have been performed and, if everything is correct and adequate, chemotherapy will be administered followed by MB02 or Avastin® (15 mg/kg IV infusion) according to the randomization schedule which will be recorded in the eCRF.

In addition to this, a Brain CT and/ or a CT Scan/ MRI will be performed any time throughout the cycle if PD is suspected or if clinically indicated. Standard 12-lead ECG and left ventricular ejection fraction may also be measured by cardiac ultrasound or multigated acquisition scan, if clinically indicated.

If the subject has died, this will be recorded in the eCRF. If the death has occurred because of an SAE, this will be reported as per Section 9.1.3.2.

8.2.6 Cycle 6 (-1/+3 Days)

Cycle 6 visit will take place 21 days (-1/+3 days) after fifth administration of study drug.

The following procedures will be performed prior to dosing:

- Physical examination.
- Determination of ECOG performance status.
- Recording of supine vital signs (including blood pressure, pulse rate, respiratory rate and body temperature) and weight.
- Collection of samples for hematology, blood chemistry, coagulation, and urinalysis tests to be conducted by a central laboratory.
- Urine or serum pregnancy test (according to local requirements; female subjects of childbearing potential only).
- Review and recording of concomitant medications, procedures and/ or surgeries.
- Review and recording of AEs and concomitant diseases. Recording/reporting of SAEs.

Once all procedures have been performed and, if everything is correct and adequate, chemotherapy will be administered followed by MB02 or Avastin® (15 mg/kg IV infusion) according to the randomization schedule which will be recorded in the eCRF.

At Week 18 (±1 week) from Cycle 1 Day 1 and/or any time throughout the cycle if clinically indicated, a CT Scan/ MRI of chest, upper abdomen and any other involved regions should be conducted. Disease status and tumor response will be assessed per RECIST version 1.1 criteria.

In addition to this, a Brain CT will be performed any time throughout the cycle if PD is suspected or if clinically indicated. Left ventricular ejection fraction may also be measured by cardiac ultrasound or multigated acquisition scan, if clinically indicated.

Also, a standard 12-lead ECG will be performed at Week 18 (±1 week), and it may be repeated at any time if clinically indicated.

If the subject has died, this will be recorded in the eCRF. If the death has occurred because of an SAE, this will be reported as per Section 9.1.3.2.

8.2.7 Additional Cycles Until Treatment Withdrawal (From Week 19 (Cycle 7) onwards, Then Every 3 Weeks; -1/+3 Days)

Subjects who complete 6 cycles can continue to receive MB02 or Avastin® monotherapy until disease progression, unacceptable toxicity, death or Week 52,whichever occurs first. The study ends at Week 52. After Week 52, all subjects (including those randomized to Avastin® during the study) will be offered the opportunity to continue receiving biosimilar MB02 monotherapy until disease progression, unacceptable toxicity, lost to follow-up, withdrawal of consent, initiation of any new treatment or death. For specific information about post Week 52 procedures refer to section 8.6

Additional Cycles will be scheduled at intervals of 3 weeks (-1/+3 days).

The following procedures will be performed prior to each monotherapy dosing:

- Physical examination.
- Determination of ECOG performance status.
- Recording of supine vital signs (including blood pressure, pulse rate, respiratory rate and body temperature) and weight.
- Collection of samples for hematology, blood chemistry, coagulation, and urinalysis tests to be conducted by a central laboratory.
- Urine or serum pregnancy test (according to local requirements, female subjects of childbearing potential only).
- Collection of a sample for serum biomarkers (antidrug antibodies). One sample needs to be collected before Cycle 7 dosing and another sample needs to be collected before Cycle 12 dosing, as applicable.
- Review and recording of concomitant medications, procedures and/ or surgeries.
- Review and recording of AEs and concomitant diseases. Recording/reporting of SAEs.

Once all procedures have been performed and, if everything is correct and adequate, MB02 or Avastin® monotherapy (15 mg/kg IV infusion) will be administered according to the randomization schedule which will be recorded in the eCRF.

Every 9 weeks (±5 days) from Week 18 and/or, any time throughout the cycles if clinically indicated, a CT Scan/ MRI of chest, upper abdomen and any other involved regions should be conducted including a brain CT (only in subjects with known or history of brain metastases). A brain CT may also be performed at any time throughout the cycle if PD is suspected or if it is clinically indicated. Disease status and tumor response will be assessed per RECIST version 1.1 criteria.

Standard 12-lead ECG and left ventricular ejection fraction may also be measured by cardiac ultrasound or multigated acquisition scan, if clinically indicated.

If the subject has died, this will be recorded in the eCRF. If the death has occurred because of an SAE, this will be reported as per Section 9.1.3.2.

8.3 End of Treatment Visit (Within 3 Weeks of Completion of Last Cycle; ±5 Days)

The End-of-Treatment Visit will take place within 3 weeks of completion of the last treatment cycle (±5 days), unless the subjects starts any subsequent antitumor therapy in which case the End-of-Treatment Visit should be performed immediately before the start of the new therapy (ideally the day before or the same day). The following procedures will be performed:

- Physical examination.
- Determination of ECOG performance status.
- Recording of supine vital signs (including blood pressure, pulse rate, respiratory rate, and body temperature) and weight.
- Collection of samples for hematology, blood chemistry, coagulation, and urinalysis tests to be conducted by a central laboratory.
- Urine or serum pregnancy test (according to local requirements; female subjects of childbearing potential only).
- Standard 12-lead ECG.
- Measurement of left ventricular ejection fraction by cardiac ultrasound or multigated acquisition scan, if not done in the previous 6 weeks.
- Brain CT scan (only in subjects with known or history of brain metastases, or if clinically indicated).
- A CT Scan/MRI of chest, upper abdomen and any other involved regions if not performed within the prior 4 weeks. Disease status and tumor response will be assessed per RECIST version 1.1 criteria.
- Collection of samples for serum biomarkers (antidrug antibodies), if not performed within the previous 3 weeks.
- Review and recording of concomitant medications, procedures and/ or surgeries.
- Review and recording of AEs and concomitant diseases. Recording/reporting of SAEs.

All these evaluations need only be repeated for parameters for which no measurement is available within 10 days before the End of Treatment Visit, or for those parameters for which values were out of range in the last assessment (grade ≥2) and were considered to be treatment related. These evaluations should be conducted when the medical condition of the subject allows.

If the subject has died, this will be recorded in the eCRF. If the death has occurred because of an SAE, this will be reported as per Section 9.1.3.2.

8.4 Additional Follow-up Visits

8.4.1 Subjects Who Discontinue Treatment Without Radiological Disease Progression Before Week 52 (9 Week Intervals; ±7 Days)

Subjects who discontinue treatment without radiological disease progression before Week 52 and do not withdraw consent will be followed up every 9 weeks (± 7 days) from End-of-Treatment Visit until disease progression, new antitumor therapy, subject decision, death, or until the Week 52 End-of-Study Visit, whichever occurs first. The following procedures will be performed at each Follow-up Visit:

- Physical examination.
- Determination of ECOG performance status.
- Recording of supine vital signs (including blood pressure, pulse rate, respiratory rate and body temperature) and weight.
- A CT Scan/ MRI of chest, upper abdomen and any other involved regions if not performed within the prior 4 weeks. Disease status and tumor response will be assessed per RECIST version 1.1 criteria.
- Collection of samples for serum biomarkers (antidrug antibodies). These samples will be collected at the beginning of Week 4, at the beginning of Week 10, at the beginning of Week 19, at the beginning of Week 34, as applicable depending on when the treatment is discontinued.
- Review and recording of concomitant medications, procedures and/ or surgeries considered related to any study drugs will be reviewed and collected.
- Review and recording of AEs and concomitant diseases. Recording/reporting of SAEs. Adverse events/SAEs ongoing at the End-of-Treatment Visit will be followed until resolution or stabilization. From 30 days after last dose onwards, AEs will be recorded and SAEs will be recorded and reported only if they are considered at least possibly related to treatment.
- Recording any other antitumor therapy treatments initiated will be recorded in the eCRF.

Those subjects who report disease progression during follow-up visits will be followed as per Section 8.4.2.

If the subject has died, this will be recorded in the eCRF. If the death has occurred because of an SAE, this will be reported as per Section 9.1.3.2.

When all of these procedures have been performed, the next visit will be scheduled, if applicable.

8.4.2 Subjects with Radiological Progression or New Antitumor Therapy Initiated (3 Months Intervals; ±14 Days)

After radiological progression is documented or a new antitumor therapy is started, subjects will be followed up at least every 12 weeks (±14 days) until death or Week 52 (End-of-Study Visit), whichever occurs first. Tumor assessment will not be conducted. Documented telephone calls are acceptable in this survival follow-up.

The following procedures will be performed at each Follow-up Visit:

- Review and recording of concomitant medications, procedures, and/ or surgeries considered related to any study drugs will be reviewed and collected.
- Review and recording of AEs and concomitant diseases. Recording/reporting of SAEs. Adverse events/SAEs ongoing at the End-of-Treatment Visit will be followed until resolution or stabilization. From 30 days after last dose onwards, AEs will be recorded and SAEs will be recorded and reported only if they are considered at least possibly related to treatment.
- Recording any other antitumor therapy initiated will be recorded in the eCRF.
- If the subject has died, this will be recorded in the eCRF. If the death has occurred because of an SAE, this will be reported as per Section 9.1.3.2.

8.5 Week 52 End-of-Study Visit (±7 Days)

The End-of-Study Visit will take place 52 weeks (±7 days) after first study drug administration. The following procedures will be performed at the Week 52 End-of-Study Visit:

- Physical examination.
- Determine of ECOG performance status.
- Recording of vital signs (including blood pressure, pulse rate, respiratory rate and body temperature) and weight.
- Standard 12-lead ECG.
- Brain CT scan (only in subjects with known or history of brain metastases, or if clinically indicated).
- In those subjects who have not shown disease progression (not started any new antitumor therapy) a CT Scan/MRI of chest, upper abdomen and any other involved regions must be done if it was not performed within the previous 4 weeks. Disease status and tumor response will be assessed per RECIST version 1.1 criteria.

- Collection of samples for serum biomarkers (antidrug antibodies). This sample needs to be collected at the end of Week 52.
- Review and recording of concomitant medications, procedures and/ or surgeries. If this visit is performed after 30 days from last dose, only those considered related to any study drugs will be reviewed and collected.
- Review and recording of AEs and concomitant diseases. If this visit is performed after 30 days from last dose, only those considered related to any study drugs will be reviewed and collected.
- Any other antitumor therapy treatments initiated will be recorded in the eCRF.

All these evaluations will be repeated for parameters for which no measurement within the previous 10 days is available.

If the subject has died, this will be recorded in the eCRF. If the death has occurred because of an SAE, this will be reported as per Section 9.1.3.2.

After Week 52, all subjects (including those randomized to Avastin® during the study) will be offered to continue receiving biosimilar MB02 monotherapy until disease progression, unacceptable toxicity or death.

