

<b>Protocol Title:</b>	A Randomised, Double-Blind, Three-Arm, Single Dose, Parallel Study To Compare the Pharmacokinetics, Safety and Immunogenicity of MB02-SP, MB02-DM (Bevacizumab Biosimilar Drugs) and US licenced Avastin® in Healthy Male Volunteers
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## PROTOCOL

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<b>Study Sites:</b>	Auckland Clinical Studies Ltd (ACS) Ground Floor 3 Ferncroft Street Grafton, Auckland 1010 New Zealand
	Christchurch Clinical Studies Trust Ltd (CCST) Level 4/264 Antigua Street, Christchurch Central City, Christchurch 8011 New Zealand
<b>Sponsor:</b>	mAbxience Research S.L. C/ Manuel Pombo Angulo, 28, 3rd floor, 28050, Madrid, Spain
<b>Contract Research Organization (CRO):</b>	Syneos Health, LLC/ Health UK Limited 1030 Sync Street, Morrisville, North Carolina 27560, United States

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**INVESTIGATOR AGREEMENT**

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

[REDACTED]  
Date / /

Principal Investigator  
Auckland Clinical Studies (ACS)

## INVESTIGATOR AGREEMENT

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

[REDACTED] Date

Principal Investigator  
Christchurch Clinical Studies Trust (CCST)

## SPONSOR AGREEMENT

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

[REDACTED] Date

Medical Advisor  
mAbxience Research S.L.

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

[REDACTED] Date

Clinical Project Manager  
mAbxience Research S.L.

## STUDY IDENTIFICATION

Syneos Health's Project Manager	[REDACTED] Project Manager, Early Phase, APAC Syneos Health 159 Port Rd, Hindmarsh SA 5007 Australia [REDACTED] [REDACTED]
Syneos Health's Medical Monitor	[REDACTED] Medical Director 159 Port Rd, Hindmarsh SA 5007 Australia Email: jon.rankin@syneoshealth.com [REDACTED] [REDACTED]
Sponsor's Project Manager	[REDACTED] Clinical Project Manager mAbxience Research S.L. C/ Manuel Pombo Angulo 28, 3 <sup>rd</sup> Floor 28050, Madrid [REDACTED] [REDACTED]
Sponsor's Medical Contact	[REDACTED] Medical Advisor mAbxience Research S.L. C/ Manuel Pombo Angulo 28, 3 <sup>rd</sup> Floor 28050, Madrid [REDACTED] [REDACTED]
Study Site	Auckland Clinical Studies (ACS) Ground Floor 3 Ferncroft Street Grafton, Auckland 1010 New Zealand
Principal Investigator	[REDACTED] [REDACTED] [REDACTED]
Clinical Laboratory	Labtests 37-41 Carbine Road Mt Wellington, Auckland 1060 New Zealand  LabPlus Gate 4, Building 31, Auckland City Hospital, Grafton, Auckland 1148 New Zealand

Study Site	Christchurch Clinical Studies Trust (CCST) Level 4/264 Antigua Street, Christchurch Central City, Christchurch 8011 New Zealand
Principal Investigators	[REDACTED] [REDACTED] [REDACTED]
Clinical Laboratory	Canterbury Health Laboratories Cnr Tuam and Hagley Ave Opposite Churchill Hospital Christchurch 8011 New Zealand
Bioanalytical Laboratory	Immunochemistry Department Covance Laboratories Ltd. Otley Road Harrogate, HG3 1PY UK
Statistician	[REDACTED] Biostatistician 159 Port Rd, Hindmarsh SA 5007 Australia [REDACTED] [REDACTED] [REDACTED]

## SYNOPSIS

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

**Objectives:**

The primary objective of the study is:

- To investigate and compare the pharmacokinetic (PK) profiles of MB02-SP (MB02 standard procedure), MB02-DM (MB02 defined media) and US-licensed Avastin® (US 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-SP, MB02-DM and US Avastin®.
- To compare the safety profile of MB02-SP, MB02-DM and US Avastin®.
- To compare the immunogenicity of MB02-SP, MB02-DM and US 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-DM with MB02-SP and US 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 3. On Day 1, subjects will receive a single 1 mg/kg intravenous (IV) dose of the study drug. Subjects will return on Days 4, 5, 6, 7, 8, 10, 14, 21, 28, 42, 56, 78 and 100 for non-residential visits for the collection of pharmacokinetics (PK) and safety assessments. Immunogenicity samples will be collected on Days -1, 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<sup>2</sup>, inclusive, and a body weight between 50 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 and exclusion criteria.

