Protocol Title:	A Randomised, Double-Blind, Three-Arm, Single Dose, Parallel Study To Compare the Pharmacokinetics, Safety and Immunogenicity of MB02 (Bevacizumab Biosimilar Drug), US-licenced Avastin® and EU-approved Avastin® in Healthy Male Volunteers
NCT Number:	NCT03293654
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PROTOCOL

A Randomised, Double-Blind, Three-Arm, Single Dose, Parallel Study To Compare the Pharmacokinetics, Safety and Immunogenicity of MB02 (Bevacizumab Biosimilar Drug), US-licenced Avastin® and EU-approved Avastin® in Healthy Male Volunteers

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Study Drug: MB02

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Covance Study Number: 8370738
PAREXEL Study Number: PXL 242186
EudraCT Number: 2017-003004-40

Sponsor:
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Principal Investigators:
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INVESTIGATOR AGREEMENT

I have read the following protocol and agree to conduct the study as described herein.

[redacted]

Investigator Name (Printed)

[redacted]

Investigator Signature

[redacted]

Date

INVESTIGATOR AGREEMENT

I have read the following protocol and agree to conduct the study as described herein.

[redacted]
Investigator Name (Printed)

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Investigator Signature

[redacted]
Date

SPONSOR AGREEMENT

I have read the following protocol and agree to conduct the study as described herein:

[redacted]

[redacted]

Date

Medical Advisor

SPONSOR AGREEMENT

I have read the following protocol and agree to conduct the study as described herein:

[redacted]

Amalia Flórez
Clinical Project Manager

[redacted]

Date

RATIONALE FOR CHANGES FROM PROTOCOL VERSION 6.0 TO VERSION 7.0

Amendment Version 7.0 for the Final Study Protocol, Version 6.0, dated 15 October 2018, has been to:

- Update the Principal Investigator for one of the study sites.

Details of the changes incorporated in this amendment are provided in the table overleaf.

Protocol Section	Description of Changes from Final Protocol, Version 6.0 (15 October 2018)
Title Page	Previous text: Principle Investigators [redacted] Amended text: Principle Investigators [redacted]
Study Identification	Previous text: Principle Investigators [redacted] Covance Clinical Research Unit Ltd. Springfield House Hyde Street Leeds, LS2 9LH UK [redacted] [redacted] PAREXEL International Level 7 Northwick Park Hospital Watford Road Harrow, HA1 3UJ

	UK [redacted] Amended text: Principle Investigators [redacted] Covance Clinical Research Unit Ltd. Springfield House Hyde Street Leeds, LS2 9LH UK [redacted] Muna Albayaty, MBChB, FFPM, MSc PAREXEL International Level 7 Northwick Park Hospital Watford Road Harrow, HA1 3UJ UK [redacted]

STUDY IDENTIFICATION

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Pharmacokineticist	[redacted] Covance Early Clinical Biometrics

SYNOPSIS

Title of study: A Randomised, Double-Blind, Three-Arm, Single Dose, Parallel Study To Compare the Pharmacokinetics, Safety and Immunogenicity of MB02 (Bevacizumab Biosimilar Drug), US-licenced Avastin® and EU-approved Avastin® in Healthy Male Volunteers.

Objectives:
The primary objective of the study is:

- To investigate and compare the pharmacokinetic (PK) profiles of MB02, US-licenced Avastin® (US Avastin®) and EU-approved Avastin® (EU Avastin®) to establish bioequivalence between the 3 study arms.

The secondary objectives of the study are:

- Evaluation and comparison of derived PK parameters not covered by the primary endpoints for MB02, US Avastin® and EU Avastin®
- To compare the safety profile of MB02 and US Avastin® and EU Avastin®
- To compare the immunogenicity of MB02, US Avastin® and EU Avastin®

Study design:
This will be a Phase 1, double-blind, randomised, parallel-group, single-dose, 3-arm study to investigate and compare the PK, safety and immunogenicity profile of MB02 with US and EU Avastin® in healthy male subjects.

Potential subjects will be screened to assess their eligibility to enter the trial within 30 days prior to study drug administration. Subjects will be admitted to the Clinical Research Unit (CRU) on Day -1, and will be confined to the CRU until discharge on Day 8. On Day 1, subjects will receive a single 3 mg/kg intravenous (IV) dose of the study drug. Subjects will return on Days 10, 14, 21, 28, 42, 56, 78 and 100 for nonresidential visits for the collection of pharmacokinetics (PK) and safety assessments. Immunogenicity samples will be collected on Days 14, 28, 56, and 78.

Number of subjects:
One hundred and fourteen (114) subjects will participate in the study.

Diagnosis and main criteria for inclusion:
Healthy male subjects of any race, in good health, between 18 and 55 years of age, inclusive, with a body mass index between 18.5 and 29.9 kg/m^2, inclusive, and a body weight between 60 and 95 kg, inclusive. Subjects will have relevant clinical laboratory evaluations within normal ranges, and be able and willing to sign an informed consent form, and to abide by the study restrictions. See protocol for detailed inclusion criteria.

Test products, dose, and mode of administration:
3 mg/kg MB02, administered as a 90 minute IV infusion
3 mg/kg US-licenced Avastin®, administered as a 90 minute IV infusion
3 mg/kg EU-approved Avastin®, administered as a 90 minute IV infusion

Duration of treatment:
Planned Screening duration: up to 29 days.
Planned study duration (Screening to final visit): maximum of 19 weeks.

Criteria for evaluation:

Pharmacokinetics:

Blood samples will be collected for the analysis of serum concentrations of bevacizumab. The primary PK endpoints for bevacizumab will be maximum observed serum concentration (C_{max}) and area under the serum concentration-time curve (AUC) from time zero to infinity ($AUC_{[0-\infty]}$). The secondary PK endpoints for bevacizumab will include time of maximum observed serum concentration (t_{max}), clearance (CL), AUC calculated to the last observable concentration at time t ($AUC_{[0-t]}$) and apparent serum terminal elimination half-life ($t_{1/2}$).

Safety:

Safety endpoints for this study include adverse events (AEs), vital signs measurements, 12-lead electrocardiograms, clinical laboratory evaluations and physical examinations.

Immunogenicity:

Blood samples will be collected for the assessment of serum concentrations of anti-MB02 and anti-Avastin® antibodies

Statistical methods:

The primary PK parameters are C_{max} and $AUC_{(0-\infty)}$. The PK parameters for bevacizumab will be calculated using standard noncompartmental methods. An analysis of covariance model will be used to analyse the log-transformed primary PK parameters ($AUC_{[0-\infty]}$.and C_{max}) and $AUC_{(0-t)}$. The model will include a fixed effect for treatment and body weight as a covariate.

All other PK parameters will not be subject to inferential statistical analysis. Estimates of geometric mean ratios together with the corresponding 90% confidence intervals will be derived for the comparisons of the PK parameters as follows:

- MB02 versus EU Avastin®
- MB02 versus US Avastin®
- EU Avastin® versus US Avastin®

PK similarity will be achieved if the 90% confidence intervals (CIs) for the biosimilar-to-reference ratios of PK endpoints ($AUC_{[0-\infty]}$ and C_{max}) fall within the predefined 0.80–1.25 acceptance similarity criteria for all 3 pairwise comparisons; MB02 versus EU-approved Avastin®; MB02 versus US-licenced Avastin®; and EU-approved Avastin® versus US-licenced Avastin®.

