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

mAbxience Research S.L.

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

Statistical Analysis Plan

Version: 2.0

PAREXEL Project Number [redacted]

SPONSOR SIGNATURE PAGE

SPONSOR Signatures

Signature below indicates that you have reviewed the document for clarity, completeness and consistency and approve it.

Signature 1: [redacted]

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Medical Advisor

Print Name: [redacted] Title:

PAREXEL SIGNATURE PAGE

Signatures below confirm that the Statistical Analysis Plan was developed in accordance with [redacted] and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

	Signatory	
Author	[redacted]	

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REVISION HISTORY

Version No.	Date	Summary of Change(s)
1.0	9 Mar 2020	New document
2.0	8 Apr 2020	Year for protocol version 7 is updated

LIST OF ABBREVIATIONS

List and define all acronyms and abbreviations used in the document here.

Abbreviation / Acronym	Definition / Expansion
AE	Adverse event
Ae	Amount excreted in urine
ATC	Anatomical therapeutic chemical
AUC	Area under the concentration-time curve
$AUC_{(0-\infty)}$	AUC from time zero extrapolated to infinity
$AUC_{(0-t)}$	AUC from time zero to the last quantifiable concentration
AUC%extrap	Percentage of $AUC_{(0-\infty)}$ that is due to extrapolation beyond T_{last}
BLQ	Below the lower limit of quantification
BMI	Body Mass Index
BP	Blood pressure
Bpm	Beats per minute
CI	Confidence interval
C_{last}	Last quantifiable concentration at t_{last}
CL	Clearance
CRF	Case Report Form
CSP	Clinical Study Protocol
C_{max}	Maximum observed concentration
CS	Clinically significant
CV	Coefficient of variation
DRM	Data Review Meeting
ECG	Electrocardiogram
EOS	End-of-study
ET	Early termination
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed consent form
IMP	Investigational Medicinal Product
IV	Intravenous

Abbreviation / Acronym	Definition / Expansion
LLOQ	Lower limit of quantification
LOQ	Limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not available
NCS	Not clinically significant
NK	Not known
OTC	Over the counter
PK	Pharmacokinetic
PKS	Pharmacokinetic analysis set
QT	The QT interval is measured from the beginning of the QRS complex to the end of the T wave
QTc	corrected QT interval
QTcB	QT corrected using Bazzett's formula
QTcF	QT corrected using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation or single dose
SE	Standard error of the mean
SUSAR	Suspected unexpected serious adverse aeaction
SOC	System Organ Class
$t_{½}$	Terminal elimination half-life
t_{last}	Time of last quantifiable concentration
TEAE	Treatment-emergent adverse event
t_{max}	Time corresponding to occurrence of C_{max}
VEGF	Human vascular endothelial growth factor
WHO-DD	World Health Organisation - Drug Dictionary
λ_z	Terminal elimination rate constant

[redacted]

1 INTRODUCTION

This study is a Randomized, Double-Blind, Three-Arm, Single Dose, Parallel Study to Compare the Pharmacokinetics, Safety and Immunogenicity of MB02 (Bevacizumab Biosimilar Drug), US-licensed Avastin® and EU-approved Avastin® in Healthy Male Volunteers.

The analyses described in this SAP are based upon the following study documents:

- Study Protocol, Version7.0 (24 January, 2020)
- Electronic source data capturing system (eSource) ClinBase study version 17.0 (October 18, 2019)
- Blinding Maintenance Plan (BMP) Version 1.0 (September 13, 2019)

This document is in compliance with the requirements of the International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use guideline for Good Clinical Practice ICH E6 –GCP and ICH E9-Statistical Principles of Clinical Trials.
This Statistical analysis does not cover pharmacokinetics and Immunogenicity analysis mentioned in the protocol and please refer PKAP for the same.

