Protocol Title:	A Randomised, Double Blind, Two-Arm, Single Dose, Parallel Phase I Study To Compare the Pharmacokinetics, Safety and Immunogenicity of MB02 (a proposed bevacizumab biosimilar drug) and EU approved Avastin® in Japanese Healthy Male Volunteers
NCT Number:	NCT04238650
Statistical Analysis Plan version date:	Version 1.0, 13 January 2020

Statistical Analysis Plan (Without PK and Immunogenicity analysis)

A RANDOMISED, DOUBLE BLIND, TWO-ARM, SINGLE DOSE, PARALLEL PHASE I STUDY TO COMPARE THE PHARMACOKINETICS, SAFETY AND IMMUNOGENICITY OF MB02 (A PROPOSED BEVACIZUMAB BIOSIMILAR DRUG) AND EU APPROVED AVASTIN® IN JAPANESE HEALTHY MALE VOLUNTEERS

Sponsor Protocol No.: MB02-A-04-18
Syneos Health Clinique Inc. Project No.: 7004567

Final Version: 1.0
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SIGNATURES

Sponsor Protocol No.: MB02-A-04-18

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LIST OF ABBREVIATIONS

ADA	Anti-Drug Antibodies
AE	Adverse Event
anti-HBs	Hepatitis B surface antibody
anti HBc	Hepatitis B core antibody
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood urea nitrogen
CI	Confidence Interval
CL	Total Body Clearance
CTCAE	Common Terminology Criteria For Adverse Events
CR/STBA	Confinement Report and Subjects to be Analyzed Form
CSR	Clinical Study Report
CV	Coefficient of Variation
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EMA	European Medicines Agency
EOI	End of Infusion
EOS	End of Study
HBsAg	Surface Antigen Of The Hepatitis B Virus
HCV	Human Hepatitis C Virus
HDL	High-Density Lipoprotein
HIV	Human Immunodeficiency Virus
HR	Heart Rate
INR	International Normalised Ratio
IV	Intravenous
kg	Kilogram

LDL	Low-density Lipoprotein
m	Meter
Max	Maximum
MedDRA	Medical Dictionary For Regulatory Activities
mg	Milligram
Min	Minimum
mL	Milliliter
mmHg	Millimeters Mercury
NAB	Neutralizing Anti-drug antibodies
QT	QT Interval
QTc	Corrected QT Interval
QTcF	QT corrected with Fridericia's formula
RR	Respiratory Rate
PT	Preferred Term
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SOC	System Organ Class
SOPs	Standard Operation Procedures
TEAEs	Treatment-Emergent Adverse Events
WBC	White Blood Cell
WHO DD	World Health Organization Drug Dictionary

1. Introduction

This statistical analysis plan (SAP) is intended to give a detailed description of the summaries and the analyses that will be generated for the mAbxience Research S.L. study protocol No. MB02-A-04-18, Version 1.2, dated 10 July 2019 (Syneos Project No. 7004567). Safety and tolerability analyses will be described.

The plan may change due to unforeseen circumstances and any changes made after the plan has been finalized will be documented. If additional analyses are required to supplement the planned analyses described in the SAP, the changes and justification for the changes will be outlined in the Clinical Study Report (CSR). No change will be made without prior approval of the study Sponsor. No revision to the SAP is required for changes that do not affect the statistical analysis methods, definitions, or rules defined in this document.

When applicable, all methodology and related processes will be conducted according to Syneos's Standard Operating Procedures (SOPs) as appropriate. Protocol deviations occurring during the study will be listed.

Shells for all statistical tables, figures and listings referred to in this SAP will be displayed in a separate document. Statistical analysis plan and shells for PK analysis and immunogenicity analysis will be displayed in a separate document and it could be provided by Covance.

2. Study Objectives

2.1 Primary objective

- To demonstrate PK similarity, as primary assessed by the Area Under the Concentration-time curve extrapolated to infinity ($AUC_{(0-\infty)}$) between the two study arms, MB02 and EU Avastin®.

2.2 Secondary objectives

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

3. Study Design

3.1 General Design

This will be a Phase 1, double-blind, randomised, parallel-group, single-dose two-arm study to investigate and compare the PK, safety and immunogenicity profiles of MB02 with EU-approved Avastin® in Japanese healthy male subjects. A total of forty-eight subjects were randomised to one of following 2 arms in a 1:1 ratio:

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

Twenty-four 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.

3.2 Study Procedures

The overall schedule of procedures and assessments is provided in the protocol.