All AEs will be listed and summarised using descriptive methodology. All observed or patient-reported AEs will be graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The incidence of AEs for each treatment will be presented by severity and by association with the study drugs as determined by the Investigator (or designee). All safety data will be listed and summarised as appropriate

Immunogenicity data (overall anti-drug antibody [ADA] incidence and titers, and neutralising ADA results) will be listed. A summary of the number and percent of subjects testing positive for ADA or neutralising antibodies before the dose of MB02, EU Avastin®, or US Avastin® (Day -1) and at scheduled postdose assessments will be presented by treatment arm.

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LIST OF ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
AUC	area under the serum concentration-time curve
$AUC_{(0-\infty)}$	AUC from time zero to infinity
$AUC_{(0-t)}$	AUC from time zero to the time of the last observable concentration
CI	confidence interval
CL	clearance
C_{max}	maximum observed serum concentration
CRU	Clinical Research Unit
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EMA	European Medicines Agency
FIH	first in human
FOLFIRI	leucovorin, fluorouracil and irinotecan
FOLFOX	leucovorin, fluorouracil and oxaliplatin
GI	gastrointestinal
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for/Conference on Harmonisation
IMP	investigational medicinal product
INR	international normalised ratio
IUD	intrauterine device
IV	intravenous
PK	pharmacokinetic(s)
QTcF	QT interval corrected for heart rate using Fridericia's method
RMP	reference medicinal product
SAE	serious adverse event
SAP	statistical analysis plan
SOP	Standard Operating Procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse event
$t_{1/2}$	apparent serum terminal elimination half-life
t_{max}	time of maximum observed serum concentration
ULN	upper limit of normal
VEGF	vascular endothelial growth factor

1 INTRODUCTION

Please refer to the Investigator's Brochure (IB)[1] for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile of the investigational medicinal product (IMP).

1.1 Overview

MB02 is a bevacizumab biosimilar product to the originator Reference Medicinal Product (RMP) Avastin®. MB02 is currently marketed in Argentina, and a first-in-human clinical study has been conducted in cancer patients. Avastin® is indicated for the treatment of multiple cancer types, administered alone or in combination with chemotherapy. Bevacizumab, the active substance of Avastin®, is a recombinant humanised monoclonal antibody that specifically binds to all isoforms of the human vascular endothelial growth factor (VEGF), neutralising its biological activity. By sequestering VEGF, bevacizumab inhibits angiogenesis, inhibiting tumour growth and progression, and sensitising tumour vasculature to chemotherapy-induced damage.

1.2 Summary of Nonclinical Experience

A number of nonclinical in vitro and in vivo characterisation and efficacy studies have been conducted to demonstrate the similarity of MB02 with the RMP Avastin®. A full in vitro characterisation was undertaken, in accordance with European Medicines Agency (EMA) guidance on similar biological medicinal products containing monoclonal antibodies.[2] MB02 was shown to be identical to Avastin® in primary structure, and similar in protein conformation, posttranslational modification, and purity. MB02 and Avastin® also displayed similar mechanism of action, and similar affinity to FcRn receptors in vitro, which was indicative of a similar pharmacokinetic (PK) profile in vivo. Based upon these results, MB02 and Avastin® were considered similar in terms of physicochemical, structural and biological properties.

An in vivo toxicokinetic study has been conducted in cynomolgus monkeys. Twice-weekly intravenous (IV) doses of 50 mg/kg MB02 or Avastin®, infused over 30 minutes for 28 days, were well tolerated, and no clear differences were observed between MB02 and the RMP. Pharmacokinetic parameters derived during the toxicokinetic study demonstrated the similarity of MB02 to the RMP. Similar levels of accumulation were observed on Day 25 between MB02 and Avastin ® (with mean accumulation ratios ranging from 3.7 to 4.2 and 3.0 to 3.1, respectively). There was no appreciable difference in sex—related differences in exposure to MB02 and the RMP, and systemic exposure of MB02 and the RMP were similar on Days 1 and 25.

1.3 Summary of Clinical Experience

MB02 has been marketed in Argentina since November 2016. A single first bioequivalence study has been conducted, comparing the PK, safety, efficacy and immunogenicity of 5 mg/kg MB02 to 5 mg/kg Avastin® when administered in combination with leucovorin, fluorouracil and oxaliplatin (FOLFOX) or leucovorin, fluorouracil and irinotecan (FOLFIRI) chemotherapy regimens as first-line treatments in patients with metastatic colorectal cancer.

1.3.1 Safety

The safety population analysed in the bioequivalence study included 140 patients: 69 in the MB02 arm and 71 in the Avastin® arm. Almost all patients (96%) experienced at least one treatment emergent adverse event (TEAE). A total of 1258 TEAEs were reported, 605 in the MB02 arm of the trial. The most frequent TEAEs (with an incidence >10%) were gastrointestinal (GI) disorders, general disorders and administration site conditions, nervous system disorders, blood and lymphatic system disorders, metabolism and nutrition disorders, infections and infestations, and investigations. Fourteen patients had at least one TEAE leading to discontinuation from the study drug (8 in the MB02 arm). There was no obvious differential pattern relating to the type of AEs in either arm of the trial, regardless of relationship to treatment.

Grade 3 or 4 TEAEs were reported at similar proportions in both arms of the study. Grade 3 and 4 TEAEs were reported in 79 patients (40 in the MB02 arm). The distribution of Grade 3 and 4 AEs remained relatively similar between the study arms, and the frequency of AEs observed appeared consistent with the known AE profile of bevacizumab and FOLFOX/FOLFIRI chemotherapy.

The safety comparability exercise shows no signals of concern with regard to prior experience with regards to Avastin®, and no obvious differences in the safety profile in terms of nature, frequency and severity of the AEs reported. The safety profile for the bevacizumab biosimilar, MB02, was similar to the reference product, Avastin®, and was within the expectations given the underlying disease and concurrent use of chemotherapy.

1.3.2 Pharmacokinetics

A total of 116 patients (55 in the MB02 arm and 61 in the Avastin® arm) were included in the PK population. Results from the PK analyses demonstrated that MB02 and Avastin® were bioequivalent in cancer patients, exhibiting similar serum concentration-time profiles, and ratios of geometric means for the area under the concentration-time curve (AUC) between time zero and 336 hours and AUC at steady state within the predefined margin of 80 to 125%. Following the end the of dosing cycle, serum bevacizumab concentrations slowly declined in a biphasic manner until the last PK timepoint at 336 h postdose, with the start of the elimination phase occurring between 24 and 168 hours postdose.