8.6 Post Week 52 Period Procedures for Subjects That Are Responding to Treatment

After Week 52, all subjects (including those randomized to Avastin® during the study) will be offered the opportunity to continue receiving biosimilar MB02 monotherapy. The following will be required:

- Subjects and investigators will remain blinded up to week 52
- Subjects will be asked to re-consent to accept the potential risk of being switched to MB02 treatment, in case they were initially randomized to Avastin®
- Subjects will receive MB02 labelled as clinical trial
- Investigators will collect safety information during the time subjects are on MB02 treatment beyond Week 52 and will enter the information in the pertinent section of the eCRF and, in case of occurrence of any SAE; it will be processed and notified as per section 9.1.3.2. No other study assessments are required, it is lead to investigator's discretion the performance of any further assessment according to local practice, but these will not be captured in the eCRF
- Subjects will continue receiving biosimilar MB02 monotherapy until disease progression, unacceptable toxicity, lost to follow-up, withdrawal of consent, initiation of any new treatment or death.
- Investigators are required to notify in advance of any patient at his/her site willing to proceed with post week 52 treatment. Likewise, investigators are required to confirm the continuation or discontinuation of the treatment in advance, per drug supply and logistics purposes.

8.7 Duration of Treatment

Cycle 1 starts on Day 1 with the first treatment administration, which will consist of paclitaxel infusion followed by carboplatin and then infusion of MB02 or Avastin®; this regimen will be applied for the first 6 cycles.

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

Treatment discontinuation can occur because of PD, unacceptable toxicity, withdrawal of consent, subject decision, lost to follow-up, protocol violation, death, investigator's decision, or if subject becomes pregnant, whichever occurs first. The study will finish once the subject has reached 52 weeks after the first dose administration (when PFS and OS are assessed and the last ADA sample is taken) or, subject withdraws his/her consent, if subject is lost to follow-up, becomes pregnant or dies; once a protocol violation is reported. Sponsor may also terminate the study.

After Week 52, all subjects (including those randomized to Avastin® during the study) will be offered the opportunity to continue receiving biosimilar MB02 monotherapy until disease progression, unacceptable toxicity, lost to follow-up, withdrawal of consent, initiation of any new treatment or death. For specific information about post Week 52 procedures, refer to Section 8.6.

9 EFFICACY, IMMUNOGENICITY, AND SAFETY VARIABLES

Efficacy, immunogenicity, and safety variables will be assessed at the time points specified in the planned schedule of assessments, which is presented in Section 7.1.1.

9.1 Efficacy, Immunogenicity, and Safety Measurements Assessed

9.1.1 Efficacy Variables

9.1.1.1 Tumor Assessments

Tumor assessments will be performed using CT and/or MRI of the chest, upper abdomen, and any other involved regions; every effort will be made to ensure that the same method of assessment used at Screening is used at all subsequent time points. Tumor response will be assessed by the IRC using the RECIST v1.1 criteria to evaluate ORR. Disease status, PFS, and OS[16] will be evaluated by investigators. The RECIST v1.1 (January 2009) guidelines for measurable, nonmeasurable, target and nontarget lesions and the objective tumor response criteria (CR, PR, stable disease [SD] or PD) are detailed in Section 16.2.

Baseline assessment should be performed up to 28 days before the start of study treatment and ideally as closely as possible to the start of study treatment; it should include all areas known for possible metastases. Thereafter, disease assessment should be repeated according to the time points presented in Section 7.1.1. Additional tumor assessments can be made at any time should the investigator consider this to be clinically indicated. Tumor measurements will also be performed during the Week 52 End-of-Study Visit if not done within the previous 4 weeks. Operational details for the IRC are described in detail in the IRC charter

Details regarding timing of tumor assessments are presented in Section 7.1.1.

9.1.2 Immunogenicity Variables

Blood samples will be taken to determine serum biomarkers (antidrug antibodies) up to 52 weeks after first study drug administration in all randomized subjects. Further details are provided in the laboratory manual; details regarding timing of immunogenicity assessments are presented in Section 7.1.1.

9.1.3 Safety Assessments

Safety will be monitored by: incidence, nature, and severity of AEs, including adverse drug reactions graded according to NCI-CTCAE (version 4.03); incidence of clinical laboratory value abnormalities (hematology, clinical chemistry, and urinalysis); physical examination; ECOG/performance status, 12-lead ECG, vital sign assessment and brain CT (in subjects with history of brain metastases only). Details regarding timing of safety assessments are presented in Section 7.1.1.

9.1.3.1 Adverse Events

Adverse event definition

An AE is defined as any untoward medical occurrence in a clinical study subject administered a medicinal product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, including MB02, Avastin®, paclitaxel and carboplatin, whether or not it is related to the medicinal (investigational) product, including MB02, Avastin®, paclitaxel and carboplatin. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses or drug interaction that is not recorded elsewhere in the eCRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

It is the responsibility of the investigator to document all AEs that occur during the study. AEs will be elicited by asking the subject a nonleading question, for example,

"Have you experienced any new or changed symptoms since we last asked/since your last visit?" Adverse events should be reported on the appropriate page of the eCRF.

Assessment of severity

Adverse events will be collected and classified according to NCI-CTCAE version 4.03.[18]

Death itself is not an AE, but rather the outcome of an event, which should be described using medical terminology. Grade 5 (death) as an intensity criterion that should only be used in those cases where either no cause for death is known (e.g., sudden death, death NOS) or death occurs as an immediate outcome of a given event (e.g., allergic reaction, sepsis leading to immediate death).

If there is a change in the grade of an AE, it must be recorded as a separate event.

If changes to a subject's left ventricular ejection fraction are judged to be grade 3, subjects will be managed according to appropriate protocols and referred to a cardiologist

Assessment of causality

Every effort will be made by the investigator to assess the relationship of the AE, if any, to the study drugs. Causality should be assessed using the categories presented in the following table:

Unrelated:	Clinical event with an incompatible time relationship to study drug administration, and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the study drug.
Unlikely:	Clinical event whose time relationship to study drug administration makes a causal connection improbable but that could plausibly be explained by underlying disease or other drugs or chemicals.
Possible:	Clinical event with a reasonable time relationship to study drug administration, but that could also be explained by concurrent disease or other drugs or chemicals.
Probable:	Clinical event with a reasonable time relationship to study drug administration and is unlikely to be attributed to concurrent disease or other drugs or chemicals.
Very Likely/Certain:	Clinical event with plausible time relationship to study drug administration and that cannot be explained by concurrent disease or other drugs or chemicals.
Unknown:	The event cannot be judged because information is insufficient or contradictory or data cannot be supplemented or verified.

Action taken

The investigator will describe the action taken in the appropriate section of the eCRF. All medication given as treatment will be reported in the appropriate page of the eCRF.

Follow-up of adverse events

All investigators should follow-up subjects with AEs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Details of AE follow-up or resolution must be documented in the eCRF.

Subjects should be followed up until 30 days after last cycle, and any AEs that occur during this time should be reported according to the procedures outlined below. Additionally, for those subjects who proceed with post Week 52 treatment, any AE occurring during this time should, also, be reported according to the procedures outlined below.

All subjects with unresolved AEs at the end of the study, except those who dropped out before randomization or starting active treatment, must be included in a safety follow-up visit to check response of AEs.

Follow-up can be waived in specific cases after consultation with the Sponsor. This permission must be documented per case and retained in the Sponsor File.

Documentation and reporting of adverse events

Adverse events should be reported and documented in accordance with the procedures outlined below; AEs will be recorded in the eCRF from the signing of the informed consent form (ICF) until 30 days after last cycle, for those subjects that do not proceed with post Week 52 treatment. For those subjects that continue to post Week 52 treatment, any AE occurring during this time will also be recorded in the eCRF. Any AEs occurring more than 30 days after last cycle of drug administration should also be recorded in the eCRF if they are considered at least possibly related to the study drugs by the investigator. The following data should be documented for each AE:

- Description of the symptom event.
- Classification as 'serious' or 'not serious'.
- Severity.
- Date of first occurrence and date of resolution (if applicable).
- Action taken.
- Causal relationship.
- Outcome of event (unknown, recovered, not yet recovered, recovered with sequelae, death [with date and cause reported]).

9.1.3.2 Serious Adverse Events

Serious adverse event definition

An SAE is any untoward medical occurrence or effect that, at any dose,

- Results in death.
- Is life threatening (an AE is life threatening if the subject was at immediate risk of death from the event as it occurred, i.e., it does not include a reaction that might have caused death if it had occurred in a more serious form).
- Requires or prolongs inpatient hospitalization. (Complications occurring during hospitalization are AEs and are SAEs if they cause prolongation of the current hospitalization. Hospitalization for elective treatment of a pre-existing non-worsening condition is not, however, considered an AE. The details of such hospitalizations must be recorded on the medical history or physical examination page of the eCRF).
- Results in persistent or significant disability/incapacity. (An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions).
- Results in a congenital anomaly/birth defect.

In addition, medical and scientific judgement is required to decide if prompt notification is required in situations other than those defined for SAEs above. This may include any event that the investigator regards as serious that did not strictly meet the criteria above

but may have jeopardized the subject or required intervention to prevent 1 of the outcomes listed above, or that would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the investigational product. These events should be collected in the eCRF under the seriousness criteria "Important Medical Event".

Disease progression is a worsening of a subject's condition attributable to the disease for which the study medication is being given. This may be an increase in severity of the disease or increase in the symptoms of the disease. The development of new, or progression of existing metastases of the primary cancer under study should be considered as disease progression and not an AE. Events that are unequivocally due to disease progression should not be reported as AEs during the study. The development of a new cancer should be regarded as an AE and reported accordingly. Generally, it will also meet at least 1 of the serious criteria. New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the subject's inclusion in the study. They do not include metastases of the original cancer.

Reporting of serious adverse events

All SAEs will be recorded in the eCRF and reported from signing of the ICF until 30 days after last cycle of any drug from the protocol treatment schedule, for those subjects that do not proceed with post Week 52 treatment. For those subjects that continue to post Week 52 treatment, any SAE occurring during this time, will also be recorded in the eCRF and reported. Any SAEs occurring or more than 30 days after last cycle of drug administration should also be recorded in the eCRF and reported if they are considered at least possibly related to the protocol treatment by the investigator. An SAE form must be sent to INC Research by email (PDF) or faxed within 24 hours for the attention of the Safety Department.

Full details for SAE reporting and contact information can be found in the Investigator Manual.

The investigator should not wait to receive additional information to fully document the event before notification of an SAE, even though additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained and transmitted to the Sponsor's Safety Department within 24 hours.

Instances of death, congenital abnormality, or event that are of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the investigator at any time after cessation of study drug administration and linked by the investigator to this study, should be reported to the Sponsor's Safety Department within 24 hours.

All SAEs must be reported, with the exception of:

- Hospitalization for administration of study treatments. Hospitalization or prolonged hospitalization for a complication of study treatment administration will be reported as an SAE.
- Hospitalization for diagnostic investigations (e.g., scans, endoscopy, sampling for laboratory tests, bone marrow sampling) that are not related to an AE.
- Prolonged hospitalization for technical, practical, or social reasons, in absence of an AE.
- Hospitalization for a procedure that was planned before study participation (i.e., before registration or randomization). This should be recorded in the source documents. Prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization for ≤24 hour (attendance at Emergency Room).
- Death due to PD, either while on treatment or during the follow-up period; this information will be included in the "Death" module of the eCRF.

Hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.

The Sponsor or Sponsor designee will promptly notify all relevant investigators and the regulatory authorities of findings that could adversely affect the safety of subjects, impact on the conduct of the study or alter the independent ethics committee (IEC)/institutional review board (IRB) approval/favorable opinion of the study. In addition, The Sponsor or Sponsor designee, will expedite the reporting to all concerned investigators, to the IECs/IRBs, where required, and to the regulatory authorities of all adverse reactions that are both serious and unexpected.

Follow-up of serious adverse events

All SAEs will be followed clinically until they are resolved or until a stable situation has been reached. Depending on the event, follow-up may require additional tests or medical procedures as indicated, and/or referral to a medical specialist. Follow-up information on SAEs should be reported until recovery or until a stable situation has been reached.

The final outcome of the SAE should be reported in a final SAE report.

Reporting of pregnancy

Details of the procedures to be followed if a pregnancy occurs are provided in Section 7.3.4.2.

Pregnancies of a female subject or the female partner of a male subject, occurring at least, while the subject is on protocol treatment or during the Follow-up period, should be reported to the Sponsor's Safety Department. Pregnancies must be reported to

Pharmacovigilance by email/fax within 24 hours after the event was known to the investigator, using the pregnancy report form.

The investigator will follow the female subject until completion of the pregnancy, and must notify the Sponsor of the outcome of the pregnancy within 5 days or as specified below. The investigator will provide Follow-up information as agreed with scheduled revisions calendar.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous or therapeutic abortion, stillbirth, neonatal death, or congenital anomaly - including that in an aborted fetus), the investigator should follow the procedures for reporting SAEs. In the case of a live "normal" birth, the Sponsor should be informed as soon as the information is available. All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs.

In addition, any infant death after 30 days from birth that the investigator suspects to be related to in utero exposure to the investigational medicinal product(s) should also be reported.

The investigator is encouraged to provide outcome information of the pregnancy of the female partner of a male subject, if this information is available to the investigator and the female partner gives her permission.

9.1.3.3 Unexpected Adverse Reactions

Unexpected Adverse Reaction Definition

An unexpected adverse reaction is any untoward and unintended response that is related to the administration of the study drug at any dose that is not consistent with the applicable product information (e.g., investigators brochure for an unauthorized investigational medicinal product or SmPC for an authorized product).

All suspected unexpected serious adverse reactions (SUSARs) will be the subject of expedited reporting. The Sponsor and/or INC Research shall ensure that all relevant information about a SUSAR that is fatal or life-threatening is reported to the relevant competent authorities and IEC/IRB within 7 days after knowledge by the Sponsor of such a case and that relevant follow up information is communicated within an additional 8 days. All other SUSARs will be reported to the relevant competent authorities and IEC/IRB within 15 days after knowledge by the Sponsor of such a case. All investigators should follow up SUSARs until the events are resolved or until, in the opinion of the investigator, the events are stabilized or determined to be chronic.

Warnings and Precautions

Warnings and precautions are presented in the MB02 investigator's brochure (version 5.0; dated 31 MAY 2017).

9.1.3.4 Clinical Laboratory Evaluation

Hematology, clinical chemistry, coagulation, and urine laboratory analyses will be performed at a central laboratory, as described in the laboratory manual. Details of sample collection methodology, sample processing, and shipping are also presented in the laboratory manual. Local site laboratories may be utilized, in addition to the central laboratory, if more rapid results are required for retreatment decisions or subject safety. If a local site laboratory sample is taken, then part of the blood sample obtained for local site laboratory assessment should also be sent to the central laboratory for analysis. Local site laboratory results obtained during the study will not be captured in the eCRF unless the investigator determines they are needed to clarify why a treatment decision was made or an AE was recorded. Laboratory parameters of interest will be graded according to NCI-CTCAE version 4.03[18] to allow for comparison of AEs and laboratory parameters.

The following laboratory safety tests will be performed:

Hematology

Complete blood count, including hemoglobin, hematocrit, white blood cell (WBC) count (with 5-part differential), red blood cell count (RBC) and platelet count.

Clinical Chemistry

Bicarbonate (HCO_3), calcium, phosphorus, magnesium, albumin, glucose, serum creatinine, total protein, and blood urea nitrogen. Liver function tests: AST, ALT, lactate dehydrogenase, alkaline phosphatase, and total and direct bilirubin.

Coagulation

International normalized ratio, prothrombin time, partial thromboplastin time and fibrinogen.

Urinalysis

At screening, a single urine sample will be sent to central laboratory for microscopy including protein, protein-to-creatinine ratio, specific gravity, glucose, and blood. If protein-to-creatinine ratio is ≥ 1, then a 24-hour urine sample will be shipped to central laboratory and must demonstrate < 1 g of protein in 24 hours.

For routine on-study assessments, dipstick is sufficient as long as the urine protein result is less than 2+ (urinalysis is also acceptable). If dipstick urine protein is ≥ 2+, 24-hour urine must demonstrate < 1 g of protein in 24 hours as assessed by a central laboratory.

9.1.3.5 Other Laboratory Variables

Screening for pregnancy (female subjects of childbearing potential only) will be performed (serum or urine β human chorionic gonadotrophin [β-HCG]) at Screening and before each cycle of treatment.

9.1.3.6 Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate and body temperature) will be recorded in a standardized manner using manual methods of measurement after the subject has rested in a supine position for 5 minutes. Weight and height will be recorded in metric units (height at Screening only).

Inadequately controlled hypertension is defined as systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg on antihypertensive medications. If medically significant hypertension cannot be controlled with antihypertensive therapy, or if the subject develops hypertensive crisis or hypertensive encephalopathy, MB02/Avastin® should be permanently discontinued.

9.1.3.7 Physical Examination

A complete physical examination will be performed. The following items and body systems will be assessed: general appearance; eyes, ears, nose and throat, head and neck; chest and lungs; cardiovascular; abdomen; musculoskeletal; lymphatic; dermatologic; neurologic; and extremities. A complete dental examination will also be performed at screening in order to identify any invasive dental procedure. It is considered a risk factor for osteonecrosis of the jaw, reported for subjects on bevacizumab.

Appropriate preventive dentistry should be considered before the start of treatment, if clinically indicated. Procedures that involve direct osseous injury and placement of dental implants should be avoided if not strictly necessary. Caution should be exercised for subjects receiving intravenous bisphosphonates.

9.1.3.8 Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group performance status will be recorded according to the grades presented in Table 1.

Table 1 Summary of Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	ECOG/performance status
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Source: http://ecog-acrin.org/resources/ecog-performance-status. Accessed: 07 April 2017

9.1.3.9 12-Lead Electrocardiogram

A standard 12-lead ECG will be performed at Screening, at Cycle 3 (before dosing), Cycle 5 (before dosing), Cycle 6 (Week 18), End-of-Treatment Visit, at Week 52 (Cycle 18 predose) and any time if clinically indicated at the investigator's discretion.

PR interval, QRS complex duration, QT interval, and QT interval corrected according to Fridericia's formula will be calculated. The ECG measurements will be made with the subject in a supine position and having rested in this position for at least 10 minutes before each time point.

Paper ECG traces will be recorded on a single A4 page at a standard paper speed of 25 mm/sec, calibrated to 1 cm/mV or to 0.5 cm/mV if the amplitude of the QRS complex requires, with a lead II rhythm strip.

Any ECG with results falling outside the normal ranges may be repeated at the discretion of the investigator. If any results falling outside the normal ranges are deemed not clinically significant by the investigator, or appropriately qualified designee, this should be clearly stated on the hard copies of the ECG and signed and dated by the investigator. If an ECG trace indicates an abnormality that is measured by the equipment but is deemed normal by the investigator, this should be clearly stated on the ECG trace as normal and signed and dated by the investigator or appropriately qualified designee. If the ECG trace indicates an abnormality that is present but deemed as not clinically significant by the investigator or appropriately qualified designee, then this should be clearly stated on the ECG trace as "NCS" and signed and dated by the investigator or appropriately qualified designee. If any results falling outside the normal

ranges are deemed clinically significant by the investigator or appropriately qualified designee these should be recorded in the eCRF as an AE/SAE.

9.1.3.10 Cardiac Ultrasound or Multigated Acquisition Scan

Left ventricular ejection fraction will be measured by cardiac ultrasound or multigated acquisition scan at Screening and End-of-Treatment Visits (if not done in previous 6 weeks). It can also be measured during any treatment cycle if clinically indicated.

9.1.3.11 Brain CT Scan

A brain CT scan will be performed only in subjects with known or history of brain metastases, and whenever is clinically indicated. Brain CT scan procedures are presented in the laboratory manual.

9.1.3.12 Survival Status

Any deaths will be recorded on the appropriate pages of the eCRF.

9.2 Data Safety Monitoring Board

To enhance the safety and integrity of the study data, a DSMB consisting of independent experts will be convened to review periodically the accumulating safety data for the study. The initial safety review by the DSMB will occur after the first 25% of subjects have been randomized and received study drug. The DSMB will provide a recommendation on study continuation, modification or termination, should a concern regarding safety arise. The specific responsibilities and composition of the DSMB are outlined in a separate document, the DSMB charter, which also includes details of outputs provided for the meetings. The DSMB will meet at the times described in the DSMB charter for periodic safety reviews; the DSMB can also request ad hoc meetings with the Sponsor should any safety concerns arise.

9.2.1 Appropriateness of Measurements

The efficacy and safety assessments planned for this study are widely used and generally recognized as reliable, accurate, and relevant to the disease condition.

10 STATISTICAL METHODS

10.1 Statistical and Analytical Plans

A detailed SAP will be created and finalized before database lock.

A blinded data review meeting will be convened to finalize assignments to the analysis sets, including the per-protocol set (PPS) shortly after all subjects have completed the scheduled procedures at Week 18 and data cleaning up to the Week 18 visit has been

completed. An additional blinded data review meeting will be held on clean data shortly before the database lock (once all subjects have completed the study).

10.1.1 Datasets or Populations Analyzed

Intention-to-treat analysis Set

The ITT analysis set will consist of all randomized subjects. Subjects from the ITT population will be analyzed under the randomized treatment group.

Per-Protocol Set

The PPS with regards to the primary endpoint will consist of all subjects in the ITT population who complete at least the first 6 cycles of treatment and for whom no major protocol deviations affecting efficacy occur until Week 18. For protocol deviations refer to Section 10.3.

Subjects from the PPS will be analyzed under the randomized treatment group.

Safety Analysis Set

The SAF will consist of all randomized subjects who received at least 1 administration of study drug. Subjects will be analyzed under the actual treatment received.

10.1.2 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics (e.g., age, sex, race, height, body weight, body mass index) will be summarized for the ITT population, PPS, and SAF.

10.1.3 Efficacy Variables

Unless otherwise stated, efficacy analyses will be performed on the ITT population.