3.3 Drug Administration

Subjects will receive a single dose of 3 mg/kg of one of the following treatments by IV infusion over 90 minutes. A total of 48 healthy adult male volunteers will be dosed; 24 subjects per treatment group, randomly assigned to one of the 2 treatment arms.

Treatment A (MB02):	3 mg/kg dose of MB02 (a proposed bevacizumab biosimilar drug), administered as a 90 minute IV infusion.
Treatment B (EU Avastin®):	3 mg/kg dose of EU-approved Avastin®, administered as a 90 minute IV infusion.

3.4 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. 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 adverse events (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.

4. Changes from the Protocol

No changes in planned analyses were done compared to the protocol.

5. Study Endpoints

5.1 Safety Endpoints

The safety outcome measures for this study are as follows (refer to Section 9):

- Incidence and severity of AEs
- Incidence of laboratory abnormalities, based on haematology, clinical chemistry, coagulation and urinalysis test results
- 12-lead electrocardiogram (ECG) parameters
- Vital sign measurements
- Physical examinations

The immunogenicity of MB02 and EU Avastin® (refer to Section 9)

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

6. Analysis Populations

The analysis of safety, tolerability and immunogenicity parameters will be based on the study population detailed in Section 6.1.

6.1 Safety Population

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

7. Interim Analyses

No formal interim analysis was planned in the protocol.

8. Study Population and Exposure

No inferential analysis will be done. Only observed data will be used.

8.1 Subject Disposition

Subject disposition will be summarized by treatments (frequency and the percentage of subjects) and overall. The following categories will be summarized by number and/or percentage.

- Screened and screen failures subjects (overall only).
- Enrolled and not enrolled subjects (overall only).
- Subjects who are dosed in each treatment and overall.
- Subjects who have completed the study in each treatment and overall.
- Subjects who discontinued in each treatment and overall.
- Primary reason for discontinuation in each treatment and overall.

In addition, the number of randomized subjects, number of subjects evaluable for safety (Safety Population) will be presented by treatment and overall.

For subjects enrolled, not enrolled and screen failures, the percentage denominator will be the number of screened subjects. For all other calculations, the percentage denominator will be the number of subjects dosed in each treatment. For overall, the percentages will be based on the overall number of subjects dosed (safety population).

Subject study completion and discontinuation information will be listed. This listing will include the following information:

- Subject identifier and randomization number
- Study day/Date of informed consent
- Study day/Date of randomization (for randomized subjects)
- Study Treatment received (for randomized subjects)
- Study Day/ Date of study completion or discontinuation
- Primary reason for discontinuation

8.2 Protocol Deviations

The protocol deviations will be categorized and listed by subject.

8.3 Demographics and Baseline Characteristics

Descriptive statistics (sample size (n), mean, median, standard deviation [SD], minimum [Min], and maximum [Max]) will be calculated for continuous variables (age, body mass index [BMI],

height, and weight) considering last results (scheduled or unscheduled) obtained at screening. Frequency counts and percentages will be tabulated for categorical variables (gender, ethnicity, and race). All summaries will be presented by treatment for safety and PK populations. All demographic characteristics will be listed by subject.

8.4 Medical History

Medical history will be listed by subject. The Medical Dictionary for Regulatory Activities (MedDRA®) Version 22.1 will be used to classify all medical history findings by System Organ Class (SOC) and Preferred Term (PT).

8.5 Prior and Concomitant Medications

The use of prior and/or concomitant medications will be monitored throughout the study and listed by subject. The World Health Organization Drug Dictionary (WHO DD) Version Sep2019, format B3 will be used to classify all medication reported during the study.

All prior and concomitant medications will be listed by subject.

8.6 Study Drug Administration

The study drug administration details (including treatment received, start and stop date and time of administration, total dose) will be listed by subject.

9. Safety Analyses

Safety and tolerability data will be evaluated through the assessment of AEs, clinical laboratory parameters (clinical chemistry, hematology, cogulation, urinalysis and serology), 12-lead electrocardiogram (ECG), vital signsand physical examination. AEs, laboratory values, 12-lead ECG and vital signs will be summarized overall or according to the treatment, as appropriate. The analysis of the safety variables will be based on safety population.

Safety data will be summarized, but will not be subjected to inferential analysis.

9.1 Physical Examination Findings

A full physical examination or symptom-directed physical examination will be performed at screening. Additionaly, symptom-directed physical examination will be performed at Day -1 (check-in) and Day 70 (End of Study (EOS)). A full physical examination or symptom-directed physical examination includes assessments of the following: Eye/Ear/Nose/Throat, General Appearance, Oral, Head and Neck, Chest/Lungs, Cardiovascular Abdomen, Musculoskeletal, Lymphatic, Dermatologic, Neurologic, Extremities, Psychiatric from the subject.