**Test products, dose, and mode of administration:**

1 mg/kg MB02-SP, administered as a 90-minute IV infusion

1 mg/kg MB02-DM, administered as a 90-minute IV infusion

1 mg/kg US Avastin®, administered as a 90-minute IV infusion

**Duration of treatment:**

Planned Screening duration: up to 30 days.

Planned study duration (Screening to end of study 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-DM, anti-MB02-SP and anti-Avastin® antibodies at the following time points (five samples in total): at baseline, prior to study drug administration, which is between Day -1 and Day 1 prior to dosing (time 0 hours) and on days: 14, 28, 56 and 78.

**Statistical methods:**

The primary PK parameters are  $C_{max}$  and  $AUC_{(0-\infty)}$ . The PK parameters for bevacizumab will be calculated using standard non-compartmental 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-SP versus MB02-DM
- MB02-SP versus US Avastin®
- MB02-DM 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-SP versus MB02-DM; MB02-SP versus US Avastin®; and MB02-DM versus US 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 5.0. 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-SP, MB02-DM, or US Avastin® (Day -1) and at scheduled post dose 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)<sup>1</sup> 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 different countries outside the European Union, and, as part of the clinical development plan, one first-in-human (FIH) study in colorectal cancer patients and two pivotal clinical trials have already been completed: a phase I comparative pharmacokinetic (PK), safety and immunogenicity study in healthy male volunteers and, a phase III comparative efficacy, safety and immunogenicity study in patients with stage IIIB/IV non-squamous, non-small cell lung cancer (NSCLC). 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.<sup>2</sup> 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

In the earlier phases of its development, the biosimilar bevacizumab candidate MB02 was manufactured according to good manufacturing practice (GMP) at CMC Biologics/Aptuit and was referred to as BEVZ92. The manufacturing process was then transferred to other facilities in Spain (GH Genhelix S.A.), and due to the change of manufacturing sites and the associated CMC procedures, the product used in the development program for MB02 intended to support mAbxience's regulatory submissions in highly regulated countries (EU, US and JP) was MB02-SP. More recently, an optimized upstream manufacturing process was implemented for MB02, using fully chemically defined media for cell culture, meeting most up-to-date industry and regulatory expectations (this product is referred to as MB02-DM). An in vitro analytical comparability was performed and confirmed the high comparability of MB02 manufactured by either manufacturing processes.

A first-in-human study in patients with metastatic colorectal cancer (BEVZ92-A-01-13) was 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 this study, a MB02 drug product made at a different manufacturing site to the to-be marketed product was used and therefore, only safety data is included here to contribute to the overall benefit/risk assessment.

As part of the clinical development programme for MB02, and, in order to obtain evidence on similar PK, efficacy and safety, including immunogenicity, two pivotal clinical studies were conducted with MB02-SP and completed.

One study (MB02-A-02-17) was a double-blind, randomised, parallel-group, single-dose 3 arm study in 114 healthy male volunteers to compare pharmacokinetic (PK), safety and immunogenicity between MB02 and RMP (Avastin). The primary objective of the study was to investigate and compare the PK profiles of MB02, US Avastin®, and EU Avastin® to establish bioequivalence between the 3 study arms. The evaluation and the comparison of the derived PK parameters not covered by the primary endpoints for MB02, US Avastin®, and EU Avastin® were included within the secondary objectives of the study. The primary endpoints were AUC(0-inf) and Cmax. PK similarity between MB02 and the RMP was achieved if the 90% CIs for MB02 to RMP ratios for the aforementioned endpoints fell within the predefined equivalence margin, [0.80–1.25]. Statistical analysis for equivalence was also undertaken for a secondary PK endpoint, area under the curve from time zero to the time of last measurable concentration (AUC0-t)."

The second pivotal study (MB02-C-02-17) is a multicenter, randomized, double-blind study conducted in 627 patients with non-squamous non-small cell lung cancer, stage IIIB/IV to assess and compare efficacy, safety and immunogenicity of MB02 with EU-approved Avastin® in combination with carboplatin and paclitaxel in patients with Stage IIIB/IV non-squamous NSCLC. The primary study objective was to confirm therapeutic equivalence in terms of response, i.e. to compare the ORRs 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), as well as assess the PFS and overall survival at week 18 and at week 52 compared to Avastin®.