10.1.3.1 Definition of Primary Efficacy Endpoint

Objective response rate: OR will be assigned for subjects if they experience either CR or PR per RECIST v1.1 at Week 18, as assessed by independent review. The ORR at Week 18 will be calculated as the proportion of subjects with OR, and the RR of the ORRs (MB02/Avastin®), and risk difference (RD) of the ORRs (MB02 minus Avastin®) will be used to determine if MB02 is equivalent to Avastin®. Any subjects who discontinue study treatment before Week 18 will be classed as non-responders in the final analysis of the primary efficacy endpoint (both for RR and RD analysis). Based on the recommendations of 2 different agencies, both Risk Ratio (FDA) and Risk Difference (EMA) will be analyzed. [19,20]

10.1.3.1.1 Analysis on primary endpoint using risk ratio

Per the US FDA recommendation the equivalence analysis will be based on the risk ratio (Type II meeting of 30th June 2017 and 31st July 2017 follow-up letter). Further to this, based on FDA recommendation (Type II meeting of 4th October 2018), the equivalence margin [0.73, 1.36] will be used to ascertain clinical equivalence of the primary efficacy endpoint.

The statistical hypotheses associated with the primary analysis of ORR at Week 18 using risk ratio is:

- H0: (ORR_{MB02} / $ORR_{Avastin} \leq 0.73$) or (ORR_{MB02} / $ORR_{Avastin} \geq 1.36$)
- H1: $0.73 < (ORR_{MB02} / ORR_{Avastin}) < 1.36$,

where ORR_{MB02} and $ORR_{Avastin}$ are the ORRs for MB02 and Avastin®, respectively.

The ORR estimate will be adjusted for the randomization strata sex (male/female), smoking status (smoker/nonsmoker), disease diagnosis (newly diagnosed/recurrent disease) and disease stage (Stage IIIB/Stage IV) using the Cochran- Mantel-Haenszel estimate of the RR and corresponding 2-sided 90% CI. The primary analysis will be conducted in the ITT population. For additional equivalence criteria on the primary endpoint required by regulatory bodies (i.e., PMDA), a 2-sided 95% CI for RR will also be provided in the ITT population.

10.1.3.1.2 Analysis on primary endpoint using risk difference

The EMA requested that the difference in ORRs should be used as the primary efficacy analysis (Follow-up Scientific Advice – 22nd June 2017). Hence, this additional analysis will be performed and included as part of the primary efficacy analysis.

The statistical hypotheses associated with the primary analysis of ORR at Week 18 using risk difference is:

- H0: (ORR_{MB02} - $ORR_{Avastin} \leq -12\%$) or (ORR_{MB02} - $ORR_{Avastin} \geq +12\%$)
- H1: $-12\% < (ORR_{MB02} - ORR_{Avastin}) < +12\%$,

where ORR_{MB02} and $ORR_{Avastin}$ are the ORRs for MB02 and Avastin®, respectively.

The ORR estimate will be adjusted for the randomization strata sex (male/female), smoking status (smoker/nonsmoker), disease diagnosis (newly diagnosed/recurrent disease) and stage (Stage IIIB/Stage IV) using the Cochran- Mantel-Haenszel estimate of the RD and corresponding 2-sided 90% CI. This primary analysis will be conducted in the ITT population. For additional equivalence criteria on the primary endpoint required by regulatory bodies (i.e., PMDA), a 2-sided 95% CI for RD will also be provided in the ITT population.

10.1.3.1.3 Sensitivity and supportive analyses for Primary Efficacy Endpoint

In order to evaluate the robustness of the primary analysis, additional evaluations will be performed as follows:

i) PPS analysis: The analysis of the primary endpoint (both RD and RR) will be repeated using the PPS as sensitivity analysis.

Other sensitivity analyses will be discussed in the SAP. For each sensitivity analysis the estimate and 90% CI will be reported for treatment effect and interaction term (if applicable).

For sensitivity analyses not involving interactions, a forest plot including the treatment effect derived from each analysis and the 90% CI will be plotted using as reference the treatment effect from the main primary analysis.

10.1.3.2 Definition and Analysis of Secondary Efficacy Endpoints

1. Progression Free Survival: PFS will be defined as the time from randomization to subsequent confirmed progression per RECIST version 1.1, or death, measured in weeks. Further details on how to build this endpoint will be provided in the SAP. Analyses will occur at Week 18 and Week 52; at each analysis, all subject data accrued during the study up to this point will be included to inform survival. Thus, at Week 18, any subjects with data occurring after Week 18 will be incorporated into the analyses of survival time.

   1.1) Kaplan-Meier figures and estimates will be presented stratified by treatment group. The log-rank test will be used to compare the survival distributions of MB02 vs Avastin®.

   1.2) If available, for descriptive purposes, the estimate of the median PFS (in weeks) as well the 90% CIs will be presented, comparing the PFS distributions of the 2 treatments. This analysis will be performed at cutoff points at Week 18 and Week 52 (12 months).

   1.3) The Cox proportional hazards model will be used to estimate the hazard ratio and its 90% CI of MB02 compared with Avastin® at Week 18 and at Week 52 (12 months). The main Cox proportional hazards model will include treatment group, with sex, smoking status, disease diagnosis, and disease stage as covariates. The proportional hazard assumption will be evaluated on all covariates (i.e., treatment and stratification factors) by graphical inspection of the Schoenfeld residuals and by Grambsch and Therneau test as well.[21] In the case of nonproportional hazards, other analyses will be implemented (e.g., stratified Cox regression).

2. Overall Survival: OS will be defined as the time from randomization to subsequent death, measured in weeks. Subjects that do not die during the study will be censored at the date of last contact (further details will be provided in the SAP). Similar to PFS, OS analyses will occur at Week 18 and Week 52; at each analysis, all subject data accrued during the study up to this point will be included to inform survival. Thus, at Week 18, any subjects with data occurring after Week 18 will be incorporated into the analyses of survival time.

   2.1) Kaplan-Meier figures and estimates will be presented stratified by treatment group. The log-rank test will be used to compare the survival distributions of MB02 vs Avastin®.

   2.2) If available, for descriptive purposes, the estimate of the median OS time (in weeks) as well the 90% CIs will be presented for the 2 treatment groups. This analysis will be performed at cutoff points at Week 18 and Week 52 (12 months).

   2.3) The Cox proportional hazards model will be used to estimate the hazard ratio and its 90% CI between Avastin® and MB02 at Week 18 and Week 52 (12 months). The main Cox proportional hazards model will include treatment, with sex, smoking status, disease diagnosis, and disease stage as covariates. Model diagnostic will follow the same procedure implemented on Cox regression for PFS outcome.

The effects of other baseline variables on the efficacy endpoints may be investigated in subgroup analyses.

10.1.4 Immunogenicity Variables

For immunogenicity, incidence of ADAs to bevacizumab, their neutralizing potential, and titer of positive will be summarized in the SAF using by frequency of ADA-positive samples for each time point and overall for each treatment separately and may be compared between treatments. Analysis of immunogenicity endpoints will be conducted by an external provider.

10.1.5 Safety Variables

Descriptive analysis of safety variables will be performed on the SAF. Further information will be provided in the SAP.

Incidence of AEs and their characteristics (frequency, severity, causality, seriousness, and action taken) in the treatment groups will be compared. Adverse events will be classified according to NCI-CTCAE version 4.03.

Physical examination, ECOG/performance status, vital signs, body weight, laboratory test results (including immunogenicity and pregnancy test), 12-lead ECG, brain CT, tumor assessment, concomitant medications, and actual values and their changes from Baseline (as appropriate) will be displayed using summary statistics by treatment at each measurement time point.

Laboratory parameters of interest will also be graded according to NCI-CTCAE version 4.03 to allow for comparison of AEs and laboratory parameters.

10.1.6 Schedule of Analyses

No interim analyses are planned; however, there will be data reviews during the study. Safety and tolerability interim data recorded during the study period will be reviewed by an independent DSMB for preliminary safety and tolerability assessments at specific intervals. The timing of the DSMB reviews will be described in the DSMB charter.

The main analysis will be performed once the primary endpoint has been achieved, i.e., once the last randomized subject has completed the study up to Week 18, and any tumor review has occurred. A further analysis will be conducted once all subjects have completed/terminated the study (maximum 52 weeks). Further details of these analyses will be included in the SAP, including procedures incorporated in order to maintain blinding for the Week 18 analysis.

10.1.7 Handling of Missing Data

Further details will be provided in the SAP.

10.2 Determination of Sample Size

Based on the recommendations of 2 different agencies, 2 different analyses will be performed: 1 based on Risk Ratio (FDA) and 1 based on Risk Difference (EMA). Hence, the sample size calculation should ensure that sufficient power is retained on both analyses. No multiplicity correction will be applied.

The determination of equivalence will be based on the ITT population. Per protocol population will be used as a supportive population for evaluating sensitivity of main analysis.

Risk Ratio

The US Food and Drug Administration (FDA) requires a primary endpoint of risk ratio based on ORR, with an equivalence margin of [0.73, 1.36]. In order to gain an understanding of the clinical effect of the reference treatment, Avastin®, a meta-analysis has been conducted to ascertain the expected ORR for the reference arm, including the following references: Sandler et al. (N Engl J Med 2006;533:2542-50), Johnson et al. (J Clin Oncol 2004;22:2184-91), Niho et al. (Lung Cancer 2012;76:362-7), Reck et al.

(Ann Oncol 2010;21:1804-9), and Zhou et al. (J Clin Oncol 2015;33:2197-204).[22,23,24,25,26] The results of this meta-analysis, conducted using StatsDirect 3 software, are as follows:

Study	Responders	N	ORR	95% CI	Weight (%)
Sandler et al.	133	381	0.349	(0.301, 0.399)	22.2%
Johnson et al.	11	34	0.324	(0.174, 0.505)	15.2%
Niho et al.	71	117	0.607	(0.512, 0.696)	20.1%
Reck et al.	114	351	0.325	(0.276, 0.377)	22.0%
Zhou et al.	74	138	0.536	(0.449, 0.621)	20.5%
Total*	403	1021	0.429	(0.322, 0.539)	100%

Abbreviations: CI = confidence interval; ORR = objective response rate.
*The random effects meta-analysis uses response rates for the reference product, Avastin® based on intent-to-treat population for all 5 studies. Weights are provided based on the random effects analysis. The corresponding fixed effects analysis provides a pooled proportion = 0.394.

The pooled ORR for the reference product was estimated to be 0.429 (42.9%), using a random effects model for the meta-analysis (i.e., individual proportion was weighted by the corresponding study size, accounting for random effects); a random effects meta-analysis is chosen in this case due to a high chance of heterogeneity (Cochran $Q = 43.8$, $P < 0.0001$, $I^2 = 90.9\%$).

Utilizing a 2-sided 90% CI for the Risk Ratio, a reference proportion of 42.9% for Avastin® and an equivalence margin of (0.73, 1.36), a sample size of 300 subjects per arm (600 total) provides approximately 89% power to show equivalence of MB02 plus chemotherapy with Avastin® plus chemotherapy on a primary endpoint of RR. In addition, approximately 81% power is achieved under the same conditions when a 95% CI is used.

Any subjects who discontinue study treatment prior to the 18-week time point, with no Week 18 tumor response assessment will be classed as non-responders in the final analysis of the primary efficacy endpoint.