Body measurements, including height and body weight, will be measured and BMI will be calculated at screening. Body weight will also be measured at Day -1 (check-in). Body measurements will be summarized (mean, median, SD, min, max, and sample size) in demographic tables (safety and PK).

Any abnormal findings judged to be clinically significant will be documented as medical history or as an AE, during screening (non a TEAE) or after receiving treatment (TEAE). Any physical examination findings documented as AEs will be included in the AE summaries.

9.2 Adverse Events

Treatment-emergent AEs (TEAEs) will be listed and summarised using descriptive methodology. TEAEs will be defined as AEs that occur on or after the date and time of study drug administration. Any AE that first occurs pre-dose but worsens in severity after the first study drug administration will also be considered a TEAE. All AEs will be collected and documented during the course of the study. Subjects will 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.

The incidence of TEAEs and treatment-related AEs will be summarized using the safety population. The Medical Dictionary for Regulatory Activities (MedDRA®), Version 22.1 will be used to classify all AEs reported during the study by SOC and PT.

Incidence of subjects who experienced TEAEs (as well as number of events) will be presented by treatment and overall, by SOC, and PT, investigator-assessed relationship and also by severity. Each subject may only contribute once to each of the incidence rates, for a TEAE following a given treatment, regardless of the number of occurrences; the highest severity or highest relationship will be presented, as appropriate. In each table, SOC will be presented in descending order of overall incidence rate in terms of frequency of subjects and then in frequency of events (alphabetical order will be used in case of equal rates). For each SOC, PT will be presented the same way.

The causal relationship of an AE to the study drug will be assessed according to the study protocol as:

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. Treatment-related AEs will be those reported as Possibly Related, Probably Related or Related to Study Drug.

The severity of an AE or serious AE (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 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". SAEs will be listed separately by subjects.

9.3 Laboratory Parameters

Clinical laboratory (clinical chemistry, hematology, coagulation and urinalysis) results will be obtained at screening, Day -1 (check-in), Day 8, Day 14, Day 21, Day 28, Day 38, Day 50, Day 62 and Day 70 (EOS).

Clinical chemistry parameters include the following: albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), Blood urea nitrogen (BUN), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, total cholesterol, Uric acid, Calcium, Chloride, Inorganic phosphate, Potassium, Creatinine, Creatine kinase, Gamma-glutamyl transferase, Lactate dehydrogenase, Glucose, Sodium, Total bilirubin, Direct bilirubin, and Total protein.

Hematology parameters include the following: Haematocrit, Haemoglobin, Mean cell haemoglobin, Mean cell haemoglobin concentration, Mean cell volume, Platelet count, Red blood cell (RBC) count, White blood cell (WBC) count and WBC differentials as Basophils, Eosinophils, Lymphocytes, Monocytes, and Neutrophils.

Coagulation parameters include the following: International normalised ratio (INR), Prothrombin time and Activated partial thromboplastin time.

Urinalysis parameters include the following: Complete microscopic examination, pH, Specific gravity, Urobilinogen, Protein, Ketones, Blood, and Glucose. Unless otherwise specified, microscopic examination will be performed on abnormal findings and results will be listed.

Serology parameters including: Hepatitis B surface antigen (HBs Ag), Hepatitis B surface antibody (anti-HBs), Hepatitis B core antibody (anti HBc), Hepatitis C antibody, Human immunodeficiency HIV antigen antibodies, and Syphilis (RPR method, TP antibody method) will be performed at screening.

Urinary drug screen including: Cotinine, Amphetamines/methamphetamines, Barbiturates, Benzodiazepines, Cocaine (metabolite), Methadone, Phencyclidine, Opiates, Tetrahydrocannabinol/cannabinoids, and Tricyclic antidepressants; and Breath alcohol test will be performed at screening and at Day -1 (check-in).

Listings of all clinical laboratory results, including those unscheduled, will be provided with the abnormal values flagged with "L" for low and "H" for high for continuous parameters, and “A” for abnormal for categorical parameters.