MB02/Avastin® plus chemotherapy was 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 which point no further assessments of efficacy would be made. Subjects eligible were randomized centrally in a 1:1 manner and stratified by sex (male/female), smoking status (smoker/non-smoker), disease diagnosis (newly diagnosed/recurrent disease) and disease stage (IIIB/IV).

### 1.3.1 Pharmacokinetics

#### Pharmacokinetics in Study MB02-A-02-17

A total of 114 subjects (38 subjects in each arm) were included in the PK population.

On Day 1, subjects received a single 3 mg/kg IV dose of the study drug. Subjects were followed for up to 100 days for the collection of PK samples, safety and immunogenicity assessments. The mean demographic parameters of age, gender, race, weight and height were well distributed across treatment arms and all subjects in the MB02, US-Avastin® and EU-Avastin® treatment arms completed the study.

Following the 90-minute IV infusion of 3 mg/kg doses of MB02, US or EU Avastin® on Day 1, the maximum observed serum concentrations of bevacizumab were delayed, with median tmax occurring between 2.51 and 4 hours after the start of infusion. Several subjects experienced a longer delay in tmax, up to 72 hours after the start of infusion. After reaching Cmax, observed serum concentrations declined in a biphasic manner with a slow terminal elimination phase.

The 3 mg/kg IV dose of MB02 and EU Avastin®, and the 3 mg/kg IV dose of EU and US Avastin® were both considered bioequivalent in terms of the AUCs and Cmax as the 90% CI for the geometric least square (LS) means ratios for all 3 protein-unadjusted parameters (the primary PK parameters [AUC0-inf and Cmax] and a secondary PK parameter [AUC0-t]) were fully contained within the predefined bioequivalence limits of 0.80 to 1.25, while the statistical comparison of 3 mg/kg IV dose of MB02 and US Avastin® was not considered to demonstrate bioequivalence as the 90% CI of geometric LS means ratios were not fully contained within the bioequivalence limits, with the upper CI exceeding the 1.25 limit for all 3 parameters.

The certificate of testing documents showed that although the protein content of each batch of MB02, US- and EU-Avastin® were within the specified range, variability existed in the actual protein content between batches. When adjusting for protein content MB02, EU-Avastin® and US-Avastin® were all considered bioequivalent (i.e. the geometric LS means ratios for all 3 protein-unadjusted parameters were fully contained within the predefined bioequivalence limits of 0.80 to 1.25).

### 1.3.2 Efficacy

As part of the overall biosimilarity exercise, the clinical development programme of MB02 was designed to demonstrate comparable clinical efficacy with the RMP and not to demonstrate efficacy per se.

The data to support equivalent clinical efficacy of MB02 and the RMP is derived from the pivotal study MB02-C-02-17, in patients with non-squamous NSCLC.

### Efficacy in Study MB02-C-02-17

A total of 627 subjects were randomized to receive MB02 (315 subjects) or Avastin® (312 subjects) and were included in the ITT set.

Objective response (OR) was assigned to subjects if they experienced either complete response (CR) or partial response (PR). At Week 18, subjects were assessed by an independent radiology review committee (IRC) using computed tomography and/or magnetic resonance imaging scanning to determine the occurrence of objective response (OR, including CR or PR), according to RECIST v1.1 criteria. The primary endpoint, Objective Response Rate (ORR), was calculated as the proportion of subjects reporting an OR at study Week 18.

At the Week 18 cut-off, the IRC assessment of OR was comparable for subjects receiving MB02 (OR of 40.3%; 95% CI: 34.9 to 46.0] or Avastin® (OR of 44.6%; 95% CI: 39.0 to 50.3) in combination with carboplatin and paclitaxel. An RR of 1.013 (90% CI: 0.957 to 1.072) was well within the boundaries of the similarity margin predefined by the FDA (0.73, 1.36). Similarly, the 95% CI of 0.947 to 1.084 was also completely contained. An RD of 0.011 (90% CI: -0.037% to 0.059) was also well within the similarity margin predefined by the EMA (-12%, +12%). Again, the 95% CI was also completely contained 0.046 to 0.068). The ORR results were consistent with the investigator response assessments. The measures suggest that for the primary efficacy endpoint of ORR, the clinical efficacy of MB02 and Avastin® is highly similar.