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

The primary objective of the study is:

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

2.2 Secondary Objective(s)

The secondary objectives of the study are:

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

2.3 Exploratory Objective(s)

There is no exploratory objective for this study.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a Phase 1, double-blind, randomized, parallel-group, single-dose 3-arm study to investigate and compare the PK, safety and immunogenicity profile of MB02 with US and EU Avastin® in healthy male subjects. A total of 114 subjects will be stratified into 2 groups based on weight (>= 60 to < 77.5 kg, and >= 77.5 to <= 95.0 kg, respectively) and then will be randomized to one of the following 3 arms in a 1:1:1 ratio:

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

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

Subjects will be admitted to the Clinical Research Unit (CRU) on Day -1, and will be confined to the CRU until discharge on Day 8. On Day 1, subjects will receive a single 3 mg/kg IV dose of the study drug. Subjects will return on Days 10, 14, 21, 28, 42, 56, 78 and 100 for non-residential visits for the collection of PK 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 final visit) is anticipated to be approximately 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.

3.2 Endpoints and Associated Variables

The main variables related to primary and secondary objectives are listed below.

3.2.1 Efficacy Variables

Not applicable.

3.2.1.1 Pharmacodynamic Variables

Not applicable.

3.2.1.2 Immunogenicity Variables

The immunogenicity of MB02, US Avastin® and EU Avastin® -

- Determination of serum concentrations of anti-MB02 and anti-Avastin® antibodies.

3.2.2 Pharmacokinetic Variables.

Primary Endpoints:

[redacted]

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

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

Secondary Endpoints:

Evaluation of all other PK parameters for MB02, US-licenced Avastin® and EU-approved Avastin®, including-

- Time of maximum observed serum concentration (t_{max})
- AUC from time zero to the time of the last observable concentration ($AUC_{[0-t]}$)
- Clearance (CL)
- Serum terminal elimination half-life ($t_{1/2}$)

Derivation of PK parameters will be the responsibility of Pharmacokinetics team of Covance and please refer PKAP of Covance.

3.2.3 Safety Variables (Secondary endpoints)

The safety outcome measures for this study are as follows:

- incidence and severity of AEs
- incidence of laboratory abnormalities, based on hematology, coagulation, clinical chemistry, and urinalysis test results
- 12-lead electrocardiogram (ECG) parameters
- vital sign measurements
- physical examinations.

3.2.4 Exploratory Variables

No exploratory objective and hence exploratory variable for this study.

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the ICH E3 clinical study report will be independently checked for consistency, integrity and in accordance with standard PAREXEL procedures.

4.2 General Presentation Considerations

Baseline Definitions

Data collected at screening, Day -1 and pre-dose Day 1 is baseline data. If an assessment is repeated during baseline, then the value closest to dosing will be used for analysis, if not stated otherwise. In rare cases where multiple measurements meet the baseline definition, with no further flag or label that can identify the chronological order then the mean of the measurement will be used as baseline.

In general, 'Baseline' is defined as the last available pre-dose assessment.

'End of Study' (EOS) The end of the study is defined as the date of the last subject's last assessment i.e. planned or unplanned.

'Study Day' will be calculated relative to the date of randomization i.e.
If the date of interest occurs on or after the Drug Administration Date then the study day will be calculated as (date of interest- Drug Administration Date) + 1.
If the date of interest occurs before the Drug Administration Date then the study day will be calculated as (date of interest – Drug Administration Date). There is no study day 0.
Following treatment sorting order and treatment labels will be used in all listings, tables and figures-

1. MB02 (T)
2. Avastin®-US (R1)
3. Avastin®-EU (R2)

Assessing the bioequivalence of MB02 with Avastin®-US and Avastin®-EU, and between Avastin®-US and Avastin®-EU will be the main focus of the statistical testing. Other components of the statistical analysis for PK, immunogenicity and safety data will be descriptive in nature. For few adverse events variable exploratory statistical treatment comparison will be carried out.

Unless otherwise specified, all dates and hours will be presented in the International Organization for Standardization (ISO) format 'yyyy-mm-dd' and 'hh:mm' respectively.

Data will be summarized by treatment arm and by study visit (residential or non-residential visit) wherever applicable.

For continuous variables (other than pharmacokinetic variables), summary statistics will include number of available observations (n), mean, median, standard deviation, minimum, and maximum. Geometric mean will be presented as applicable. If minimum value from the data is zero, geometric mean will not be calculated.