1.3.3 Immunogenicity

Measurement of anti-drug antibodies occurred in all patients dosed in the first-in-human study of MB02. Six patients tested positive for anti-drug antibodies (ADAs) at Screening (2 in the MB02 arm and 4 in the Avastin® arm). Following treatment, 2 de novo positive results for ADA were found, both in patients administered MB02. One patient was positive for ADA at Screening and after treatment in the Avastin® treatment arm; however, no boost in ADA titre was found post-treatment. In the 3 ADA-positive patients, no concerns were raised regarding the efficacy, safety or PK data relative to ADA-negative patients.

1.4 Study Rationale

Previous nonclinical studies and an open-label bioequivalence study of MB02 have demonstrated that MB02 is bioequivalent to EU-approved Avastin®. This study will conduct

a comparison between MB02, EU Avastin® and US Avastin®, fulfilling the criteria for a PK bridging study to address regulatory requirements for biosimilars.[3,4]

1.5 Benefit-risk Assessment

Healthy male subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study. The risks of participation are primarily those associated with adverse reactions to the study treatments, although there may also be some discomfort from collection of blood samples and other study procedures. More information about the known and expected benefits, risks and reasonably anticipated AEs associated with MB02 may be found in the IB.[1]

2 OBJECTIVES

2.1 Primary Objective

The primary objective of the study is:

- To investigate and compare the PK profiles of MB02, US-licenced Avastin® (US Avastin®) and EU-approved Avastin® (EU Avastin®) to establish bioequivalence between the 3 study arms.

2.2 Secondary Objectives

The secondary objectives of the study are:

- Evaluation and comparison of derived PK parameters not covered by the primary endpoint for MB02, US Avastin® and EU Avastin®
- To compare the safety profile of MB02 and US Avastin® and EU Avastin®
- To compare the immunogenicity of MB02, US Avastin® and EU Avastin®

3 ENDPOINTS

3.1 Primary Endpoints

The PK outcome endpoints of MB02 and Avastin® derived from the serum concentration-time profile from Days 1 to 100 following IV administration are as follows:

- area under the serum concentration- time curve from time zero to infinity ($AUC_{[0-\infty]}$)
- maximum observed serum concentration (C_{max})

3.2 Secondary Endpoints

- Evaluation of all other PK parameters for MB02, US-licenced Avastin® and EU-approved Avastin®, including
    - Time of maximum observed serum concentration (t_{max})
    - AUC from time zero to the time of the last observable concentration ($AUC_{[0-t]}$)
    - Clearance (CL)
    - Apparent serum terminal elimination half-life ($t_{1/2}$)
- The safety outcome measures for this study are as follows:
    - incidence and severity of AEs
    - incidence of laboratory abnormalities, based on haematology, clinical chemistry, and urinalysis test results
    - 12-lead electrocardiogram (ECG) parameters
    - vital sign measurements
    - physical examinations.

- The immunogenicity of MB02, US Avastin® and EU Avastin®
    - Determination of serum concentrations of anti-MB02 and anti-Avastin® antibodies.

4 INVESTIGATIONAL PLAN

4.1 Study Design

This will be a Phase 1, double-blind, randomised, parallel-group, single-dose 3-arm study to investigate and compare the PK, safety and immunogenicity profile of MB02 with US and EU Avastin® in healthy male subjects. A total of 114 subjects will be randomised to one of following 3 arms in a 1:1:1 ratio:

- Arm 1: MB02 as a 90 minute IV infusion
- Arm 2: Avastin® sourced from the US, as a 90 minute IV infusion
- Arm 3: Avastin® sourced from the EU, as a 90 minute IV infusion.

Thirty-eight subjects will be dosed in each arm. Potential subjects will be screened to assess their eligibility to enter the trial within 30 days prior to study drug administration.

Subjects will be admitted to the Clinical Research Unit (CRU) on Day -1, and will be confined to the CRU until discharge on Day 8. On Day 1, subjects will receive a single 3 mg/kg IV dose of the study drug. Subjects will return on Days 10, 14, 21, 28, 42, 56, 78 and 100 for nonresidential visits for the collection of PK samples and safety assessments. Immunogenicity samples will be collected on Days 14, 28, 56, and 78.

The total duration of trial participation for each subject (from Screening through to the final visit) is anticipated to be a maximum of 19 weeks. The end of the study is defined as the date of the last subject's last assessment (planned or unplanned).

A Schedule of Assessments is presented in Appendix 1.

4.2 Discussion of Study Design

The clinical PK properties of MB02 have been investigated in a previous open-label study conducted in metastatic colorectal cancer patients, which demonstrated that MB02 was bioequivalent to the RMP, Avastin®. This study aims to compare PK, immunogenicity and safety of MB02 versus EU and US-sourced Avastin® in healthy volunteers.

A single-dose, parallel-group design was chosen for this study due to the long half-life of bevacizumab of approximately 20 days, and the potential of ADA response, as recommended in EMA guidance [2,5] The study will be double-blinded as the secondary objective of comparing the safety profile of MB02 to Avastin® is considered subjective. The collection of serum samples through Day 1 to Day 100 will allow the PK parameters for MB02 and Avastin® to be adequately described.

Assessment of PK in a single-dose study in healthy volunteers was expected to be the most sensitive setting possible to detect differences in PK between MB02 and Avastin®. The use of

healthy volunteers avoids factors that can confound the interpretation of PK, safety and tolerability results in patient studies, including varying tumour burden and complications arising from the disease state, comorbidities and concomitant therapies and medications. The selection of only male subjects avoids the documented influence of sex upon bevacizumab clearance.[5]

4.3 Selection of Doses in the Study

Intravenous doses were chosen for this study as this is the intended clinical route of administration for MB02 and Avastin®. Therapeutic doses in the prescribing instructions for Avastin® range from 5 mg/kg every 2 weeks up to 15 mg/kg every 3 weeks. A lower dose level of 3 mg/kg for MB02 and Avastin® was chosen based upon the dosages used in previously published studies of bevacizumab PK[6,7], and to balance considerations of safety in healthy volunteers and the need to capture the full PK profile. The results of the in vivo repeating dose toxicokinetic study demonstrated the similarity of MB02 to the RMP, with regards to the pharmacokinetic parameters, and further supported the safe administration of MB02 at doses <5 mg/kg in clinic.

5 SELECTION OF STUDY POPULATION

5.1 Inclusion Criteria

Subjects must satisfy all of the following criteria at the Screening visit unless otherwise stated:

1. Males of any race, between 18 and 55 years of age, inclusive, at Screening.
2. Body mass index between 18.5 and 29.9 kg/m^2, inclusive, at Screening.
3. Total body weight between 60 and 95 kg, inclusive, at Screening.
4. In good health, determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital sign measurements, and clinical laboratory evaluations (congenital nonhaemolytic hyperbilirubinemia [eg, Gilbert's syndrome] is acceptable) at Screening or Check-in as assessed by the Investigator (or designee).
5. Relevant clinical laboratory evaluations of haematology, coagulation, urinalysis and clinical chemistry within normal range at Screening and Check-in as follows. A single repeat test will be allowed at each timepoint.
    - Absolute neutrophil count ≥1.5 × 10^9 L
    - Platelet count ≥100 × 10^9 L
    - Haemoglobin >10 g/dl
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ ULN
    - Alkaline phosphatase (ALP) ≤1.5 × ULN
    - Total bilirubin <1.5 × ULN (<51.30 µmol/L in subjects with Gilbert's syndrome)
    - Blood urea nitrogen ≤1.5 × ULN
    - Creatinine <132.63 µmol/L
    - Serum albumin: >35 g/L
    - Low density lipoprotein cholesterol ≤ ULN
    - High density lipoprotein cholesterol ≥ lower limit of normal
    - Creatine kinase (CK) <2 × ULN
    - International normalised ratio (INR) 0.8 to 1.3
    - Urine dipstick for proteinuria <2+
6. Systolic blood pressure ≥90 mmHg and ≤140 mmHg and diastolic blood pressure ≥50 mmHg and ≤90 mmHg at Screening and Check-in.
7. Subjects agree to use contraception as detailed in Section 7.6.
8. Able to comprehend and willing to sign an informed consent form (ICF) and to abide by the study restrictions. Subjects must have signed an informed consent before any study-related procedure or evaluation is performed.