The ORR results for MB02 and Avastin® were also similar to the published data of bevacizumab.

The results of the secondary efficacy endpoints were also similar between treatment groups. There was no significant difference in median PFS between subjects treated with MB02 (33.6 weeks; 90% CI: 28.7 to 35.6) and those treated with Avastin® (36.3 weeks; 90% CI: 34.9 to 39.0). Likewise, there was no significant difference in RMST estimates of OS in subjects treated with MB02 (17.1 weeks) and those treated with Avastin® (17.4 weeks). Importantly, data from 82.6% of subjects was censored (259 subjects in each group) at the Week 18 cut-off because the subjects were alive.

### **1.3.3 Safety**

In the studies for which safety data are currently available, studies MB02-A-02-17 (Healthy Volunteers), MB02-C-02-17 (non-squamous NSCLC) and BEVZ92-A-01-13 (mCRC), the safety profiles were within expectations for the respective study populations, concomitant therapies and were consistent with the labelling information for the RMP (Avastin SmPC, 2019).

Comparative analysis of the number of patients with particular AEs in the BEVZ92/MB02 and RMP treatment arms reported a similar profile of AEs in the two treatment groups in all studies.

No new safety signals were reported for MB02 and no significant differences in the incidence of AEs of special interest (gastrointestinal perforations and fistulae, posterior reversible encephalopathy syndrome, proteinuria, wound-healing complications, hypertension, arterial and venous thromboembolism, congestive heart failure, haemorrhage, pulmonary haemorrhage, haemoptysis, neutropenia and infections, hypersensitivity reactions and osteonecrosis of the jaw) between BEVZ92/MB02 and RMP were observed in patients with mCRC and non-squamous NSCLC receiving concomitant chemotherapy.

### Safety in Study MB02-A-02-17

A total of 114 healthy male subjects aged between 18 and 55 years, inclusive, were randomized to one of 3 treatment arms in a 1:1:1 ratio (38 subjects per treatment arm). All subjects were included in the safety population. Single 3 mg/kg IV doses of MB02, US and EU Avastin® were generally well tolerated by healthy subjects in this study. There were no treatment arm-related trends in the number of subjects who reported a TEAE, and the majority of TEAEs were considered unrelated or unlikely related to study drug. The most common drug-related TEAE reported was nausea, reported by 4 subjects (3.5%) in total. There were no apparent treatment-related trends in mean vital signs or ECG data following dosing. A single subject, administered US Avastin®, reported an SAE which resolved without treatment by study completion. The general profile of TEAEs reported in this study was similar to that observed in previous studies.

### Safety in Study MB02-C-02-17

A total number of 627 patients were randomized in this study, but 621 were considered within the Safety population (6 randomized patients did not receive any dose of study medication). Safety data has been obtained up to the Week 18 cut-off point, which corresponds to the complete treatment period of bevacizumab (MB02 or EU-Avastin®) in combination with carboplatin and paclitaxel chemotherapy. The majority of subjects receiving at least one dose of either MB02 or EU-Avastin®, in combination with carboplatin and paclitaxel, experienced TEAEs (571/621 subjects [91.7%]).

There was no statistically significant difference in the number of subjects experiencing TEAEs in the MB02 group (287 subjects [92.3%]) compared to the EU-Avastin® group (284 subjects [91.6%]). Likewise, when only TEAEs considered related to study drug were considered, no statistically significant differences were observed in the TEAEs experienced by subjects in the MB02 group (116 subjects [37.3%] and the EU-Avastin® group (112 subjects [36.1%]).

The number of subjects experiencing a TEAE leading to study drug discontinuation before Week 18 was also comparable between treatment groups (42 [13.5%] subjects administered MB02 and 27 [8.7%] subjects administered EU-Avastin®). A total of 109 (17.6%) subjects experienced serious TEAEs during the study, with no statistically significant difference in serious TEAEs observed between the treatment groups, and for 66 (10.6%) subjects the serious TEAEs were considered related to study drug (33 subjects in each treatment group).