Missing data will not be imputed.

All data will be listed according to the number of decimal places presented in the original data. Derived parameters will be calculated using original data.

The following conventions are applied for reporting descriptive statistics of all continuous data ('d' refers to the number of decimal places reported for the original data):

- Mean: d + 1 decimal digits
- SD, SEM: d + 2 decimal digits
- Min: d decimal digits
- Median: d + 1 decimal digits
- Max: d decimal digits

Point estimates & Confidence Intervals (CIs) obtained from statistical analysis will be displayed two decimal places.

In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical endpoints will be summarized using subjects providing data at the relevant time point (n), frequency, and percentages. If there is missing data, count of missing data also will be presented where necessary to account for it.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using 'n' as the denominator.

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

Other Considerations

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001".

Data will be displayed in all listings sorted by treatment group, subject number (unique subject identifier) and study day, as applicable. In cases where more additional sorting is required, other variables will be included in the sort order as applicable.

Listings will include all scheduled, unscheduled, and early discontinuation data with the scheduled visit originally recorded on the eCRF.

EOS visit of early termination results or unscheduled visit results will not be included in the summaries.

4.3 Software

All tables, figures, and listings (TFLs) for clinical study report (CSR) will be produced using SAS® version 9.3 or a later version in a secure and validated environment. Validated statistical computing environment. The version of SAS actually used for the analysis will be specified in the CSR.

All TFLs will be provided to the Sponsor in Microsoft Word document.

4.4 Study Subjects

4.4.1 Disposition of Subjects

Subject disposition data will be presented using all Screened subjects.

Subject disposition will be summarized (n and percentages) by treatment arm and overall. Percentages will be based on the number of randomized subjects.

The tabulation will include the following information:

- Total number of screened subjects
- Number of randomized subjects
- Number of subjects who received study treatment
- Number of subjects who completed the study
- Number of subjects who discontinued the study with the primary reason for discontinuation

Subject disposition listing will include the following information based on randomized population:

- Subject identifier
- Randomization number
- Study day/Date of informed consent
- Study day/Date of randomization (for randomized subjects)
- Study Treatment received (for randomized subjects)
- Study completion status
- Study day/Date of disposition Event
- Primary reason for discontinuation

4.4.2 Protocol Deviations

Major protocol deviations are defined as those deviations from the protocol likely to have an impact on the pharmacokinetics and/or safety of study treatments.

All protocol deviations will be assessed between PAREXEL and the Sponsor during the Blinded Data Review Meeting (BDRM) before database lock and unblinding. Major protocol deviations will include but not be limited with the following:

- Deviation from the inclusion and exclusion criteria
- Deviation from study medication compliance in terms of medical conditions and/or AEs that may have interfered with drug absorption or with respect to factors likely to affect the primary PK endpoints
- Non-compliance to study procedures or deviations from study procedures likely to

[redacted]

affect the primary PK endpoints

- Subjects receiving prohibited concomitant medications

Time window deviations for PK blood sampling and safety assessments will also be listed as protocol deviations.

Tolerance windows for safety and PK assessments are provided in the final Windows Allowance Document.
If subjects were,

- Randomized but not treated, then they will be reported under their randomized treatment arm for any presentation of All Randomized Subjects. However, they are by definition excluded from the safety, PK and immunogenicity analyses as actual treatment is missing.
- Treated but not randomized (i.e., somehow got study medication but was never given a randomization number and had no post-randomization assessments) , then by definition they will be excluded from the PK analyses as subjects with a "Major" protocol violation since they are not randomized, but they will have all safety events reported including immunogenicity.
- Randomized but received incorrect treatment, then they will be reported under their randomized treatment arm for any presentation of All Randomized Subjects. However, they will be reported under the treatment group they actually received for all safety, PK and immunogenicity analyses.

All time window deviations for both PK and safety assessments will be "generally " considered as minor protocol deviations. Major protocol deviations will be identified at the BDRM. Subjects with major protocol deviations may be excluded from the analyses based on the decisions at the BDRM.