5.2 Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria at the Screening visit unless otherwise stated:

1. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, haematological, pulmonary, cardiovascular, gastrointestinal, neurological, respiratory, endocrine, or psychiatric disorder, as determined by the Investigator (or designee).
2. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee).
3. Any current or recent history of active infections, including localised infections.
4. History of, or planned surgery, including suturing, dental surgery or wound dehiscence within 30 days of dosing, or within 30 days of the last study visit.
5. Presence of a nonhealing wound or fracture.
6. Known history of clinically significant essential hypertension, orthostatic hypotension, fainting spells or blackouts for any reason, cardiac failure or history of thromboembolic conditions.
7. Medically significant dental disease or dental neglect, with signs and/or symptoms of local or systemic infection that would likely require a dental procedure during the course of the study.
8. Clinically relevant history of alcoholism, addiction or drug/chemical abuse prior to Check-in, and/or positive alcohol breath test and/or urinary drug test screen (Appendix 3, confirmed by repeat) at Screening or Check-in.
9. History of bleeding disorders or protein C, protein S, and/or factor V Leiden deficiency.
10. History of clinically significant haemorrhage, epistaxis, GI bleeding, haemorrhoids and/or haemoptysis.
11. History of GI perforation, ulcers, gastro-oesophageal reflux, inflammatory bowel disease, diverticular disease, or any fistulae.
12. Alcohol consumption of >24 units per week. One unit of alcohol equals ½ pint (285 mL) of beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits.
13. Positive hepatitis panel, positive human immunodeficiency test (Appendix 3). Subjects whose results are compatible with prior immunisation and not infection may be included at the discretion of the Investigator.
14. Participation in a clinical study involving administration of an investigational drug (new chemical entity) in the past 90 days prior to Check-in, or within 5 half-lives of the investigational drug used in the study.
15. Use or intend to use slow-release medications/products considered to still be active within 30 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).

16. Use or intend use of any prescription medications/ nonprescription products known to alter drug absorption, metabolism, or elimination processes, including St. John's wort, within 30 days prior to Check-in, unless deemed acceptable by the Investigator or designee.
17. Use or intend to use any nonprescription medications/products including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations within 7 days prior to Check-in, unless deemed acceptable by the Investigator (or designee).
18. Have received a live or attenuated vaccine from 3 months prior to Screening, or have the intention to receive a vaccine during the study.
19. Intend to travel to a region where a vaccination will be required due to endemic disease within 3 months of dosing.
20. Previous treatment with an anti-VEGF antibody or any other protein or antibody targeting the VEGF receptor.
21. Use of tobacco- or nicotine-containing products within 1 year prior to Check-in, or positive cotinine test upon Screening or Check-in.
22. Receipt of blood products within 60 days prior to Check-in.
23. Donation of blood from 90 days prior to Screening, plasma from 14 days prior to Screening, or platelets from 42 days prior to Screening.
24. Poor peripheral venous access.
25. History of abnormal peripheral sensation including paraesthesia and/or numbness in arms and/or legs.
26. Have previously completed or withdrawn from this study or any other study investigating bevacizumab, and/or have previously received bevacizumab.
27. Subjects who, in the opinion of the Investigator (or designee), should not participate in this study.

Subjects may previously have been screened on a generic basis to determine their eligibility for inclusion in Phase 1 clinical studies conducted at the CRU. If generic Screening was performed within the specified study Screening window, selected study-specific procedures will be repeated either at an additional Screening visit or on admission to the CRU on Day -1. If generic Screening was performed outside the specified Screening window, all study-specific Screening assessments will be repeated either at an additional Screening visit or on admission to the CRU on Day -1.

5.3 Subject Number and Identification

After signing the ICF, subjects will be assigned a unique Screening number by the study site. Subjects will be assigned a subject number upon randomisation at the time of the first dosing occasion. Replacement subjects (Section 5.4) will be assigned a subject number corresponding to the number of the subject he is replacing plus 1000 (eg, Subject 1101 replaces Subject 101).

Subjects will be identified by subject numbers only on all study documentation. A list identifying the subjects by subject number and Screening number will be kept in the Site Master File.

5.4 Subject Withdrawal and Replacement

A subject is free to withdraw from the study at any time. In addition, a subject will be withdrawn from dosing if any of the following criteria are met:

- Change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects subject safety as determined by the Investigator (or designee)
- Noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the Investigator (or designee)
- Any clinically relevant sign or symptom that in the opinion of the Investigator (or designee) warrants subject withdrawal.

If a subject is withdrawn from dosing, the Sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic Case Report Form (eCRF). If a subject is withdrawn, efforts will be made to perform all Follow-up assessments, if possible (Appendix 1). Other procedures may be performed at Investigator's (or designee's) and/or Sponsor's discretion. If the subject is in-house, these procedures should be performed before the subject is discharged from the clinic. The Investigator (or designee) may also request that the subject return for an additional Follow-up Visit. All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator (or designee) to have stabilised.

Subjects who are withdrawn for nondrug related reasons may be replaced following discussion between the Investigator and the Sponsor. Subjects withdrawn as a result of AEs thought to be related to the study drug will generally not be replaced.

5.5 Study Termination

The study may be discontinued at the discretion of the Investigator (or designee), Sponsor, or Sponsor's Medical Monitor if any of the following criteria are met:

- Adverse events unknown to date (ie, not previously reported in any similar investigational study drug trial with respect to their nature, severity, and/or duration)
- Increased frequency and/or severity and/or duration of known, anticipated, or previously reported AEs (this may also apply to AEs defined at Check-in as baseline signs and symptoms)
- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of subjects
- Cancellation of drug development.

6 STUDY TREATMENTS

6.1 Description, Storage, Packaging, and Labelling

The IMP (MB02 IV solution, 25 mg/mL), US, and EU Avastin® (bevacizumab IV solution, 25 mg/mL) will be supplied by the Sponsor, along with batch/lot numbers and certificates of analysis.