Risk difference

The EMA requested that the risk difference (RD) in ORRs is used as the primary efficacy analysis, using an equivalence margin of (-12%, +12%). Utilizing a 2-sided 90% CI for the RD, 300 subjects per arm are sufficient to show equivalence of MB02 plus chemotherapy with Avastin® plus chemotherapy on RD with approximately 82% power.

All sample size calculations are conducted using PASS13 software.

10.3 Protocol Deviations

Major protocol deviations may include, but are not limited to:

- Randomization criteria violations.
- Inclusion/Exclusion criteria violations.
- Inadequate compliance with study drug.
- Prohibited medications taken.
- Significant deviations from the study drug administration schedule.
- No valid evaluation of the primary efficacy endpoint.
- Other protocol deviations that could affect subjects' efficacy outcomes.

The final list of major protocol deviations will be defined during the blinded data review meeting.

11 QUALITY ASSURANCE AND QUALITY CONTROL

11.1 Audit and Inspection

Study centers and study documentation may be subject to Quality Assurance audit during the course of the study by the Sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

11.2 Monitoring

Data for each subject will be recorded on an eCRF. Data collection must be completed for each subject who signs an ICF and is administered study drug; the minimum information collected (i.e., for Screen Failure subjects) will be ICF, inclusion/exclusion criteria, disease medical history, vital signs, demographics, and AEs. Any reason for screening failure should be recorded.

In accordance with GCP and ICH guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable.

The investigator must permit the monitor, the IEC/IRB, the Sponsor’s internal auditors, and representatives from regulatory authorities direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the eCRFs.

11.3 Data Management and Coding

INC Research will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data

generated within this clinical study will be handled according to the relevant standard operating procedures of the data management and biostatistics departments of INC Research.

Study centers will enter data directly into an electronic data capture (EDC) system by completing the eCRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study center. Data to be recorded directly on the eCRF will be identified and the eCRF will be considered the source document for these data. Any changes to the data entered into the EDC system will be recorded in the audit trail and will be FDA CFR 21 Part 11 compliant. Subject identifiers will be used to prevent identification of individual subjects.

Medical coding will use Medical Dictionary for Regulatory Activities (MedDRA) for concomitant diseases and AEs and WHO Drug for medications.

Missing or inconsistent data will be queried in writing to the investigator through the EDC for clarification and until resolution. Subsequent modifications to the database will be documented.

12 RECORDS AND SUPPLIES

12.1 Drug Accountability

On receipt of the study drug (including rescue medication, if relevant), the investigator (or deputy) will conduct an inventory of the supplies and verify that study drug supplies are received intact and in the correct amounts before completing a supplies receipt. The investigator will retain a copy of this receipt at the study center and return the original receipt to the study monitor. The monitor may check the study supplies at each study center at any time during the study.

It is the responsibility of the study monitor to verify that the investigator (or deputy investigator) has correctly documented the amount of the study drug received, dispensed, and returned on the dispensing log that will be provided. A full drug accountability log will be maintained at the study center at all times. If study centers have appropriate facilities, they should destroy unused expired medication according to local regulations. If they do not have appropriate facilities, the study monitor will arrange collection of unused study drug for destruction. The study monitor will also perform an inventory of study drug at the close-out visit to the study center. All discrepancies must be accounted for and documented.

12.2 Financing and Insurance

Financing and insurance of this study will be outlined in a separate agreement between INC Research and the Sponsor.

13 ETHICS

13.1 Independent Ethics Committee or Institutional Review Board

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the subjects, and any other relevant study documentation will be submitted to the appropriate IEC/IRB. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the study drug is released to the investigator. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IEC/IRB with the approved ICF must be filed in the study files.

The investigator will report promptly to the IEC/IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The investigator will submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

13.2 Regulatory Authorities

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

13.3 Ethical Conduct of the Study

The investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines, and the applicable national and local laws and regulatory requirements.

13.4 Informed Consent

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to GCP.

The investigator is responsible for ensuring that no subject undergoes any study related examination or activity before that subject has given written informed consent to participate in the study.

The investigator or designated personnel will inform the subject of the objectives, methods, anticipated benefits, and potential risks and inconveniences of the study. The subject should be given every opportunity to ask for clarification of any points s/he does not understand and, if necessary, ask for more information. At the end of the interview, the subject will be given ample time to consider the study. Subjects will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived

by the investigator in the investigators study file. A signed and dated copy of the subject ICF will be provided to the subject or their authorized representative.

It should be emphasized that the subject may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the study, a new ICF will be approved by the IEC(s)/IRB(s) (and regulatory authorities, if required). The study subjects will be informed about this new information and reconsent will be obtained.

13.5 Subject Confidentiality

Monitors, auditors, and other authorized agents of the Sponsor and/or its designee, the IEC(s)/IRB(s) approving this research, and the US FDA, as well as that of any other applicable agency(ies), will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identities will remain confidential.

14 REPORTING AND PUBLICATION, INCLUDING ARCHIVING

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study (end of study defined is the date of the last visit of the last subject), all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file. This file will be available for inspection by the Sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years after the discontinuation of clinical development of the investigational product or longer if required by local regulations. It is the responsibility of the Sponsor to inform the study center when these documents no longer need to be retained. The investigator must contact the Sponsor before destroying any study related documentation. In addition, all subject medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

The Sponsor must review and approve any results of the study or abstracts for professional meetings prepared by the investigator(s). Published data must not compromise the objectives of the study. Data from individual study centers in multicenter studies must not be published separately.

15 REFERENCES

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin. 2011;61:69–90.

2. Forman D, Bray F, Brewster DH, et al. Cancer Incidence in Five Continents. Lyon, France: IARC Press, 2013.

3. Willett CG, Boucher Y, Di Tomaso E, et al. Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. Nat Med. 2004;10:145–7.

4. Ferrara N. Role of vascular endothelial growth factor in physiologic and pathologic angiogenesis: therapeutic implications. Semin Oncol. 2002;29(6 Suppl 16):10–4.

5. Avastin® Summary of Product Characteristics. Available at: http://www medicines.org.uk/emc/medicine/15748/SPC/. Accessed 07 April 2017.

6. MB02 Investigator's Brochure. Version 7.0; 16 July 2018.

7. CDER/CBER, FDA. Guidance for Industry - Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Draft Guidance. 2012.

8. CHMP, EMA. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005). 2006.

9. CHMP, EMA. Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues: EMA/CHMP/BMWP/403543/2010. 2012.

10. Carboplatin Summary of Product Characteristics. Available at: https://www.gelbe-liste.de/produkte/Carboplatin-Bendalis-10-mg-ml-Konzentrat-zur-Herstellung-einer-Infusionsloesung_546307/fachinformation. Gelbe-Liste Pharmindex. Accessed 23 Nov 2018.

11. Carboplatin Summary of Product Characteristics. Available at: http://www.tevauk.com/mediafile/id/40602.pdf. Teva Pharmaceuticals Europe B.V. Version 3.0, 26 April 2016.

12. Carboplatin Summary of Product Characteristics. http://www medicines.org.uk/emc/product/3787/smpc. Accessed 23 Nov 2018.

13. Paclitaxel Summary of Product Characteristics. Available at: https://www.teva.de/assets/products/de/label/Paclitaxel-GRY%206%20mg%20ml%20Konzentrat%20zur%20Herstellung%20einer%20Infusionslosung%20-%202.pdf?pzn=399054. Teva GmbH Version 2, Sep 2017.

14. Paclitaxel Summary of Product Characteristics. Available at: http://www.tevauk.com/mediafile/id/40077.pdf. Teva UK Ltd. Accessed 23 Nov 2018.

15. Paclitaxel Summary of Product Characteristics. Available at: http://www medicines.org.uk/emc/product/6362/smpc. Actavis UK Ltd. Accessed 16 June 2017.

16. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.

17. The Criteria Committee of the New York Heart Association. (1994). Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. (9th ed.). Boston: Little, Brown & Co. pp. 253–256.

18. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.03. Available at: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Published 14 Jun 2010. Accessed 05 Apr 2017.

19. US Department of Health and Human Services. Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. Available at: https://www fda.gov/downloads/drugsGuidanceComplianceRegulatoryInformation/Guidance/UCM071590.pdf. Accessed 13 April 2017.

20. Expert Committee on Biological Standardization, WHO. Guidelines on evaluation of similar biotherapeutic products (SBPs). 2009.

21. Grambsch, PM and TM Therneau. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika. 1994:81(3):515–526.

22. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006;355(24):2542-50.

23. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol. 2004;22:2184–91.

24. Niho S, Kunitoh H, Nokihara H, et al. Randomized phase II study of first-line carboplatin-paclitaxel with or without bevacizumab in Japanese patients with advanced non-squamous non-small-cell lung cancer. Lung Cancer. 2012;76:362-267.

25. Reck M, von Pawel J, Zatloukal P, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for non-squamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). Ann Oncol. 2010;21:1804–9.

26. Zhou C, Wu YL, Chen G, et al. BEYOND: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase III Study of First-Line Carboplatin/Paclitaxel Plus Bevacizumab or Placebo in Chinese Patients With Advanced or Recurrent Nonsquamous Non–Small-Cell Lung Cancer. J Clin Oncol. 2015;33:2197-2204.

16 APPENDICES

16.1 Investigator Signature Page

Protocol Title: 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)

Protocol Number: MB02-C-02-17

Confidentiality and cGCP Compliance Statement

I, the undersigned, have reviewed this protocol (and amendments), including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), GCP, and relevant ICH guidelines.

Once the protocol has been approved by the IEC/IRB, I will not modify this protocol without obtaining previous approval of mAbxience and of the IEC/IRB. I will submit the protocol amendments and/or any ICF modifications to mAbxience and IEC/IRB, and approval will be obtained before any amendments are implemented.

I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all eCRFs, laboratory samples, or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

Information developed in this clinical study may be disclosed by mAbxience, to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

_____ _____

Investigator Signature Date

_____

Printed Name

Institution

16.2 Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 Guidelines (January 2009)

The following paragraphs are a quick reference to RECIST criteria (version 1.1). The complete criteria are included in the published RECIST document also available at http://www.eortc.be/RECIST.

1) Measurability of tumor lesions at Baseline

1.1) Definitions

Measurable disease. the presence of at least 1 measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions. tumor lesions that can be accurately measured in at least 1 dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray, and as ≥10 mm with CT or clinical examination [using calipers]. Malignant lymph nodes must be ≥ 15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters) by use of a ruler or calipers. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Non-measurable lesions. All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis or pulmonitis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Nodes that have a short axis less than 10 mm at baseline are considered nonpathological and should not be recorded or followed.

Target lesions. When more than 1 measurable tumor lesion or malignant lymph node is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), and be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. Note that pathological nodes must meet the criterion of a short axis of ≥ 15 mm by CT, and only the short axis of these nodes will contribute to the baseline sum. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be calculated and recorded.

Nontarget lesions. All non-measurable lesions (or sites of disease) including pathological nodes (those with short axis ≥ 10 mm but < 15 mm), plus any measurable lesions over and above those listed as target lesions are considered nontarget lesions. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent".

All Baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

2.1 Methods of measurements

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during Follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy, which may be treatment arm dependent. While on study, all target lesions recorded at baseline should have their actual measurements recorded on the eCRF at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has probably disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions that fragment/split, add together the longest diameters of the fragmented portions; for lesions that coalesce, measure the maximal longest diameter for the "merged lesion".

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

Chest X-ray. Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint, since CT is more sensitive than x-ray, particularly in identifying new lesions. However, lesions more than 20 mm on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT based on the assumption that CT slice thickness is 5 mm or less. When CT have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). Although positron emission tomography (PET) is not considered adequate to measure lesions, PET-CT may be used providing that the measures are obtained from the CT and the CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

Tumor markers. Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a subject to be considered in CR.

2.2 Measurability of tumor lesions at End-of-Treatment/Follow-up

For the endpoint of best overall response, each subject will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point at least 4 weeks later. Refer to the table below.

2.1) **Response categories**.

Complete Response (CR): disappearance of all *target* and *nontarget* lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures less than 10 mm (Note: Continue to record the measurement even if < 10 mm and considered CR). Tumor markers must have normalized. Residual lesions (other than nodes < 10 mm) thought to be nonmalignant should be further investigated (by cytology or PET) before CR can be accepted.

Partial Response (PR): At least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Nontarget lesions must be non-PD.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including at baseline) AND an absolute increase of ≥ 5 mm. Appearance of new lesions will also constitute PD (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of nontarget disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment, for example where the tumor burden appears to have increased by at least 73% in volume (which is the increase in volume when all dimensions of a single lesion increase by 20%). Modest increases in the size of 1 or more nontarget lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or nontarget), treatment may continue until the next assessment, but on further documentation, the earlier date must be used.

Table 1: Integration of Target, Nontarget and New Lesions into Response Assessment

Target Lesions	**Nontarget Lesions**	**New Lesions**	**Overall Response**	**Best Response for this category also requires**
Subjects with Target lesions ± nontarget lesions				
CR	CR	No	CR	Normalization of tumor markers, tumor nodes < 10 mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	Documented at least once ≥ 6-8 wks. from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Subjects with Nontarget lesions ONLY				
No Target	CR	No	CR	Normalization of tumor markers, all tumor nodes < 10 mm
No Target	Non-CR/non-PD	No	Non-CR/ non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes	PD	
Note: Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression [or evidence of unequivocal disease progression] at that time should be reported as "*symptomatic deterioration"* This is a reason for stopping therapy, but is NOT objective PD Every effort should be made to document the objective progression even after discontinuation of treatment				

Complete response or PR may be claimed only if the criteria for each are met at a subsequent time point at least 4 weeks later. The best overall response can be interpreted as below:

Response: First time point	Subsequent time point	BEST overall response	Also requires
CR	CR	CR	Normalization of tumor markers, tumor nodes < 10 mm
CR	PR	SD, PD or PR (see comment*)	
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD	
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD	
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE	
PR	CR	PR	
PR	PR	PR	
PR	SD	SD	
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD	
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE	
NE	NE	NE	
* may consider PR providing initial "CR" likely PR on subsequent review – then original CR should be corrected Recurrence of lesion after true CR is PD			

2.2) Date of progression

This is defined as the first day when the RECIST (version 1.1) criteria for PD are met. In the cases of subjects with only nonmeasurable disease, care must be taken to explicitly describe the findings which would qualify for PD for those subjects**.**

1) Reporting of tumor response

All subjects included in the study must be assessed for response to treatment, even if there is a major protocol treatment deviation or if they are ineligible, or not followed/re-evaluated. Each subject will be assigned 1 of the following categories: CR, PR, SD, progressive disease, early death from malignant disease, early death from toxicity, early death from other cause or unknown (not assessable, insufficient data).

Early death is defined as any death occurring before the first per protocol time point of tumor re-evaluation. The responsible investigator will decide if the cause of death is malignant disease, toxicity, or other cause.

Subjects for whom response is not confirmed will be classified as "unknown", unless they meet the criteria for SD (or the criteria for PR in case of an unconfirmed CR). Subjects' response will also be classified as "unknown" if insufficient data were collected to allow evaluation per these criteria.
Refer to the second table in Section 2.1 of this appendix.

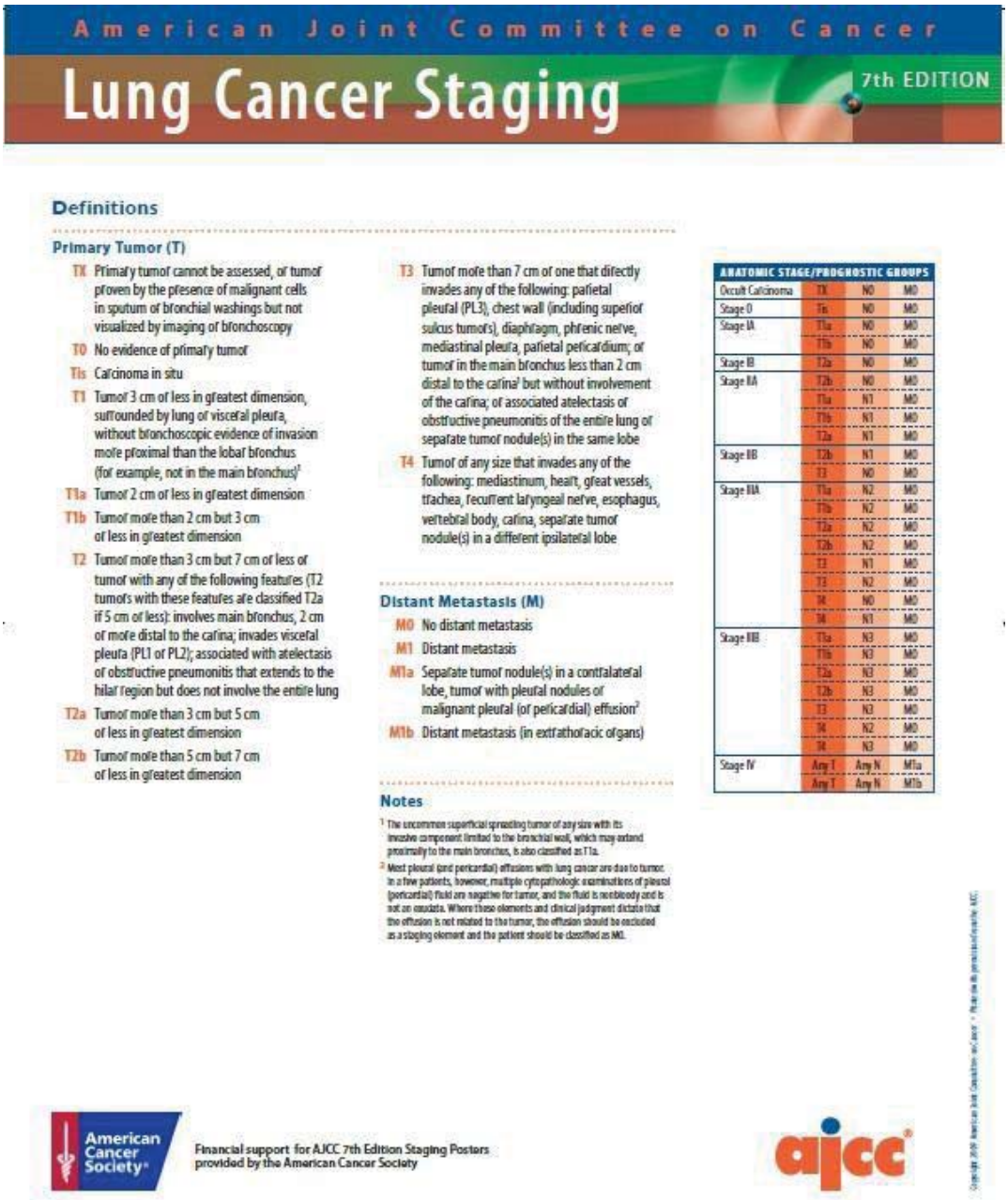
2) Response duration

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented.

3) Stable disease duration

Stable disease duration will be measured from the time of start of treatment (or randomization for randomized studies) until the criteria for progression is met.

16.3 American Joint Committee on Cancer; Lung Cancer Staging, 7th edition



American Joint Committee on Cancer

Lung Cancer Staging 7th EDITION

Definitions

Primary Tumor (T)

- **TX** Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
- **T0** No evidence of primary tumor
- **Tis** Carcinoma in situ
- **T1** Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (for example, not in the main bronchus)[1]
- **T1a** Tumor 2 cm or less in greatest dimension
- **T1b** Tumor more than 2 cm but 3 cm or less in greatest dimension
- **T2** Tumor more than 3 cm but 7 cm or less or tumor with any of the following features (T2 tumors with these features are classified T2a if 5 cm or less): involves main bronchus, 2 cm or more distal to the carina; invades visceral pleura (PL1 or PL2); associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
- **T2a** Tumor more than 3 cm but 5 cm or less in greatest dimension
- **T2b** Tumor more than 5 cm but 7 cm or less in greatest dimension
- **T3** Tumor more than 7 cm of one that directly invades any of the following: parietal pleural (PL3), chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina[2] but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
- **T4** Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in a different ipsilateral lobe

Distant Metastasis (M)

- **M0** No distant metastasis
- **M1** Distant metastasis
- **M1a** Separate tumor nodule(s) in a contralateral lobe, tumor with pleural nodules or malignant pleural (or pericardial) effusion[3]
- **M1b** Distant metastasis (in extrathoracic organs)