Further, no differences in the severity of reported TEAEs between the MB02 and EU-Avastin® treatment groups were observed with the majority of TEAEs classified as Grade 1 or 2. Comparison of the frequency of subjects with Grade 3–4 TEAEs did not reveal any statistically significant differences. Grade 5 TEAEs were also comparable between treatment groups. The frequency of subjects with study drug-related Grade 3 or 4 TEAEs (10.3% vs. 10.3%) was also comparable between treatment groups. No clear treatment group-related trends were observed for study drug-related TEAEs.

The most common TEAEs by preferred term (PT) were alopecia (51.2%) and anaemia (31.2%), with no clinically significant differences between treatment groups and no observable trends within System Organ Classes (SOCs) were reported. When only study drug-related TEAEs were considered anaemia (5.0%) and hypertension (4.8%) were the most frequently observed.

Six subjects had fatal TEAEs considered related to MB02 and three subjects had fatal TEAEs related to EU-Avastin®. Fatal TEAEs considered related to study drug only or study drug in combination with carboplatin/paclitaxel included: pulmonary haemorrhage (two subjects),

acute kidney injury, nephrotic syndrome, haemoptysis, gastric ulcer, acute myocardial infarction, cardio-respiratory arrest, and pulmonary embolism (one subject each).

No observable risk difference between treatment groups with regard to subjects reporting TEAEs of special interest was seen.

Overall, the number, type, and severity of TEAEs, including those of special interest were in alignment with the safety profile reported in the bevacizumab Summary of Product Characteristics (SmPC) in this population of patients (Avastin SmPC, 2019). There were no new signals or observable trends reported for MB02-treated subjects.

#### Safety in Study BEVZ92-A-01-13

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.

#### **1.3.4                   Immunogenicity**

Comparisons of MB02 and EU-approved Avastin® immunogenicity are among the secondary objectives of the completed pivotal study MB02-A-02-17 and study MB02-C-02-17 (pivotal study in patients with non-squamous NSCLC).

As described below, immunogenicity data is currently available from the completed pivotal study MB02-A-02-17 and the Primary Endpoint Analysis (through Week 18) of MB02-C-02-17.

#### Immunogenicity in Study MB02-A-02-17

The overall incidence of immunogenicity in both the MB02 and EU-Avastin® treatment arms was low. The majority of positive tests for ADAs were transient and occurred at a single timepoint with a low titter value. A subject in the MB02 treatment arm, at study Day 28, gave a positive result for a treatment-induced nAb with a low titre (< 1).

No discernible trend or correlation between ADA status and the measured values for PK parameters (AUC<sub>0-inf</sub>, C<sub>max</sub> and CL) could be observed for either the MB02 or EU-Avastin® treatment arms. Likewise, those subjects who developed an ADA or nAb response did not report any treatment-emergent adverse events (TEAEs) related to infusion reactions or any TEAEs considered temporally associated with the development of ADAs or nAbs.

#### Immunogenicity in Study MB02-C-02-17

Initial immunogenicity data from study MB02-C-02-17 is available from the Primary Endpoint Analysis and comparable immunogenicity of MB02 and EU-Avastin® was reported.

The majority of subjects tested negative for ADAs at all timepoints (620 subjects analyzed). The global incidence of post-treatment ADAs through Week 18 was 16.9%, with comparable rates observed between treatment groups (17.4% vs. 16.5% in the MB02 and EU-Avastin® groups, respectively). No discernible trend or correlation between ADA status and safety or efficacy were seen. The presence of ADAs was apparently not associated with serious infusion-related reactions or anaphylactic reactions

#### **1.4 Study Rationale**

This study will conduct a comparison of the PK profile of MB02-SP, MB02-DM and US Avastin® in healthy volunteers, fulfilling the criteria for a PK bridging study to generate clinical evidence to support minor changes in upstream process.

#### **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.<sup>1</sup>

## **2 OBJECTIVES**

### **2.1 Primary Objective**

The primary objective of the study is:

- To investigate and compare the PK profiles of MB02-SP (MB02 standard procedure), MB02-DM (MB02 define media) and US Avastin® (US-licensed 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 endpoints for MB02-SP, MB02-DM and US Avastin®.
- To compare the safety profile of MB02-SP, MB02-DM and US Avastin®.
- To compare the immunogenicity of MB02-SP, MB02-DM and US Avastin®.