MB02 and Avastin® will be diluted to the required dose for administration with 100 mL of sodium chloride (9 mg/mL, 0.9%) solution for injection using aseptic technique.[5]

6.2 Study Treatment Administration

Doses of MB02 and Avastin® will be administered as a slow IV infusion, (duration approximately 90 minutes). Subjects will be dosed in numerical order while supine.

In the event of a significant infusion reaction, the infusion will be slowed or stopped, depending on the symptoms/signs present.

In the event of acute hypertension (increase by >20mmHg diastolic or >160/100 mmHg if previously within normal limits) during the infusion, the infusion will be stopped and may be resumed at a slower rate if blood pressure returns to the pretreatment range within one hour.

If the infusion is slowed, the infusion should be completed at the slower rate, as tolerated. If the infusion is stopped, a single attempt to restart the infusions at a lower rate may be made after resolution of symptoms. Supportive care should be employed in accordance with the symptoms and signs.

Any changes or stopping of infusions should be recorded in the subject's eCRF alongside the AE which caused the slowing or stopping of the infusion.

6.3 Randomisation

The randomisation code will be produced by the statistics department at Covance Early Clinical Biometrics using a computer-generated pseudo-random permutation procedure. Subjects will be randomly assigned to 1 of 3 treatment arms and stratified into 2 groups based on weight (≥60.0 to <77.5kg, and ≥77.5 to <95.0 kg respectively). Prior to the start of the trial, a copy of the master randomisation code will be supplied to the Covance CRU pharmacy staff, PAREXEL pharmacy staff, the analyst at Covance Laboratories Ltd.

6.4 Blinding

The following controls will be employed to maintain the double blind status of the study:

- The Investigator and other members of staff involved with the study will remain blinded to the treatment randomisation code during the assembly procedure.

To maintain the blind, the Investigator will be provided with a sealed randomisation code for each subject, containing coded details of the treatment. These individual sealed envelopes will be kept in a limited access area that is accessible 24 hours a day. If, in order to manage subject safety (in the event of possibly treatment related SAEs or severe AEs), the decision to

unblind resides with the Investigator. Whenever possible, and providing it does not interfere with or delay any decision in the best interest of the subject, the Investigator will discuss the intended code-break with the Sponsor. If it becomes necessary to break the code during the study, the date, time and reason will be recorded in the subject's source data and on the individual envelope and will be witnessed by a second person.

Where the subject experiences a suspected unexpected serious adverse reaction (SUSAR) the Sponsor pharmacovigilance team may be unblinded prior to notification of the relevant competent authorities and ethics committee in order to provide appropriate information.

6.5 Study Treatment Compliance

The following measures will be employed to ensure treatment compliance:

- All doses will be administered under the supervision of suitably qualified study site staff
- At each dosing occasion, a predose and postdose inventory of MB02 and Avastin® will be performed.

6.6 Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of the IMP and study drugs received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until completion of the study.

At the completion of the study, retention samples allowing for 5 separate full characterisation assays to be performed will be retained at the Study Site. Any additional unused MB02 and Avastin® will be returned to the Sponsor or disposed of by the Study Site, per the Sponsor's written instructions.

7 CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

7.1 Concomitant Medications

Subjects will refrain from use of any prescription and/or nonprescription medications/products during the study until the final visit, unless the Investigator (or designee) and/or Sponsor have given their prior consent.

Paracetamol (up to 2 g/day for up to 3 consecutive days) is an acceptable concomitant medication if prescribed by the Investigator due to an AE. The administration of any other concomitant medications during the study is prohibited without prior approval of the Investigator (or designee), unless its use is deemed necessary in a medical emergency. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data.

Premedication for infusions is not planned. However, if an infusion reaction occurs, appropriate medication may be used as determined by the Investigator.

7.2 Diet

While confined at the study site, subjects will receive a standardised diet at scheduled times that do not conflict with other study-related activities. Subjects will be fasted overnight (at least 8 hours) before collection of fasting blood samples for safety laboratory tests.

On Day 1 the subjects will be fasted overnight (at least 8 hours) prior to dosing. Food will be allowed from 4 hours post end of infusion.

Caffeine-containing foods and beverages will not be allowed from 36 hours before Check-in until discharge and from 36 hours before non-residential visits.

Decaffeinated tea and coffee will be available with morning and evening meals whilst resident at the clinic.

Consumption of alcohol will not be permitted from 48 hours prior to Check-in and non-residential visits. Alcohol intake will be limited to a maximum of 2 units/day on all other days, whilst not in the CRU, from Screening through the final visit.

7.3 Smoking

Subjects will not be permitted to use tobacco- or nicotine-containing products within 1 year prior to Check-in until the final visit.

7.4 Exercise

Subjects are required to refrain from strenuous exercise from 7 days before Check-in and 7 days before non-residential visits and will otherwise maintain their normal level of physical activity during this time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

7.5 Blood Donation

Subjects are required to refrain from donation of blood from 90 days prior to Screening, plasma from 14 days prior to Screening, or platelets from 42 days prior to Screening until 90 days after the final visit.

7.6 Contraception

Subjects with partners of childbearing potential must use a male barrier method of contraception (ie, male condom with spermicide) in addition to a second method of acceptable contraception. The acceptable methods of contraception include:

- Intrauterine device (IUD; eg, Mirena)
- Established use of oral, implanted, transdermal, or hormonal method of contraception associated with inhibition of ovulation

- Male sterilisation, with verbal confirmation of surgical success
- Bilateral tubal ligation
- Established use of progesterone only oral contraception, where inhibition of ovulation is not the primary mode of action
- Diaphragm, cap, or sponge in conjunction with spermicide.

Subjects who practice true abstinence, because of the subject's lifestyle choice (ie, the subject should not become abstinent just for the purpose of study participation) are exempt from contraceptive requirements. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. If a subject who is abstinent at the time of signing the ICF becomes sexually active they must agree to use contraception as described above.

Sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms are used from the time of dosing until 120 days after dosing. Male subjects are required to refrain from donation of sperm from Check-in until 120 days after the dose of study drug.

For subjects who are exclusively in same sex relationships, a barrier method of contraception (ie male condom) should be used from the time of dosing until 120 days after dosing.

8 STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- Dosing
- Blood samples
- Any other procedures (ECGs will be scheduled before vital sign measurements).

8.1 Pharmacokinetic Assessments

8.1.1 Pharmacokinetic Blood Sample Collection and Processing

Blood samples (approximately 1 x 3.5 mL for bevacizumab) will be collected by venepuncture or cannulation at the times indicated in the Schedule of Assessments in Appendix 1. Procedures for collection, processing, and shipping of PK samples will be detailed in a separate document.

8.1.2 Analytical Methodology

Serum concentrations of bevacizumab will be determined using a validated analytical procedure. Specifics of the analytical method will be provided in a separate document.

8.2 Immunogenicity Assessments

8.2.1 Immunogenicity Blood Sample Collection and Processing

Blood samples (approximately 1 x 3.5 mL) will be collected by venepuncture or cannulation at the times indicated in the Schedule of Assessment in Appendix 1. Procedures for cannulation, processing and shipping of immunogenicity samples will be detailed in a separate document.