Notes

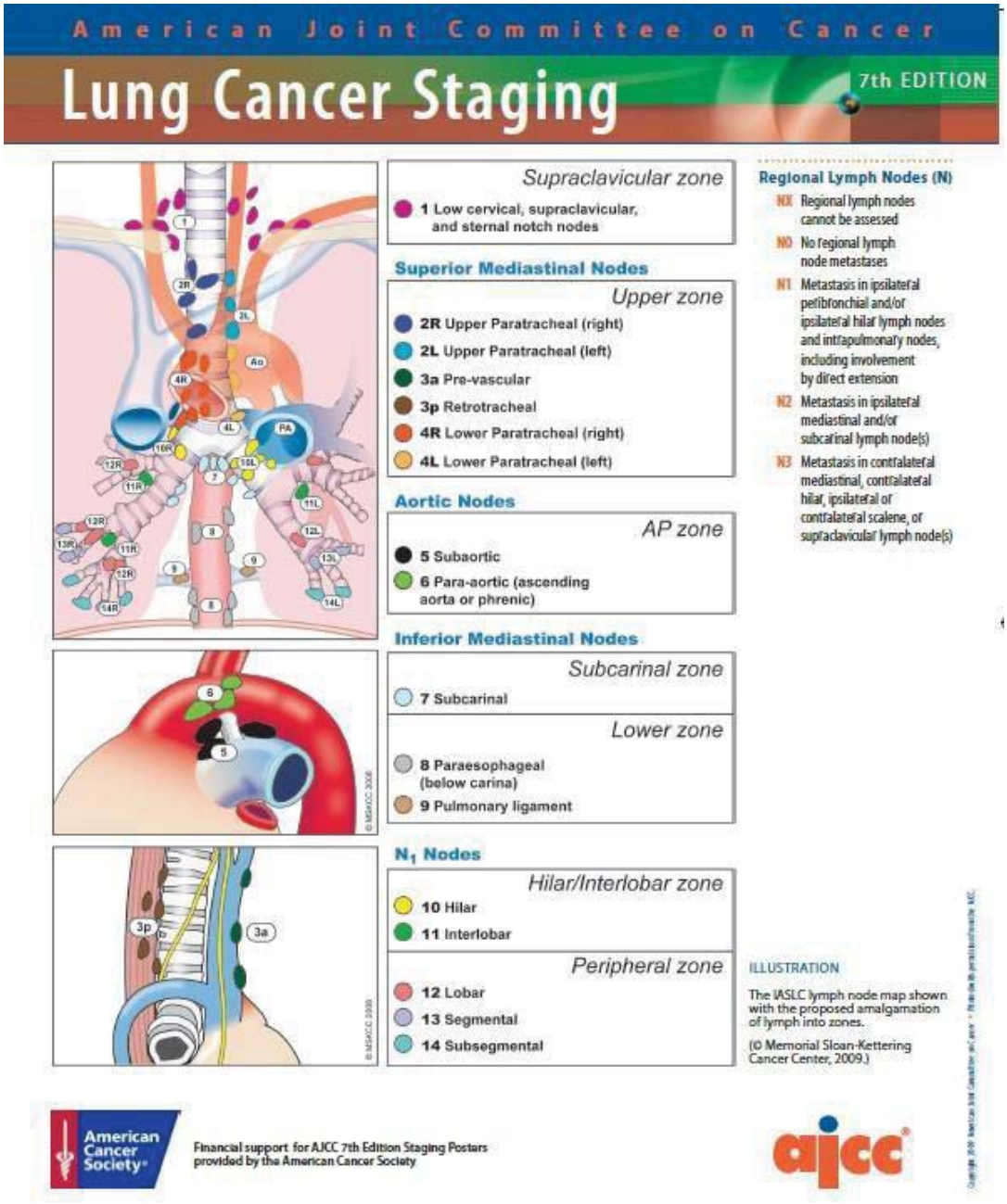
[1] The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.

[2] Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as M0.

ANATOMIC STAGE/PROGNOSTIC GROUPS			
Occult Carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
	T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T1a	N1	M0
	T1b	N1	M0
	T2a	N1	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a	N2	M0
	T1b	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T3	N2	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	T1a	N3	M0
	T1b	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N3	M0
	T4	N2	M0
	T4	N3	M0
Stage IV	Any T	Any N	M1a
	Any T	Any N	M1b

American Cancer Society®
Financial support for AJCC 7th Edition Staging Posters provided by the American Cancer Society

ajcc®



Source: http://cancerstaging.org/references-tools/quickreferences/documents/lungmedium.pdf

16.4 Protocol Amendment 2 Summary of Changes

This section details the changes made to final protocol MB02-C-02-17 version 3.0, Amendment 1 dated 03 Dec 2018, with Amendment 2 to the protocol. The integrated protocol, MB02-C-02-17 version 4.0, including Amendment 2, was issued on 24 May 2019.

The main reason to issue the present amendment is clarify the procedures applicable to Subjects that are responding to treatment at week 52 and are offered the opportunity to be treated with biosimilar MB02 monotherapy until disease progression, unacceptable toxicity, or death.

Overview of Changes

1. Clarification in section 3 Protocol Synopsis, study design paragraph: removing the wording no further study assessments will be performed beyond Week 52 and adding that the opportunity to continue treatment for subjects beyond Week 52 is only for subjects that are responding to study treatment. It refers to a new section Section 8.6, where the details are explained for this situation.
2. Incorporation of Section 8.6 to clarify the specific procedure applicable beyond week Week 52.
3. Schedule of Assessment table 7.1.1. update incorporating specific information to be collected beyond Week 52.
4. Clarification in Section 8.6 specifying that only Subjects that are benefiting from study treatment at Week 52 will be offered the possibility to continue treatment with biosimilar MB02 monotherapy.

Changes to the Protocol Text

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. Additions to the protocol text are shown in **bold** and deletions are shown in ~~strike through~~ text. Minor editorial and grammatical corrections are not specified.

Section 3, Protocol Synopsis

Study Design:

The study ends at Week 52~~; no further study assessments will be made after this time. A~~**,** **a**fter Week 52, all subjects (including those randomized to Avastin® during the study) will be offered the opportunity to continue receiving biosimilar MB02 monotherapy until **disease progression, unacceptable toxicity, lost to follow-up, withdrawal of consent, initiation of any new treatment or death**~~disease progression, unacceptable toxicity or death, as required.~~ **For specific information about post Week 52 procedures refer to Section 8.6.**

Number of Subjects:

Based on recommendation of two different agencies, two different analyses will be performed: one based on Risk Ratio (**United States [**US**]** Food and Drug Administration [FDA]) and one based on Risk Difference (**RD;** European Medicines Agency [EMA]).

Risk Ratio:

The ~~United States (~~US~~)~~ FDA requires a primary endpoint of risk ratio (RR) based on ORR, with an equivalence margin of [0.73, 1.36].

Study	Responders	N	ORR	95% CI	Weight (%)
Sandler et al.	133	381	0.349	(0.301, 0.399)	22.2%
Johnson et al.	11	34	0.324	(0.174, 0.505)	15.2%
Niho et al.	71	117	0.607	(0.512, 0.696)	20.1%
Reck et al.	114	351	0.325	(0.276, 0.377)	22.0%
Zhou et al.	74	138	0.536	(0.449, 0.621)	20.5%
Total*	403	1021	0.429	(0.322, 0.539)	100%

Abbreviations: **CI = confidence interval;** ORR = objective response rate

Utilizing a 2-sided 90% **confidence interval (**CI**)** for the RR, a reference proportion of 42.9% for Avastin® and an equivalence margin of (0.73, 1.36), a sample size of 300 subjects per arm (600 total) provides approximately 89% power to show equivalence of MB02 plus chemotherapy with Avastin® plus chemotherapy on a primary endpoint of RR.

Risk Difference:

The ~~European Medicines Agency (~~EMA~~)~~ requested that the risk difference (RD) in ORRs is used as the primary efficacy analysis, using an equivalence margin of (-12%, +12%).

Dose Adjustment of MB02/Avastin®:

As osteonecrosis of the jaw has been reported for ~~patients~~**subjects** on bevacizumab and invasive dental procedures are an identified risk factor, a dental examination and appropriate preventive dentistry should be considered before the start of treatment, if clinically indicated. Procedures that involve direct osseous injury and placement of dental implants should be avoided if not strictly necessary. Caution should be exercised for ~~patients~~**subjects** receiving intravenous bisphosphonates.

Concomitant medications allowed:

- Primary and secondary prophylaxis with granulocyte colony-stimulating factor, according to the investigator's ~~judgment~~**judgement**.

Section 5.1, Background: Non-Small Cell Lung Cancer

Global cancer statistics show that deaths from lung cancer exceed those from any other malignancy; primary lung cancer is the second-most common malignancy.[1] Non-small cell lung cancers **(NSCLCs)** account for 85%–90% of lung cancers[1] and there are 3 main subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.

Therefore, newer therapies that disrupt critical growth factor/receptor signaling pathways involved in tumor angiogenesis and lymphangiogenesis are required. One potential treatment target is **vascular endothelial growth factor (**VEGF**)**, which induces the proliferation, migration, and survival of vascular endothelial cells and stimulates the recruitment of bone marrow-derived endothelial progenitor cells to new blood vessels serving the tumor.

Section 5.2, Introduction – Reference Therapy (Bevacizumab; Avastin®)

The main toxicities anticipated (on the basis of the product label for **European Union** [EU-] approved Avastin®) in this study are as follows:

Section 5.3.2, Clinical Data

Data from the BEVZ92-A-01-13 study showed MB02 and Avastin® to have equivalent PK in terms of AUC and similar efficacy in terms of tumor response in the sensitive population of metastatic colorectal ~~patients~~**subjects**.

Section 7.1, Investigational Plan – Overall Study Design and Plan: Description

The study ends at Week 52~~; no further study assessments will be made after this time. A~~**,** **a**fter Week 52, all subjects (including those randomized to Avastin® during the study) will be offered the opportunity to continue receiving biosimilar MB02 monotherapy until **disease progression, unacceptable toxicity, lost to follow-up, withdrawal of consent, initiation of any new treatment or death**~~disease progression, unacceptable toxicity, or death, as required . No further study-related procedures are intended to be performed after Week 52; any assessments after Week 52 should be performed based on the investigator's discretion and according to local standard practice~~**. For specific information about post Week 52 procedures refer to Section 8.6.**

Subjects who withdraw for any reason other than **progression of disease (**PD**)** or withdrawal of consent will be followed up every 9 weeks with tumor assessment until PD and/or the start of new antitumor treatment, subject decision, death, or Week 52 (End-of-Study Visit) whichever occurs first.

The primary endpoint is ORR (**i.e., complete response [CR] or partial response [PR] per** RECIST version 1.1) at Week 18; an independent radiology review committee (IRC) will assess the primary efficacy endpoint using **computed tomography (**CT**)** and/or **magnetic resonance imaging (**MRI**)** according to RECIST version 1.1 criteria.

A **Data Safety Monitoring Board (**DSMB**)** will assess the safety data periodically and will recommend to the Sponsor whether to continue, modify or stop the trial.

- Subjects with no radiological disease progression will be assessed for: tumor evaluation, initiation of other treatments, physical examination, **Eastern Cooperative Oncology Group (**ECOG**)** performance status, supine vital signs, concomitant medications, surgeries, procedures, AEs/SAEs , concomitant diseases and immunogenicity will be recorded in the electronic case report form (eCRF) at follow-up visits at intervals of 9 weeks up to disease progression and/or the start of new antitumor treatment, death, or Week 52 (End-of-Study Visit).

After Week 52, all subjects (including those randomized to Avastin® during the study) will be offered to continue receiving biosimilar MB02 monotherapy until **disease progression, unacceptable toxicity, lost to follow-up, withdrawal of consent, initiation of any new treatment or death**~~disease progression, unacceptable toxicity, or death, as required .~~**.For specific information about post Week 52 procedures refer to Section 8.6.**

Section 7.71.1, Schedule of Assessments

New column added for post Week 52 visits detailing assessments to be performed: Re consent risk of potential switch from Avastin® to MB02 if subjects were randomized to Avastin arm. Confirmation that subjects and investigators will remain blinded up to Week 52. (clarification added in footnote q) of Schedule of Assessment table.

Footnote:

~~NSCLC = non-small cell lung cancer;~~ **Abbreviations: ADA = antidrug antibodies; CT = computed tomography,** ECOG = Eastern Cooperative Oncology Group; **HIV = human**

immunodeficiency virus; LVEF=left ventricular ejection fraction; **NSCLC = non-small cell lung cancer;** ~~CT = computed tomography, ADA = antidrug antibodies;~~ PD=progression of disease; WOCBP=women of ~~child bearing~~**childbearing** potential;

[k] For those ~~patients~~**subjects** who discontinue treatment without radiological disease progression, tumor assessment should be performed every 9 weeks (±5 days) until Week 52, PD, start of new treatment, subject decision, or death, whichever occurs first. Once radiological disease progression is documented, subjects are no longer required to undergo additional tumor assessment.