## 3 ENDPOINTS

### 3.1 Primary Endpoints

The PK outcome endpoints of MB02-DM, MB02-SP and US 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-SP, MB02-DM and US 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-SP, MB02-DM and US Avastin®.
  - Determination of serum concentrations of anti-MB02-DM, anti-MB02-SP 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-DM with MB02-SP and US 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-SP as a 90-minute IV infusion
- Arm 2: MB02-DM as a 90-minute IV infusion
- Arm 3: US Avastin® sourced from the US, 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 3. On Day 1, subjects will receive a single 1 mg/kg IV dose of the study drug. Subjects will return on Days 4, 5, 6, 7, 8, 10, 14, 21, 28, 42, 56, 78 and 100 for non-residential visits for the collection of PK samples and safety assessments. Immunogenicity samples will be collected on Days -1, 14, 28, 56, and 78.

The total duration of trial participation for each subject (from Screening through to the end of study 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-DM versus MB02-SP and US 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 <sup>2,5</sup>. The study will be double-blinded as the secondary objective of comparing the safety profile of MB02-DM and, MB2-SP to US Avastin® is considered subjective. The collection of serum samples through Day 1 to Day 100 will allow the PK parameters for MB02-DM, MB02-SP and US Avastin® to be adequately described.

Assessment of PK in a single-dose study in healthy volunteers is expected to be the most sensitive setting possible to detect differences in PK between MB02-DM, MB02-SP and US 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.<sup>5</sup>

#### **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-DM, MB02-SP and US 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 1 mg/kg for MB02-DM, MB02-SP and US Avastin® was chosen based upon the dosages used in previously published studies of bevacizumab PK<sup>6,7</sup>, 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<sup>2</sup>, inclusive, at Screening.
3. Total body weight between 50 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 non-haemolytic 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  $\geq 1.5 \times 10^9$  L
  - Platelet count  $\geq 100 \times 10^9$  L
  - Haemoglobin  $> 10$  g/dL
  - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)  $\leq 1.5 \times$  ULN
  - Alkaline phosphatase (ALP)  $\leq 1.5 \times$  ULN
  - Total bilirubin  $< 1.5 \times$  ULN ( $< 51.30$   $\mu$ mol/L in subjects with Gilbert's syndrome)
  - Blood urea nitrogen  $\leq 1.5 \times$  ULN
  - Creatinine  $< 132.63$   $\mu$ mol/L
  - Serum albumin:  $> 35$  g/L
  - Low density lipoprotein cholesterol  $\leq 4.9$  mmol/L
  - High density lipoprotein cholesterol  $\geq 0.85$  mmol/L
  - Creatine kinase (CK)  $< 2 \times$  ULN
  - International normalised ratio (INR) 0.8 to 1.3
  - Urine dipstick for proteinuria  $< 2+$
6. Systolic blood pressure  $\geq 90$  mmHg and  $< 140$  mmHg and diastolic blood pressure  $\geq 50$  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 (Within 2 months prior Screening Visit for any serious infection which requires hospitalization or intravenous anti-infective, and within 14 days prior Screening Visit for any active infection which requires oral treatment).
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.
28. Vulnerable subjects (e.g. persons kept in detention).
29. Subjects who are study site employees or immediate family members of a study site or Mabxience employee.

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 Subject number at Screening which will be used to identify subjects on all study documentation.

Replacement subjects ([Section 5.4](#)) will be assigned a subject number corresponding to the number of the subject they are replacing plus 1000 (eg, Subject 1101 replaces Subject 101). This will be followed for all subjects, regardless of whether they are dosed or not.

### 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

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

MB02-DM, MB02-SP and US 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.<sup>5</sup>

### 6.2 Study Treatment Administration

Doses of MB02-DM, MB02-SP and US 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 pre-treatment 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

A computer generated randomization schedule will be prepared by the assigned biostatistician (a Syneos Health biostatistician) prior to the start of the study. The schedule will be generated through the statistical analysis system (SAS) software, version 9.4.

Subjects will be randomly assigned to 1 of 3 treatment arms and stratified into 2 groups based on weight ( $\geq 50.0$  to  $< 72.5$ kg, and  $\geq 72.5$  to  $\leq 95.0$  kg respectively).

For subjects who are replaced the replacements should take the same treatment assignment as the original subject to ensure that the planned treatment allocation ratio is retained.

### 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-DM, MB02-SP and US 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, as per regulatory requirements. Any additional unused MB02-DM, MB02-SP and US 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 non-prescription medications/products during the study until the end of study 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. In addition to this, same fasting rule applies for all non-residential visits.