Descriptive statistics (mean, median, SD, min, max, and sample size) for each clinical laboratory test (continuous variables) will be presented by treatment for each timepoints. Change from baseline descriptive statistics for post-dose measurements as well as for EOS will be presented. Baseline will be defined as the last results (scheduled or unscheduled) obtained prior to the study drug administration. Unscheduled results will not be included in the summary tables except for baseline calculation if applicable. For categorical variables (urinalysis tests), the number of subjects (frequency and percentage) will be tabulated for each individual result (e.g., negative, positive, trace). Results from repeat tests will not be included in the summary statistics unless the repeat was required (and documented as such) due to technical reasons or an invalid initial result.

A summary table of shifts from baseline to EOS measurements will be provided. Baseline will be defined in the same manner as described in the preceding paragraph for continuous variables. The shift tables will include normal, low, and high relative to the laboratory reference ranges (or normal-abnormal for categorical variables). Results from repeat tests will not be included in the summary statistics unless the repeat was required (and documented as such) due to technical reasons or an invalid initial result.

9.4 Vital Signs

Supine blood pressure, supine pulse rate, respiratory rate (RR) will be assessed at screening, Day -1 (check-in), predose, 0.5H, 1H, End of infusion (EOI) and 2H of Day 1, Day 2, Day 5, Day 8, Day 10, Day 14, Day 21, Day 28, Day 38, Day 50, Day 62 and Day 70 (EOS). Tympanic membrane or axilla body temperature will be assessed at screening, Day 2, Day 10, Day 21 and Day 70 (EOS) and pulse oximetry (PO) will be assessed at screening only.

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

Descriptive statistics (mean, median, SD, min, max, and sample size) will be presented by treatment for each timepoint and for each vital sign measurement. Change from baseline descriptive statistics for post-dose measurements as well as for EOS will be presented. Baseline

will be defined as the last results (scheduled or unscheduled) obtained prior to the study drug administration. Unscheduled results will not be included in the summary tables except for baseline calculation if applicable. Results from repeat tests will not be included in the summary statistics unless the repeat was required (and documented as such) due to technical reasons or an invalid initial result.

A listing of all vital signs results will be provided by subject.

9.5 Electrocardiogram

12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at screening, Day 1(predose), Day 3, Day 8 and Day 70 (EOS). The quantitative ECG measurements are heart rate (HR), PR interval, QRS interval, QT interval, QTcF (Fridericia formula correction). 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.

Descriptive statistics (mean, median, SD, min, max, and sample size) will be presented by treatment for screening, Day 1(predose), Day 3, Day 8 and Day 70 (EOS) for each ECG measurement. Change from baseline descriptive statistics for post-dose measurements as well as for EOS will be presented. Baseline will be defined as the last results (scheduled or unscheduled) obtained prior to the study drug administration. Unscheduled results will not be included in the summary tables except for baseline calculation if applicable. Results from repeat tests will not be included in the summary statistics unless the repeat was required (and documented as such) due to technical reasons or an invalid initial result.

A listing of all ECG results will be provided with the abnormal values flagged.

Additionally, the listing of QT interval corrected for HR using Fridericia's method (QTcF) > 500 msec and QTcF change from the baseline (predose) is > 60 msec will be provided by subjects.

10. Percentages and Decimal Places

If not otherwise specified, the following rules will be applied, with the exception of PK tables and listings described below:

- Percentages will be presented to one decimal place.
- Percentages equal to 0 or 100 will be presented as such without a decimal place.
- Minimum and maximum will be presented with the same precision as the original values and, mean, standard deviation, and median will be presented with one more decimal place than the original values.

11. Data Handling

The safety data will be received as SAS® datasets from the Syneos data management facility. Screening failures and ineligible volunteer's data (subject disposition) will be received from the clinical site as source data. The serum concentrations and Immunogenicity data will be provided by Covance.

12. Handling of Missing Data

For safety,

- If an AE is recorded with an onset date corresponding to a dosing day, but the time is missing, then the AE will be assigned to the treatment.
- If an AE is recorded with an onset date that does not correspond to the dosing day, but the time is missing, then the AE will be assigned to the treatment if AE onset date is after dosing date.
- If an AE is recorded with an onset date where day and time are both missing, then the AE allocation to the treatment will be done on a case by case basis considering available information (e.g., AE onset date, AE end date, AE comments, subject disposition).

13. Software to be Used

The safety data tables and listings will be created using SAS®, release 9.2 or a higher version. PK figures will be created using R version 3.2.2 or higher. The study report text will be created using Microsoft® Office Word 2010, or a higher version.

14. Reference List

- Chuang-Stein C. Summarizing laboratory data with different reference ranges in multi-center clinical trials. Drug Information Journal. 1992; 26:77-84.
- Karvanen J. The statistical basis of laboratory data normalization. Drug Information Journal. 2003; 37:101-107.