8.2.2 Analytical Methodology

Serum concentrations of anti-MB02 and anti-Avastin® antibodies will be determined using a validated analytical procedure. Specifics of the analytical method will be provided in a separate document.

8.3 Safety and Tolerability Assessments

8.3.1 Adverse Events

Adverse event definitions, assignment of severity and causality, and procedures for reporting SAEs are detailed in Appendix 2.

The condition of each subject will be monitored from time of signing the ICF to final discharge from the study. In addition, subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as “How have you been feeling since you were last asked?”, at least once each day while resident at the study site and at each study visit. Subjects will also be encouraged to spontaneously report AEs occurring at any other time during the study.

Any AEs and remedial action required will be recorded in the subject’s source data. The nature, time of onset, duration, and severity will be documented, together with an Investigator’s (or designee’s) opinion of the relationship to drug administration.

Adverse events recorded during the course of the study will be followed up, where possible, until resolution. This will be completed at the Investigator’s (or designee’s) discretion.

8.3.2 Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations (including clinical chemistry, haematology, urinalysis, coagulation, and serology) at the times indicated in the Schedule of Assessments in Appendix 1. Clinical laboratory evaluations are listed in Appendix 3.

Subjects will be asked to provide urine samples for a drugs of abuse screen, cotinine test, and undergo an alcohol breath test at the times indicated in the Schedule of Assessments in Appendix 1. An Investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

8.3.3 Vital Signs

Supine blood pressure, supine pulse rate, respiratory rate, oral body temperature and pulse oximetry will be assessed at the times indicated in the Schedule of Assessments in Appendix 1. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

All measurements will be performed singly, and repeated once if outside the relevant clinical reference range.

Subjects must be supine for at least 5 minutes before blood pressure and pulse rate measurements.

8.3.4 12-Lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 1. Single 12-lead ECGs will be repeated once if either of the following criteria apply:

- QT interval corrected for heart rate using Fridericia's method (QTcF) > 500 msec
- QTcF change from the baseline (predose) is > 60 msec.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The Investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

8.3.5 Physical Examination

A full physical examination or symptom-directed physical examination will be performed at the timepoints specified in the Schedule of Assessments in Appendix 1.

9 SAMPLE SIZE AND DATA ANALYSES

A detailed statistical analysis plan (SAP) describing full details of the planned analyses will be issued to the Sponsor for review and will be finalised prior to database lock. The following analyses represent an outline of the planned methodology.

9.1 Determination of Sample Size

Up to 114 subjects will be enrolled in order that 108 complete the study.

A sample size of 36 subjects per arm (108 subjects in total) will provide at least 90% power for all the pairwise comparisons for primary endpoints (AUC and C_{max}) using a percent coefficient of variation (CV%) of 25% in both PK parameters for the similarity objective if the true ratio is equal to 1.05 or less.

A conservative estimate of CV% was based on a prior MB02 study [8] and information from the public domain [9]. Model-based simulations from a developed population PK literature

model, accounting for similarity between bevacizumab sources (EU/US), intrinsic PK altering factors (body weight, sex, serum albumin and alkaline phosphatase), between subject variability and residual variability, showed that a sample size of 90 subjects provided at least 90% probability of concluding PK similarity for the all pairwise comparisons in terms of C_{max} and $AUC_{(0–\infty)}$.

Simulations also showed that the probability of concluding PK similarity in terms of $AUC_{(0\text{-}t)}$ is almost the same as $AUC_{(0–\infty)}$

A maximum of 5% loss of data due to premature discontinuation is expected therefore, the sample size is increased to 114 subjects in total, with 38 subjects per arm.

9.2 Analysis Populations

9.2.1 Pharmacokinetic Population

The PK population will include all subjects who received the full dose of MB02 or Avastin®, did not have any major protocol deviations, and have evaluable PK data for at least one timepoint.

Further details of subjects considered for exclusion from the PK population will be provided in the SAP, detailing major deviations (for statistical analyses) prior to database lock.

9.2.2 Safety Population

The safety population will include all subjects exposed to MB02 or Avastin®, and have at least 1 postdose safety assessment.

9.3 Pharmacokinetic Analyses

The primary PK parameter endpoints are C_{max} and $AUC_{0\text{-}\infty}$ for bevacizumab. The secondary PK endpoints will include all other PK parameters for bevacizumab, including t_{max}, $t_{1/2}$, CL and $AUC_{(0\text{-}t)}$.

The serum PK parameters of bevacizumab will be calculated using standard noncompartmental methods. An analysis of covariance model will be used to analyse the log-transformed primary PK parameters ($AUC_{[0\text{-}\infty]}$ and C_{max}) and $AUC_{(0\text{-}t)}$. The model will include a fixed effect for treatment and body weight as a covariate.

All other PK parameters will not be subject to inferential statistical analysis.

Estimates of geometric mean ratios together with the corresponding 90% confidence intervals (CI) will be derived for the comparisons of the PK parameters as follows:

- MB02 versus EU Avastin®
- MB02 versus US Avastin®
- EU Avastin® versus US Avastin®

PK similarity will be achieved if the 90% CIs for the biosimilar-to-reference ratios of PK endpoints ($AUC_{[0–\infty]}$ and C_{max}) fall within the predefined 0.80–1.25 acceptance similarity

criteria for all 3 pairwise comparisons; MB02 versus EU-approved Avastin®; MB02 versus US-licenced Avastin®; and EU-approved Avastin® versus US-licenced Avastin®.

9.4 Safety Analysis

All AEs will be listed and summarised using descriptive methodology. All observed or patient-reported AEs will be graded by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. The incidence of AEs for each treatment will be presented by severity and by association with the study drugs as determined by the Investigator (or designee). Each AE will be coded using the Medical Dictionary for Regulatory Activities. All safety data will be listed and summarised as appropriate.

Immunogenicity data (overall ADA incidence and titers, and neutralising ADA results) will be listed. A summary of the number and percent of subjects testing positive for ADA or neutralising antibodies before the dose of MB02, EU Avastin®, or US Avastin® (Day -1) and at scheduled postdose assessments will be presented by treatment arm. All safety data and immunogenicity data summaries will be based on the safety analysis population. Select analyses may be repeated for subsets with or without ADA and de novo ADA formation as appropriate.

9.4.1 Medical Safety Monitoring

It is the responsibility of the Investigator to oversee the safety of the subject at the clinical site. This safety monitoring will include careful assessment and appropriate reporting of AEs as noted above.

A safety review committee comprising at minimum the Principal Investigator and Sponsor Medical Contact will review all available safety data monthly, or more frequently if indicated. In advance of each meeting, Covance will prepare blinded tables/listings based on a snapshot of data available in the eCRFs, including those for subject status, AEs, and laboratory results.

9.5 Interim Analysis

No interim analyses are planned for this study.

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Auditing

Quality control and quality assurance will be performed according to Covance standard operating procedures (SOPs) or per Sponsor request and as applicable according to the contract between Covance and the Sponsor.

The study may be audited or reviewed by an independent quality assurance department, Ethics Committee (EC), and/or regulatory authority at any time. The Investigator will be given notice before an audit occurs. The study site will permit study-related monitoring, audits, EC review, and regulatory inspections by providing direct access to source data/documents.