Caffeine-containing foods and beverages will not be allowed from 24 hours before Check-in until discharge and from 24 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 collision sports throughout the whole participation in the study and 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) 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 for ADA and 1 x 3.5 mL for NAB) 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-DM, anti-MB02-SP 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, aural 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 <sup>8</sup> and information from the public domain <sup>9</sup>. 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  $AUC_{(0-t)}$  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-DM, MB02-SP or US 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-DM, MB-SP or US Avastin®, and have at least 1 post dose safety assessment.

### 9.3 Pharmacokinetic Analyses

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

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 ( $AUC_{[0-\infty]}$  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 (CI) will be derived for the comparisons of the PK parameters as follows:

- MB02-SP versus MB02-DM
- MB02-SP versus US Avastin®
- MB02-DM 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-SP versus MB02-DM; MB02-SP versus US Avastin®; and MB02-DM versus US 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 5.0. 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-SP, MB02-DM, or US Avastin® (Day -1) and at scheduled post dose 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, Syneos Health 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 Syneos Health standard operating procedures (SOPs) or per Sponsor request and as applicable according to the contract between Syneos Health 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**

Syneos Health will designate a Blinded Study Monitor and an Unblinded 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**

Syneos Health 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.

Syneos Health 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 Syneos Health, using Syneos Health 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 Syneos Health 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 in the study site archive for at least 15 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 non substantial 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 most updated version of 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 one original of the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving their informed consent. A copy will be given to the subject, and the original 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 non substantial 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 9.0, 19 May 2020)
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](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.



**Appendix 1: Schedule of Assessments**

	Screening (Day -30 to -1)	Day																	
		-1	1	2	3	4 (±1)	5 (±1)	6 (±1)	7 (±1)	8 (±1)	10 (±1)	14 (±1)	21 (±1)	28 (±1)	42 (±1)	56 (±1)	78 (±1)	100/ EOS (±1)	
Informed consent	X																		
Inclusion/exclusion criteria	X	X																	
Demographic data	X																		
Medical history	X																		
Urinary drug screen and cotinine test	X <sup>a</sup>	X																	
Alcohol breath test	X	X																	
Serology	X																		
Height and body weight <sup>b</sup>	X	X																	
<b>Study residency:</b>																			
Randomisation		X																	
Check-in		X																	
Check-out					X														
Non-residential visit <sup>g</sup>	X					X	X	X	X	X	X	X	X	X	X	X	X	X	
<b>Study drug administration:</b>																			
MB02 or Avastin <sup>®</sup>			Day 1 (0 h)																
<b>Pharmacokinetics:</b>																			
Blood sampling <sup>e</sup>			Predose, EOI <sup>f</sup> , 2, 3, 4, 5, 6, 8, 12 h	24 h	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
<b>Immunogenicity:</b>																			
Blood sampling		X <sup>g</sup>											X		X		X	X	X
<b>Safety and tolerability:</b>																			
Adverse event recording	X	X	Ongoing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serious adverse event recording	X	X	Ongoing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Prior/concomitant medication monitoring	X	X	Ongoing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

	Screening (Day -30 to -1)	Day																
		-1	1	2	3	4 (±1)	5 (±1)	6 (±1)	7 (±1)	8 (±1)	10 (±1)	14 (±1)	21 (±1)	28 (±1)	42 (±1)	56 (±1)	78 (±1)	100/ EOS (±1)
Clinical laboratory evaluations	X	X			X					X		X	X	X	X	X	X	X
Supine blood pressure, pulse rate, respiratory rate <sup>e</sup>	X	X	Predose, 0.5, 1, EOI <sup>f</sup> , 2h	X			X			X	X		X					X
Pulse oximetry	X																	
Aural body temperature	X			X							X		X					X
12-lead ECG	X	X			X						X							X
Physical examination	X <sup>c</sup>	X <sup>d</sup>																X <sup>d</sup>

Abbreviations: ECG = electrocardiogram

<sup>a</sup>. To be performed during screening period, from Day -3 to Day -1. This procedure may be done in-house, if positive result, this should be repeated at local laboratory.

<sup>b</sup>. Height measured at Screening only

<sup>c</sup>. Can be performed between the Screening visit and predose assessments

<sup>d</sup>. Symptom-directed physical examination

<sup>e</sup>. All times stated are post-start of infusion.