A complete list of protocol deviations will be compiled prior to the BDRM and all protocol deviations will be listed in the study report with the classifications of Major or Minor as finalized and agreed by the sponsor. Population analysis flags based on classified protocol deviations for subject exclusions will be summarized in the BDRM report which will be signed off by sponsor.

A summary of the number and percentage of subjects with at least one protocol deviation will be provided by treatment and overall and by category of deviation for the randomized population.

Subjects taking prohibited concomitant medications will be noted in the summary of protocol deviations.

All protocol deviations will be listed by subject and will include the subject identification, the study day/date &time, treatment received, category/coded term of deviation, description of the deviation, deviation classification (major or minor), and exclusion from relevant analysis populations (Safety and PK).

4.5 Analysis Sets

Randomized Population: All subjects who are randomized to study treatment will be included in Randomized Population.

Pharmacokinetic Population: The PK population will include all subjects who received the full dose of MB02 or Avastin®, did not have any major protocol deviations, and have an evaluable PK serum concentration time profile.

The PK summaries and analyses will be based on the PK Analysis Population.

Safety Population: The safety population will include all subjects exposed to MB02 or Avastin® and have at least 1 post dose safety assessment.
The safety including immunogenicity summaries and analyses will be based on the Safety Population.

If a subject is allocated the incorrect study treatment and not as per the study randomization list, subjects will be summarized and analyzed 'as treated' i.e. under treatment arm representing actual received treatment for PK and Safety summaries.

If a subject is allocated the incorrect study treatment and not as per the study randomization list, subjects will be summarized and analyzed 'as randomized' i.e. by randomized treatment arm.

The number and percentages subjects included in each analysis population will be summarized.

A by-subject listing of exclusions from PK analysis population will be provided. This will include: subject identifier, protocol deviation, date and study day of occurrence, deviation category (major or minor), primary endpoint for which exclusion applies, and reason for exclusion. This listing will be based on all randomized subjects.

Upon database release, protocol deviations and analysis set listing will be produced and will be sent to mAbxience Research S.L. (Sponsor) for review. An analysis population classification meeting will be arranged to discuss and to decide which subjects and/or subject data will be excluded from PK analyses. Decisions made regarding the exclusion of subjects and/or subject data from PK analyses will be made prior to unblinding and will be documented and approved by mAbxience Research S.L. (Sponsor).

4.6 Demographics and Baseline Characteristics

The following demographic information as recorded on eCRF will be listed and summarized:

Continuous variables include:

- Age
- Body weight (kg)

- Height (centimeters [cm])
- Body Mass Index (BMI) (kg/m2)
- Alcohol consumption per week in units (where one unit = 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)

Categorical variables include:

- Race (White, Asian, Black, Mixed, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Caucasian, Black and Oriental)
- Ethnicity (Hispanic, Not of Hispanic origin and Unknown)
- Smoker
- Ex-Smoker
- Cigarettes per day
- Weight group (>= 60 to < 77.5 kg, and >= 77.5 to <= 95.0 kg)

Demographic characteristics will be listed by subject and summarized by treatment arm and overall for the Safety Population (SAF). Continuous variables will be summarized by number of available observations (n), mean, standard deviation, minimum, median, and maximum. Categorical variables will be summarized by 'n, and percentage. The denominator for the percentages will be the number of subjects in the safety population for each treatment or overall, as appropriate.

4.7 Medical History and Concomitant Illnesses

Medical history will be coded with Medical Dictionary for Regulatory Activities (MedDRA version 22.0).

Medical history will be summarized and listed for Safety Population by subject and will include at least the following: treatment group, description of disease/procedure, MedDRA system organ class (SOC), MedDRA preferred term (PT), start date and end date (or ongoing, if applicable).

4.8 Prior and Concomitant Medications

Prior/concomitant medications data will be listed and summarized descriptively by treatment arm using the Safety Population.

Medications given prior to first administration of treatment (i.e., with start date/time prior to date/time of first treatment administration) which stopped prior to first administration of treatment (i.e., with an end date/time prior to date/time of first treatment administration) will be defined as prior medications.