[l] Once ~~patient~~**subject** discontinues treatment, ADA sample will follow specified weeks as scheduled.

[q] Subjects will be asked to reconsent for the potential risk of switching treatment to MB02 in case they have been randomized to Avastin ® treatment. Subjects will remain blinded.

Section 7.4.3, Packaging and Labelling

Study packaging will be performed by **Clinical Supplies Management (**CSM**)** Europe SA, Mont-Saint-Guibert, Belgium

Section 7.4.7, Blinding

The pharmacist at each study site and a specific clinical team from INC Research and the Sponsor will be unblinded to treatment assigned. ~~Patients~~**Subjects** as well as investigators, all other study staff, laboratories and the rest of the INC Research and Sponsor team will remain blinded to treatment assignment up to Week 52.

Section 7.4.8.1, Prohibited Medication/ Therapy

As osteonecrosis of the jaw has been reported for ~~patients~~**subjects** on bevacizumab and invasive dental procedures are an identified risk factor, a dental examination and appropriate preventive dentistry should be considered before the start of treatment, if clinically indicated. Procedures that involve direct osseous injury and placement of dental implants should be avoided if not strictly necessary. Caution should be exercised for ~~patients~~**subjects** on intravenous bisphosphonates.

Section 8.1.1, Screening Visit (Days -28 to -1; Visit 1)

Up to 14 days before first study drug administration

- Urine or serum pregnancy test (according to local requirements, female subjects of ~~child bearing~~**childbearing** potential only).

Up to 7 days before first study drug administration

It is considered a risk factor for osteonecrosis of the jaw, reported for ~~patients~~**subjects** on bevacizumab. Appropriate preventive dentistry should be considered, if clinically indicated (Section 7.4.8.1).

Section 8.2.1, Cycle 1 (-1/+3 Days)

- Urine or serum pregnancy test (according to local requirements, female subjects of ~~child bearing~~**childbearing** potential only).

Section 8.2.2, Cycle 2 (-1/+3 Days)

- Urine or serum pregnancy test (according to local requirements, female subjects of ~~child bearing~~**childbearing** potential only).

Section 8.2.3, Cycle 3 (-1/+3 Days)

- Urine or serum pregnancy test (according to local requirements, female subjects of ~~child bearing~~**childbearing** potential only).

Section 8.2.4, Cycle 4 (-1/+3 Days)

- Urine or serum pregnancy test (according to local requirements, female subjects of ~~child bearing~~**childbearing** potential only).

Section 8.2.5, Cycle 5 (-1/+3 Days)

- Urine or serum pregnancy test (according to local requirements, female subjects of ~~child bearing~~**childbearing** potential only).

Section 8.2.6, Cycle 6 (-1/+3 Days)

- Urine or serum pregnancy test (according to local requirements, female subjects of ~~child bearing~~**childbearing** potential only).

Section 8.2.7, Additional Cycles Until Treatment Withdrawal (From Week 19 (Cycle 7) onwards, Then Every 3 Weeks; -1/+3 Days)

Subjects who complete 6 cycles can continue to receive MB02 or Avastin® monotherapy until disease progression, unacceptable toxicity**, death** or Week 52,whichever occurs first. **The study ends at Week 52. After Week 52, all subjects (including those randomized to Avastin® during the study) will be offered the opportunity to continue receiving biosimilar MB02 monotherapy until disease progression, unacceptable toxicity, lost to follow-up, withdrawal of consent, initiation of any new treatment or death. For specific information about post Week 52 procedures refer to section 8.6**

- Urine or serum pregnancy test (according to local requirements, female subjects of ~~child bearing~~**childbearing** potential only).

Section 8.3, End of Treatment Visit (Within 3 Weeks of Completion of Last Cycle; ±5 Days)

- Urine or serum pregnancy test (according to local requirements, female subjects of ~~child bearing~~**childbearing** potential only).

Section 8.4.1, Subjects Who Discontinue Treatment Without Radiological Disease Progression Before Week 52 (9 Week Intervals; ±7 Days)

Those ~~patients~~**subjects** who report disease progression during follow-up visits will be followed as per Section 8.4.2.

Section 8.5, Week 52 End-of-Study Visit (±7 Days)

- In those ~~patients~~**subjects** who have not shown disease progression (not started any new antitumor therapy) a CT Scan/MRI of chest, upper abdomen and any other involved regions must be done if it was not performed within the previous 4 weeks. Disease status and tumor response will be assessed per RECIST version 1.1 criteria.

Section 8.6, Post Week 52 Period Procedures for Subjects That Are Responding to Treatment

New Section added

After Week 52, all subjects (including those randomized to Avastin® during the study)will be offered the opportunity to continue receiving biosimilar MB02 monotherapy. The following will be required:

- **Subjects and investigators will remain blinded up to week 52**
- **Subjects will be asked to re-consent to accept the potential risk of being switched to MB02 treatment, in case they were initially randomized to Avastin®**
- **Subjects will receive MB02 labelled as clinical trial**
- **Investigators will collect safety information during the time subjects are on MB02 treatment beyond Week 52 and will enter the information in the pertinent section of the eCRF and, in case of occurrence of any SAE, it will be processed and notified as per section 9.1.3.2. No other study assessments are required, it is left to investigator's discretion the performance of any further assessment according to local practice, but these will not be captured in the eCRF**
- **Subjects will continue receiving biosimilar MB02 monotherapy until disease progression, unacceptable toxicity, lost to follow-up, withdrawal of consent, initiation of any new treatment or death.**
- **Investigators are required to notify in advance of any patient at his/her site willing to proceed with post week 52 treatment. Likewise, investigators are required to confirm the continuation or discontinuation of the treatment in advance, per drug supply and logistics purposes.**

Section 8.7, Duration of Treatment

After Week 52, all subjects (including those randomized to Avastin® during the study) will be offered the opportunity to continue receiving biosimilar MB02 monotherapy until **disease progression, unacceptable toxicity, lost to follow-up, withdrawal of consent, initiation of any new treatment or death** ~~disease progression, unacceptable toxicity or death~~. For specific information about post Week 52 procedures, refer to Section 8.6.

Section 9.1.1, Tumor Assessment

Tumor response will be assessed by the IRC using the RECIST v1.1 criteria to evaluate ORR. Disease status, PFS, and OS[16] will be evaluated by ~~Investigators~~**investigators**. The RECIST v1.1 (January 2009) guidelines for measurable, nonmeasurable, target and nontarget lesions and the objective tumor response criteria (CR, PR, stable disease [SD] or PD) are detailed in Section 16.2.

Section 9.1.3.1, Adverse Events

Follow-up of adverse events

Subjects should be followed up until 30 days after last cycle, and any AEs that occur during this time should be reported according to the procedures outlined below. **Additionally, for those subjects who proceed with post Week 52 treatment, any AE occurring during this time should, also, be reported according to the procedures outlined below.**

Documentation and reporting of adverse events

Adverse events should be reported and documented in accordance with the procedures outlined below; AEs will be recorded in the eCRF from the signing of the informed consent form (ICF) until 30 days after last cycle**, for those subjects that do not proceed with post**

Week 52 treatment. For those subjects that continue to post Week 52 treatment, any AE occurring during this time, will also be recorded in the eCRF. Any AEs occurring more than 30 days after last cycle of drug administration should also be recorded in the eCRF if they are considered at least possibly related to the study drugs by the investigator. The following data should be documented for each AE:

Section 9.1.3.2, Serious Adverse Events

Reporting of serious adverse events

All SAEs will be recorded in the eCRF and reported from signing of the ICF until 30 days after last cycle of any drug from the protocol treatment schedule**, for those subjects that do not proceed with post Week 52 treatment. For those subjects that continue to post Week 52 treatment, any SAE occurring during this time, will also be recorded in the eCRF and reported.** Any SAEs occurring or more than 30 days after last cycle of drug administration should also be recorded in the eCRF and reported if they are considered at least possibly related to the protocol treatment by the investigator. An SAE form must be sent to INC Research by email (PDF) or faxed within 24 hours for the attention of the Safety Department.

Section 9.1.3.4, Clinical Laboratory Evaluation

Local site laboratories may be utilized, in addition to the central laboratory, if more rapid results are required for ~~re-treatment~~**retreatment** decisions or ~~patients~~**subject** safety. If a local site laboratory sample is taken, then part of the blood sample obtained for local site laboratory assessment should also be sent to the central laboratory for analysis. Local site laboratory results obtained during the study will not be captured in the eCRF unless the ~~Investigator~~**investigator** determines they are needed to clarify why a treatment decision was made or an AE was recorded. Laboratory parameters of interest will be graded according to NCI-CTCAE version 4.0318 to allow for comparison of AEs and laboratory parameters.

Section 9.1.3.5, Other Laboratory Variables

Screening for pregnancy (female subjects of ~~child-bearing~~**childbearing** potential only) will be performed (serum or urine β human chorionic gonadotrophin [β-HCG]) at Screening and before each cycle of treatment.

Section 9.1.3.6, Vital Signs

If medically significant hypertension cannot be controlled with antihypertensive therapy, or if the ~~patients~~**subject** develops hypertensive crisis or hypertensive encephalopathy, MB02/Avastin® should be permanently discontinued.

Section 9.1.3.7, Physical Examination

It is considered a risk factor for osteonecrosis of the jaw, reported for ~~patients~~**subjects** on bevacizumab.

Caution should be exercised for ~~patients~~**subjects** receiving intravenous bisphosphonates.

Section 9.1.3.10, Cardiac Ultrasound or Multigated Acquisition Scan

Left ventricular ejection fraction will be measured by cardiac ultrasound or multigated acquisition scan at Screening and End-of-Treatment **Visits** (if not done in previous 6 weeks). It can also be measured during any treatment cycle if clinically indicated.

Section 10.2, Determination of Sample Size

Risk Ratio

Study	Responders	N	ORR	95% CI	Weight (%)
Sandler et al.	133	381	0.349	(0.301, 0.399)	22.2%
Johnson et al.	11	34	0.324	(0.174, 0.505)	15.2%
Niho et al.	71	117	0.607	(0.512, 0.696)	20.1%
Reck et al.	114	351	0.325	(0.276, 0.377)	22.0%
Zhou et al.	74	138	0.536	(0.449, 0.621)	20.5%
Total*	403	1021	0.429	(0.322, 0.539)	100%

Abbreviations: **CI = confidence interval;** ORR = objective response rate

Risk Difference

The ~~European Medicines Agency (~~EMA)~~-~~requested that the risk difference (RD) in ORRs is used as the primary efficacy analysis, using an equivalence margin of (-12%, +12%).

Section 12.2, Drug Accountability

It is the responsibility of the study monitor to verify that the investigator (or deputy **investigator**) has correctly documented the amount of the study drug received, dispensed, and returned on the dispensing log that will be provided.