Measures will be undertaken to protect the confidentiality of records that could identify subjects, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements.

10.2 Monitoring

Covance will designate an independent Study Monitor who will be responsible for monitoring this clinical study. The Study Monitor will monitor the study conduct, eCRF and source documentation completion and retention, and accurate study drug accountability. To this end, the Study Monitor will visit the study site at suitable intervals and be in frequent contact through verbal and written communication. It is essential that the Study Monitor has access to all documents, related to the study and the individual participants, at any time these are requested. In turn, the Study Monitor will adhere to all requirements for subject confidentiality as outlined in the ICF. The Investigator and Investigator's staff will be expected to cooperate with the Study Monitor, to be available during a portion of the monitoring visit to answer questions, and to provide any missing information.

11 DATA HANDLING AND RECORD KEEPING

11.1 Data Handling

Covance will be responsible for data management of this study, including quality checking of the data. The study site will be responsible for data entry into the electronic data capture (EDC) system. A comprehensive validation check program will verify the data. Discrepancies will be generated automatically in the system at the point of entry or added manually for resolution by the study site staff.

Covance will produce a Data Management Plan that describes the quality checking to be performed on the data. Laboratory data and other electronic data will be sent directly to Covance, using Covance standard procedures to handle and process the electronic transfer of these data.

11.2 Case Report Form

Data from all parts of the trial will be captured on source paper or electronic data documents and then entered into the EDC system by staff at the trial site. Following data entry, the eCRF pages and the data entry will undergo quality control checks in accordance with Covance procedures. Any discrepancies will be resolved in the database.

Following all data validation steps, the Principal Investigator (or designee) will electronically sign the completed electronic data prior to database lock.

11.3 Records

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the in the study site archive for at least 5 years after the end of the study. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 Ethics Committee

Prior to the start of the study, the following documents will be reviewed and approved by the appropriate EC:

- protocol
- ICF

The EC will be informed by the Investigator (or designee) of any changes to the approved protocol.

The EC must provide written approval of any substantial protocol amendments likely to affect the safety of the subjects or the conduct of the study. The EC must be notified of nonsubstantial protocol amendments.

The EC will be informed by the Investigator (or designee) of serious and unexpected AEs. The Investigator will provide the EC with progress reports at least annually and a report following completion, termination, or discontinuation of the Investigator's participation in the study.

12.2 Regulatory Considerations

The study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences Ethical Guidelines
- International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice
- Applicable local laws and regulations.

The Investigator will be responsible for the overall conduct at the study site and adherence to the requirements of the ICH guidelines and all other applicable local regulations.

12.3 Informed Consent

Prior to starting participation in the study, each subject will be provided with a study-specific ICF giving details of the study drugs, procedures, and potential risks of the study. Subjects will be instructed that they are free to obtain further information from the Investigator (or designee) and that their participation is voluntary and they are free to withdraw from the study at any time.

Following discussion of the study with CRU personnel, subjects will sign 2 copies of the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving their informed consent. One copy will be given to the subject, and the other will be maintained in the subject's records.

12.4 Subject Confidentiality

The results from Screening and data collected during the study will be recorded in the subject's eCRF. To maintain confidentiality, the subjects will be identified only by a unique subject identification number.

Subject medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the ICF signed by the subject, unless permitted or required by law.

12.5 Protocol Amendments

Substantial protocol amendments will be submitted to the EC and to regulatory authorities in accordance with local regulatory requirements. Approval must be obtained from the EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to subjects or any nonsubstantial changes, as defined by regulatory requirements.

13 ADMINISTRATIVE ASPECTS

13.1 Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

13.2 Reports and Publications

Any publication of the results, either in part or in total (eg, articles in journals or newspapers, oral presentations, abstracts) by the Investigator or their representative, shall require prior notification and review, within a reasonable time frame, by the Sponsor, and cannot be made in violation of the Sponsor's confidentiality restrictions or to the detriment of the Sponsor's intellectual property.

13.3 Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

14 REFERENCES

1. MB02– Investigator's Brochure. (Version 6.0, 28 July 2017)

2. EMA Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: clinical and nonclinical issues, CHMP/BMWP/42832/2005 Rev1 of 18 December 2014 (effective 1 July 2015)

3. Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product. US Dept of Health and Human Services; Food and Drug Administration; Centre

for Drug Evaluation and Research (CDER); Center for Biologics Evaluation and Research (CBER). December 2016.

4. EMA Guideline on similar biological medicinal products. CHMP/437/04 Rev 1 of 23 October 2014 (effective 30 April 2015).

5. Genentech Inc (2016) Avastin® (bevacizumab) prescribing information. http://www.gene.com/download/pdf/avastin_prescribing.pdf. Accessed 29 June 2017.

6. Willem Hettema et. al. A randomised, single-blind, Phase I trial (INVICTAN-1) assessing the bioequivalence and safety of BI 695502, a bevacizumab biosimilar candidate, in healthy subjects. *Expert Opin Investig Drugs.* 2017, Aug;26(8):889-896

7. N Tajima et. al. A phase 1 study comparing the proposed biosimilar BS-503a with bevacizumab in healthy male volunteers. *Pharmacol Res Perspect*. 2017, 20;5(2):e00286.

8. mAbxience; Bioequivalence Study Bevacizumab Biosimilar (BEVZ92) Versus Bevacizumab (AVASTIN®) in First-line Treatment mCRC Patients (MB02-A-01-13). mAbxience SA, Madrid, Spain.

9. Beverly Knight, Danielle Rassam, Shanmei Liao, Reginald Ewesuedo. A phase I pharmacokinetics study comparing PF-06439535 (a potential biosimilar) with bevacizumab in healthy male volunteers. *Cancer Chemother Pharmacol*. 2016; 77: 839–846.

15 APPENDICES

Appendix 1: Schedule of Assessments

Study Procedures	Screening	Day -1	Day 1	Day 2	Day 3 to Day 8	Day 10	Day 14 to Day 78	Day 100
Informed consent	X							
Inclusion/exclusion criteria	X	X	X					
Demographic data	X							
Medical history	X	X[a]						
Urinary drug screen and cotinine test	X	X						
Alcohol breath test	X	X						
Serology	X							
Height and body weight[b]	X	X						
Study residency:								
Randomisation			X					
Check-in		X						
Check-out					Day 8			
Nonresidential visit[g]	X					X	Day 14, 21, 28, 42, 56, 78	X
Study drug administration:								
MB02 or Avastin®			Day 1 (0 h)					
Pharmacokinetics:								
Blood sampling[e]			Predose, 1.5[f], 2, 3, 4, 5, 6, 8, 12 h	24 h	Day 3, Day 4, Day 5, Day 6, Day 7 and Day 8	X	Day 14, Day 21, Day 28, Day 42, Day 56, Day 78	X
Immunogenicity:								
Blood sampling		X					Day 14, 28, 56, 78	
Safety and tolerability:								
Adverse event recording	X	X	Ongoing	X	X	X	X	X