Medications given on or after the first administration of treatment (i.e., with start date/time on or after date/time of first IMP administration) will be defined as concomitant medications.

Medications that were given prior to dosing (i.e., with start date/time prior to date/time of first IMP administration), but which ended after first IMP administration (i.e. with an end date/time after date/time of first IMP administration) will be classified as prior and concomitant medications.

Concomitant medication will be coded with World Health Organization - Drug Dictionary (WHO-DD; Version 2019_B3).

Prior, concomitant and prior & concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) code and Generic preferred name (PT) by showing frequencies and percentages and presented by treatment. Prior and concomitant medications will be listed by subject (and treatment, where possible) and include the following information: medication name (trade name), Prohibited Concomitant, dose (and dose units), frequency, route of administration, start and end date/time, indication and origin (medical history or AE).

The duration of prior or concomitant medications will be calculated based on the start and end date.

4.9 Treatment Exposure / Compliance

4.9.1 Treatment Exposure

This is a single-dose study and no exposure analysis is planned. Exposure will be listed by subject and treatment and summarized by treatment arm.

Planned dose (mg) and actual administered dose (mg) of MB02, Avastin-EU, and Avastin-US will be summarized for the safety population by treatment group using descriptive statistics (number, mean, standard deviation, minimum, median and maximum).

Planned dose for the subject is derived as = Body weight in kg * 3mg.

Treatment exposure data will also be listed by subject for the safety population. The listing will include treatment arm, whether subject received the correct treatment, start date/start time of drug infusion, end date/end time of drug infusion, planned dose (unit), actual dose (unit), route of administration, duration of infusion (Duration of infusion =End time of drug infusion – start time of drug infusion).

A by-subject listing of data on subject dose interruptions and the corresponding reasons will be produced.

4.9.2 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. A pre-dose and post-dose inventory of MB02 and Avastin® will be performed by study monitor on regular basis. Any dosing deviations/non-compliance will be captured as protocol deviations.

No analysis will be performed

4.10 Efficacy Evaluation

Efficacy evaluation is not applicable.

4.10.1 Analysis and Data Conventions

Study hypothesis is that MB02 is biosimilar to commercially available Avastin®-US and Avastin®-EU. For data convention please refer Section 4.2.

4.10.1.1 Multi-center Studies

This section is not applicable as this study is conducted in a single center.

4.10.1.2 Adjustments for Covariates

The primary PK endpoint analysis will adjust the stratification factor based on baseline weight in kg in the model as a covariate.

Stratum 1 = >= 60 to < 77.5 kg
Stratum 2 = >= 77.5 to < = 95.0 kg

4.10.1.3 Handling of Dropouts or Missing Data

Missing data from early discontinuations or otherwise will not be imputed.

4.10.1.4 Multiple Comparisons/Multiplicity

No multiplicity adjustment is required in this study since the two primary PK parameters C_{max} and $AUC_{(0-\infty)}$ are both expected to meet bioequivalence criteria.

4.10.1.5 Interim Analyses

Interim analysis is not planned for this study.

4.10.1.6 Examination of Subgroups

If subjects with ADA are observed during the study conduct an additional subgroup analysis for subjects with/without ADA may be performed.

4.10.2 Primary Efficacy Variable(s)

Not applicable.

4.10.3 Secondary Efficacy Variables

Not applicable.

4.10.4 Pharmacokinetics

Please refer latest version of the PKAP for pharmacokinetics analysis developed by Covance.

4.11 Safety Evaluation

All safety summaries and analyses will be based upon the Safety Population as defined in Section 4.4.

4.11.1 Adverse Events

An AE is any untoward medical occurrence in a study subject administered an IMP which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP. Adverse events may include the onset of new illness and the exacerbation of pre-existing conditions.

All observed, or patient reported AEs will be graded by the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.

Any AE that occurs during the study is a study adverse event.

A treatment-emergent adverse event (TEAE) is defined as an AE that begins or that worsens in severity after first dose of the study drug has been administered.

Any study emergent AE that starts prior to dosing with any study drug, is considered a pre-treatment-emergent adverse event (pre-TEAE).