<sup>f</sup>. EOI: End of infusion.

<sup>g</sup> The following windows are allowed:

Procedure	Time Point	Tolerance Window	Notes
PK (Blood Samples)	Predose	- 10 min to 0 h	
	1,5h post*	- 0 / + 5 min	Immediately after the end of Infusion
	2h post	±5 min	
	3h – 6h post	±10 min	
	8h – 24h post	±20 min	
	Day 3, 4, 5, 6, 7, 8	±30 min	
	Day 10, 14, 21, 28, 42, 56, 78, 100	±1440 min	
Immunogenicity (Blood Samples)	Day -1	Day -1 to 0 h	
	Day 14, 28, 56, 78	±1440 min	
Clinical Safety Laboratory Sampling	Day 14, 21, 28, 42, 56, 78, 100	±1440 min	
Supine blood pressure, pulse rate, respiratory rate	Predose	-90 min to 0 h	
	30min – 2h post	±10 min	Except 1.5h post
	1.5h post *	-0 / +10 min	After the end of Infusion
	Day 2, 5, 8	±30 min	
	Day 10, 21, 100	±1440 min	

Procedure	Time Point	Tolerance Window	Notes
Aural body temperature	Screening	Normally done during the visit - no windows needed	
	Day 2	$\pm 30$ min	
	Day 10, 21, 100	$\pm 1440$ min	
12-lead ECG	Screening	Normally done during the visit - no windows needed	
	Day -1	Day -1 to 0 h	
	Day 3, 8	$\pm 30$ min	
	Day 100	$\pm 1440$ min	
IV infusion time	Day 1	No window allowed	

## 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 5.0, outlined below:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2 Moderate; minimal, local or non-invasive 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	Haematocrit	Blood
Albumin	Haemoglobin	Glucose
Alkaline phosphatase	Mean cell haemoglobin	Ketones
Aspartate aminotransferase	Mean cell haemoglobin concentration	pH
Calcium	Mean cell volume	Protein
Chloride	Platelet count	Specific gravity
Total cholesterol	Red blood cell (RBC) count	Urobilinogen
HDL cholesterol	White blood cell (WBC) count	Microscopic examination <sup>c</sup>
LDL cholesterol	WBC differential:	
Creatinine	Basophils	
Creatine kinase	Eosinophils	
Gamma-glutamyl transferase	Lymphocytes	
<b>Lactate dehydrogenase</b>	Monocytes	
Glucose	Neutrophils	
Inorganic phosphate		
Potassium		
Sodium		
Total bilirubin		
Direct bilirubin		
Total protein		
Triglycerides		
Urea		
Uric acid		
Serology <sup>a</sup> :	Urinary drug screen <sup>b</sup> :	Coagulation
Hepatitis B surface antigen	Including but not limited to:	International normalised ratio
Hepatitis B surface antibody (anti-HBs)	Cotinine	Prothrombin time
Hepatitis B core antibody (anti HBc)	Amphetamines/methamphetamines	Activated partial thromboplastin time
Hepatitis C antibody	Barbiturates	
Human immunodeficiency (HIV-1 and HIV-2) antibodies	Benzodiazepines	
	Cocaine (metabolite)	
	Methadone	
	Phencyclidine	
	Opiates	
	Tetrahydrocannabinol/cannabinoids	
Alcohol breath test		

<sup>a</sup> Only analysed at Screening. The following tests should be performed: Hepatitis B surface antigen (HbsAg) and Hepatitis B core antibody (anti HBc). If both negatives, no further tests are required. If Hepatitis B surface antigen (-) and Hepatitis B core antibody (+) then Hepatitis B surface antibody (anti HBs) should be performed.

<sup>b</sup> Only analysed at Screening and Check-in.

<sup>c</sup> Upon a positive urine test from leucocytes, blood, nitrite or protein, the Investigator may require further urine analysis, such as flow cytometry. Results of additional urine analyses will be included in the database. If the flow cytometry examination shows a different result than the urine sticks, the urine will be investigated by fully automated digital imaging where leukocytes, erythrocytes, casts in urine will be analyzed.

#### 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	11	106.7
Serology	3.5	1	3.5
Bevacizumab pharmacokinetics	3.5	24	84
Immunogenicity samples:			
ADA	3.5	5	17.5
NAB	3.5	5	17.5
Total:			229.2

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.