Study Procedures	Screening	Day -1	Day 1	Day 2	Day 3 to Day 8	Day 10	Day 14 to Day 78	Day 100
Serious adverse event recording	X	X	Ongoing	X	X	X	X	X
Prior/concomitant medication monitoring	X	X	Ongoing	X	X	X	X	X
Clinical laboratory evaluations	X	X					Day 14, 21, 28, 42, 56, 78	X
Supine blood pressure, pulse rate, respiratory rate[e]	X	X	Predose, 0.5, 1, 1.5h[f], 2h	X	Day 5, Day 8	X	Day 21	X
Pulse oximetry	X							
Oral body temperature	X			X		X	Day 21	X
12-lead ECG	X	X			Day 3, Day 8			X
Physical examination	X[c]	X[d]						X[d]

Abbreviations: ECG = electrocardiogram
[a] Interim medical history
[b] Height measured at Screening only
[c]. Can be performed between the Screening visit and predose assessments
[d]. Symptom-directed physical examination
[e]. All times stated are post-start of infusion.
[f]. 1.5 hour timepoint is immediately after end of infusion.
[g] All nonresidential visits on Days 14 to 100 can be conducted within ±1 day of the planned date.

Appendix 2: Adverse Event Reporting

Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and/or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

The causal relationship between an AE and the study drug will be defined as below:

- **Not Related**: when the AE is definitely caused by the subject's clinical state, or the study procedure/conditions
- **Unlikely Related**: when the temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE
- **Possibly Related**: when the AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the subject's clinical state or the study procedures/conditions
- **Probably Related**: when the AE has a reasonable time relationship to study drug administration and is unlikely to be attributed to concurrent disease or other drugs or chemicals
- **Related**: when the AE follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesised cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced

The severity of an AE or SAE will be recorded in the eCRF following the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, outlined below:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care activities of daily living
- Grade 4 Life-threatening consequences; urgent intervention indicated
- Grade 5 Death related to AE

An AE that is assessed as severe (CTCAE Grade 3 or higher) should not be confused with a SAE. Severity is a category utilised for rating the intensity of an event; both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets one of the predefined outcomes, as described in the section "Serious Adverse Events", outlined below.

Every reasonable effort will be made to follow-up subjects who have AEs. Any subject who has an ongoing AE at the final visit will be followed up, where possible, until resolution or until, in the opinion of the Investigator, the event is stabilised or determined to be chronic. Details of AE follow-up or resolution must be documented in the eCRF. This will be completed at the Investigator's (or designee's) discretion.

Adverse Drug Reactions

All noxious and unintended responses to an IMP (ie, where a causal relationship between an IMP and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions.

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator's Brochure for an unapproved IMP).

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 stabilised or determined to be chronic. Details of AE follow-up or resolution must be documented in the eCRF.

Subjects should be followed up until final discharge from the study, and any AEs that occur during this time should 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 randomisation 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 final discharge from the study. 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, recovering, not yet recovered, recovered with sequelae, death [with date and cause reported]).

Serious Adverse Events

A serious AE (SAE) is defined as any untoward medical occurrence that at any dose either:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered SAEs when, based upon appropriate medical judgement, they may jeopardise the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. These events should be collected in the eCRF under the seriousness criteria "Important Medical Event".

Instances of death or congenital abnormality, if brought to the attention of the Investigator at any time after cessation of the study treatment and considered by the Investigator to be possibly related to the study treatment, will be reported to the Sponsor.

Definition of Life-threatening

An AE is life-threatening if the subject was at immediate risk of death from the event as it occurred (ie, does not include a reaction that might have caused death if it had occurred in a more serious form). For instance, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

Definition of Hospitalisation

Adverse events requiring hospitalisation should be considered serious. In general, hospitalisation signifies that the subject has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment which would not have been appropriate at the CRU. When in doubt as to whether hospitalisation occurred or was necessary, the AE should be considered as serious.

Hospitalisation for elective surgery or routine clinical procedures, which are not the result of an AE, need not be considered AEs and should be recorded on a Clinical Assessment Form and added to the electronic Case Report Form. If anything untoward is reported during the procedure, this must be reported as an AE and either 'serious' or 'nonserious' attributed according to the usual criteria.

Serious Adverse Event Reporting

The Investigator will complete an SAE report form and forward it by facsimile to the Sponsor Safety Department immediately (no more than 24 hours) after becoming aware of an SAE.

Full details for SAE reporting and contact information can be found in the Site Safety Instruction.

All serious adverse reactions will be considered as SUSARs, and will follow the expedited SUSAR reporting process described below. The Investigator should not wait to receive additional information to fully document the event before notification of a SAE, though additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained.

Instances of death, congenital abnormality, or an event that is 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 Safety department within 24 hours.

Other events subject to immediate notification (within 24 hours), include but are not limited to:

- Pregnancy of female partner of a study subject
- Infusion site reaction (grade 3 according to the CTCAE and higher or classified as serious to be reported)
- Medication errors, namely overdose, leading to a suspected adverse reaction.

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

Pregnancies of the female partner of a male subject 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 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. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, 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.

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 (eg, Investigators Brochure for an unauthorised investigational medicinal product or summary of product characteristics for an authorised product).

All SUSARs will be the subject of expedited reporting. The Sponsor and/or delegate shall ensure that all relevant information about a SUSAR that is fatal or life-threatening is reported to the relevant competent authorities and EC 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 EC 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 stabilised or determined to be chronic.

Appendix 3: Clinical Laboratory Evaluations

Clinical chemistry:	**Haematology:**	**Urinalysis:**
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Blood urea nitrogen Calcium Chloride Total cholesterol HDL cholesterol LDL cholesterol Creatinine Creatine kinase Gamma-glutamyl transferase **Lactate** dehydrogenase Glucose Inorganic phosphate Potassium Sodium Total bilirubin Direct bilirubin Total protein Triglycerides Urea Uric acid	Haematocrit Haemoglobin Mean cell haemoglobin Mean cell haemoglobin concentration Mean cell volume Platelet count Red blood cell (RBC) count White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Blood Glucose Ketones pH Protein Specific gravity Urobilinogen Microscopic examination
Serology[a]:	**Urinary drug screen[b]:**	**Coagulation**
Hepatitis B surface antigen Hepatitis B surface antibody (anti-HBs) Hepatitis B core antibody (anti HBc) Hepatitis C antibody Human immunodeficiency (HIV-1 and HIV-2) antibodies	Including but not limited to: Cotinine Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Methadone Phencyclidine Opiates Tetrahydrocannabinol/cannabinoids Tricyclic antidepressants Alcohol breath test	International normalised ratio Prothrombin time Activated partial thromboplastin time

[a] Only analysed at Screening
[b] Only analysed at Screening and Check-in.

Appendix 4: Total Blood Volume

The following blood volumes will be withdrawn for each subject.

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Clinical laboratory evaluations	9.7	9	87.3
Serology	3.5	1	3.5
Bevacizumab pharmacokinetics	3.5	24	84
Immunogenicity	3.5	5	17.5
Total:			192.3

If extra blood samples are required, the maximum blood volume to be withdrawn per subject will not exceed the volume of a normal blood donation.