Any AEs with incomplete start and end dates/times will be treated as follows:

Adverse events with unknown start and/or end times (but where the date is known) will be imputed with a time of 00:00 h for the tabulations but will be shown as NK: NK in the listings (where NK = Not Known).

Adverse events with completely unknown start dates will be considered as treatment-emergent for the tabulations and will be shown as NK in the listings. Partially complete AE dates will not be imputed in the listings and the available day, month and year components will be used to determine if an adverse event is treatment- emergent taking the first dosing date and end of study date as references.

Where dates are missing, or partially missing, adverse events will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the adverse event started prior to the first dose of study treatment.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.

In the AE overview table AEs will be summarized with the following data: total number of AEs, total number of pre-TEAEs, total number of TEAEs. It will also summarize the number of subjects with at least one TEAE, drug-related TEAE, serious TEAE, drug-related serious TEAE, severe TEAE (Grade >3) and drug-related severe TEAE as well as the subjects who discontinued from study due to TEAE, discontinued from study due to drug-related TEAE death, and AE leading to dose interruptions.

Adverse event summaries will be ordered in terms of decreasing frequency and alphabetically for SOC, and PT within SOC, in each treatment arm.

A summary of the number and percentage of subjects reporting a pre-treatment adverse events by treatment arm, SOC, and PT

A summary of the number and percentage of subjects of treatment-emergent adverse events by treatment arm, SOC, and PT.

A summary of the number and percentage of subjects reporting a treatment-emergent adverse event with an incident >=5% by treatment arm, SOC and PT

A summary of the number and percentage of subjects reporting a treatment-emergent adverse event by treatment group, severity, SOC and PT

A summary of the number and percentage of subjects reporting a treatment-emergent adverse event by treatment group, causality, SOC and PT

A summary of the number and percentage of subjects reporting a treatment related treatment emergent adverse event by treatment group, SOC and PT by severity

In the AE incidence by intensity table, a subject will only be counted for the most severe symptom, if a subject has the same symptoms with different severities. The same principle will be used in the AE incidence by relationship table.

The denominator for the percentages will be the number of subjects in the Safety Population for each treatment. If more than one event with the same preferred term occurred for the same subject, then the subject was counted only once for that preferred term

AEs collected in pre-treatment phase will be summarized separately.

For each subject and each adverse event, the worst severity recorded will be attributed and used in the by-severity summaries. Similarly, the worst causality (most related to treatment) will be attributed and used in the by-causality summaries. If severity or causality is missing, the worst case will be assumed.

All AEs recorded during the study will be listed. A by-subject listing of all adverse events (including non-treatment-emergent events) will be provided. This listing will be presented by treatment arm and will include: center, subject identifier, age, race, adverse event (SOC, PT, and verbatim term), AE Start date (Time), AE End date (Time), duration, severity, seriousness, action taken, outcome and causality. In addition, serious cases (ticked as serious AE) and SUSAR will be marked. A listing for pre-treatment adverse events will be provided separately. A treatment related treatment emergent adverse events will be listed separately.

4.11.2 Adverse Events Leading to Trial or Treatment Discontinuation

AEs leading to withdrawal/discontinuation from the study treatment will be listed for each subject and summarized by treatment, SOC and PT. Only TEAEs will be included in the tabulation.

Separate summaries of TEAEs leading to study discontinuations by 'Causality' and by 'Severity' will be produced.

4.11.3 Deaths, Serious Adverse Events, and Other Significant Adverse Events

An AE will be classified as a SAE if it fulfills the following criteria:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- 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
- Is an important medical event based on medical judgement

All serious adverse reactions (treatment related treatment emergent serious adverse events) will be considered as SUSARs, and will follow the expedited
SUSAR reporting process as described in the protocol.
A summary of the number and percentage of subjects reporting the serious adverse events and SUSARs (All serious adverse reactions will be considered as SUSARs) by treatment arm, SOC and PT.

A listing of death, serious adverse events and SUSAR will be provided.

An statistical pairwise comparison between each of the treatment arm will be carried out. Chi-square or Fisher exact test (if expected cell count is less than 5) will be used to compare the randomized treatment group and P-vales will be presented. The difference between treatment groups in the percentages of 'subjects with at least one TEAE', 'subject with at least one severe adverse event' and "subject with at least one SAE" and "subject with at least one treatment

discontinuation" will be provided along with their two -sided 95% CI is obtained by the Wald method without continuity correction.

4.11.4 Clinical Laboratory Evaluation

Individual safety laboratory measurements will be listed by subject, treatment and time point (where applicable) for the following:

- Hematology
- Chemistry
- Coagulation
- Urinalysis
- Urinary drug screen
- Serology

For by-visit summaries, the last non-missing assessment (including repeat assessments) recorded at each visit will be summarized. If visit windows are to be used, the non-missing assessment closest to the mid-point of the visit window will be summarized (including repeat and unscheduled assessments). For across visit summaries (e.g. maximum post-baseline value), scheduled, unscheduled and repeat assessments will be considered.

A subject will be defined as having a treatment-emergent laboratory abnormality if any of the following conditions are satisfied for a specific laboratory parameter:

- Laboratory result within the normal range at Baseline and either a result below the lower limit of the normal range or above the upper limit of the normal range at any post-baseline time point.
- Laboratory result below the lower limit of the normal range at Baseline and a laboratory result above the upper limit of the normal range at any post-baseline time point.
- Laboratory result above the upper limit of the normal range at Baseline and a laboratory result below the lower limit of the normal range at any post-baseline time point.

For laboratory tests covered by Common Terminology Criteria for Adverse Events (CTCAE), a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

All listings will include the result, change from baseline (for quantitative measurements, where applicable), date and time of measurement, reference range and flags for measurements that are outside the reference range (where applicable). Abnormal values will be flagged as "L" (for values lower than the lower limit of the reference range) and "H" (for values higher than the upper limit of the reference range). Clinical significance will be indicated as abnormal, "CS" (clinically significant) or abnormal, "NCS" (not clinically significant). Categorical results of laboratory tests will be presented by treatment arm using frequencies and percentages for each time point.

A separate listing of all results outside the reference ranges will be presented.

The baseline laboratory test result(s) for clinical assessment for a particular test parameter will be defined as the last measurement performed prior to the initial dose administration of the investigational product. No changes from baseline will be calculated for Screening and follow up (FU) measurements.

Summary tabulations for laboratory parameters will be presented by treatment and time point, and overall by time point. Measurements obtained at Screening will be included in the tabulations in the overall column.

Laboratory values will be categorized whether they are clinically significant or not and frequencies and percentages of clinically significant values will be provided. Categorical results of laboratory tests will be presented by treatment using frequencies and percentages for each time point.

Any laboratory values given as <X.X in the database will be imputed with the value of the number without the sign for the descriptive statistics and the calculation of changes from baseline, e.g., a value of <2.2 will be imputed as 2.2 for the calculations. There will be no imputation in the data listings; all values will be displayed as recorded in the database.

4.11.5 Vital Signs, Physical Findings and Other Observations Related to Safety

Vital Signs

Vital signs (Supine blood pressure, supine pulse rate, respiratory rate, oral body temperature and pulse Oximetry) measurements and changes from baseline (where applicable) will be listed by subject, treatment and time point, including flags for measurements outside the reference ranges and the corresponding Investigator assessment (CS or NCS).

The baseline for vital signs is defined as last non-missing value prior to the treatment administration. Summary tabulations will be presented by treatment and time point, and overall by time point.

12-Lead Electrocardiogram

Electrocardiogram parameter measurements will be listed by subject, treatment and time point, including flags for measurements outside the reference ranges and the corresponding Investigator assessment (CS or NCS) and interpretation.

Summary tabulations will be presented for each of the ECG parameter by overall by time point. The following ECG parameters will be recorded:

- QT-interval (msec)
- QRS-duration (msec)
- PR-interval (msec)
- RR-interval (msec)
- QT-interval (QTcB and QTcF) (msec)
- Heart Rate (bpm)

QTcf will be derived in the using following formula.

$QTcf = QT/\sqrt[3]{RR}$

Where QT in milliseconds (ms) and RR interval in seconds (s).

Physical Examination

The results of the physical examination will be listed by subject, treatment and time point for each body system.

4.11.6 Safety Monitoring (Independent Data Monitoring Committee [IDMC], Data Monitoring Committee [DMC], Data and Safety Monitoring Board [DSMB])

Not Applicable.

4.12 Other Analyses

Immunogenicity Analyses

Please refer latest version of the PKAP for Immunogenicity analysis developed by Covance.

4.13 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 ($AUC_{(0-\infty)}$ and C_{max}) using a percent coefficient of variation (CV%) of 25% in both PK parameters for the similarity objective if the true ratio is equal to 1.05 or less.
A conservative estimate of CV% was based on a prior MB02 study [8] and information from the public domain [9]. Model-based simulations from a developed population PK literature model, accounting for similarity between bevacizumab sources (EU/US), intrinsic PK altering factors (body weight, sex, serum albumin and alkaline phosphatase), between subject variability and residual variability showed that a sample size of 90 subjects provided at least 90% probability of concluding PK similarity for the all pairwise comparisons in terms of C_{max} and $AUC_{(0-\infty)}$.

Simulations also showed that the probability of concluding PK similarity in terms of $AUC_{(0-t)}$ 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.

4.14 Changes in the Conduct of the Study or Planned Analysis

Not applicable.

5 REFERENCES

[1] ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994

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

[3] 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.

[4] SAS® Version 9.4 of the SAS System for Personal Computers. Copyright © 2002-2003. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

[5] Phoenix®WinNonlin® Professional Software Version 8.0. https://www.certara.com

6 APPENDICES

6.1 Schedule of Assessments

Table 51 Schedule of Assessments

Study Procedures	Day -30 to Day -2	Day -1	Day 1	Day 2	Day 3 to Day 8	Day 10	Day 14 to Day 78	Day 100
Informed consent	X							
Inclusion/exclusion criteria	X	X						
Demographic data	X							
Medical history	X	X[a]						
Urinary drug screen and cotinine test	X	X						
Alcohol urinary test	X	X						
Serology	X							
Height and body weight[b]	X	X						
Study residency:								
Randomisation		X						
Check-in		X						
Check-out					Day 8			
Nonresidential visit[e]	X					X	Day 14, 21, 28, 42, 56, 78	X
Study drug administration:								
MB02 or Avastin®			Day 1 (0 h)					
Pharmacokinetics:								
Blood sampling[c]			Predose, EOI[d], 2, 3, 4, 5, 6, 8, 12 h	24h	Day 3, Day 4, Day 5, Day 6, Day 7 and Day 8	X	Day 14, 21, 28, 42, 56, 78	X
Immunogenicity:								
Blood sampling		X					Day 14, 28, 56, 78	
Safety and tolerability:								
Adverse event recording	X	X	Ongoing	X	X	X	X	X

[redacted]

Study Procedures	Day -30 to Day -2	Day -1	Day 1	Day 2	Day 3 to Day 8	Day 10	Day 14 to Day 78	Day 100
Serious adverse event recording	X	X	Ongoing	X	X	X	X	X
Prior/concomitant medication monitoring	X	X	Ongoing	X	X	X	X	X
Clinical laboratory evaluations	X	X					Day 14, 21, 28, 42, 56, 78	X
Supine blood pressure, pulse rate, respiratory rate[c]	X	X	Predose, 0.5, 1, EOI[d], 2h	X	Day 5, Day 8	X	Day 21	X
Pulse oximetry	X							
Oral body temperature	X			X		X	Day 21	X
12-lead ECG	X	X			Day 3, Day 8			X
Physical examination	X	X						X

Abbreviations: ECG = electrocardiogram.
[a]. Interim medical history.
[b]. Height measured at Screening only.
[c]. All times stated are post-start of infusion.
[d]. EOI: End of infusion.
[e]. All non-residential visits on Days 10 to 100 can be conducted within ±1 day of the planned date.

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