Statistical Analysis Plan Title:	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
NCT Number:	NCT04408989
Statistical Analysis Plan version date:	Version 1.0, 20 May 2021

Statistical Analysis Plan (Without PK and Immunogenicity analysis)

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

Sponsor Protocol No.: MB02-A-06-20
Syneos Health Clinique Inc. Project No.: 7012755

Final Version: 1.0
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Revision History

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Signature Approvals

I confirm that I have reviewed this document and agree with the content.

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Name, Title Sponsor Contact	Signature	Date (DD-Mmm-YYYY)

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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-06-20, Version 1.0, dated 26 May 2020 (Syneos Project No. 7012755). 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 investigate and compare the pharmacokinetic (PK) profiles of MB02-SP (MB02 standard procedure), MB02-DM (MB02 defined media) and US-licenced Avastin® (US Avastin®) to establish bioequivalence between the 3 study arms.

2.2 Secondary objectives

- 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. Study Design

3.1 General 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 profiles of MB02-DM with MB02-SP and US Avastin® in healthy male subjects. A total of One hundred and fourteen (114) subjects will be randomised to one of following 3 arms in a 1:1:1 ratio:

- Arm 1: MB02-SP (MB02 standard procedure) as a 90 minute IV infusion
- Arm 2: MB02-DM (MB02 defined media) 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.

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 1 mg/kg of one of the following treatments by IV infusion over 90 minutes. A total of 114 healthy adult male volunteers will be dosed; 38 subjects per treatment group, randomly assigned to one of the 3 treatment arms.

- 1 mg/kg dose of MB02-SP (bevacizumab biosimilar drug), administered as a 90 minute IV infusion.
- 1 mg/kg dose of MB02-DM (bevacizumab biosimilar drug), administered as a 90 minute IV infusion.
- 1 mg/kg dose of US 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.

3.5 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 Cmax) 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 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.

3.6 Randomization and Blinding

A computer generated randomization schedule will be prepared by the assigned 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 (≥50.0 to <72.5kg, and ≥72.5 to ≤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.

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.

4. Changes from the Protocol

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

5. Study Endpoints

5.1 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})

5.2 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, coagulation 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, MB02-SP, and anti-Avastin® antibodies.

6. Analysis Populations

The analysis of safety and tolerability 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-DM, MB02-SP or US Avastin®, and have at least one post dose safety assessment.

7. General Aspects for Statistical Analysis

7.1 General Methods

SAS® for Windows, Release 9.4 (SAS® Institute Inc., Cary, NC, USA) software will be used to perform all data analyses.

All data in the database will be presented in the data listings. Unless otherwise stated, all listings will be sorted by randomized treatment group, subject number and assessment date/time

The following labels for treatment will be used on all tabulations where the results are displayed by treatment, in the following order:

- 1 mg/kg MB02 - SP IV
- 1 mg/kg MB02 - DM IV
- 1 mg/kg US - Avastin® IV

7.2 Summary Statistics:

Unless otherwise stated, continuous variables will be summarized using the number of observations (n), and the statistics mean, median, standard deviation (SD), minimum and maximum. The minimum and maximum values will be presented to the same number of decimal places as recorded in the case report form (CRF), mean and median will be presented to one more decimal place than the raw data and the SD will be presented to two more decimal places than the raw data. Summaries of change-from-baseline variables will include only subjects who have both a baseline value and corresponding value at the timepoint of interest. Categorical variables will be summarized with frequency counts and percentages. Percentages will be rounded to one decimal place, with the denominator being the number of subjects in the relevant population, unless otherwise stated.

Only data from nominal protocol scheduled visits will be included in the summary tables. Data from unscheduled visits will not be included in the summary tables (unless they were used as baseline) but will be included in the listings and figures.

7.3 Key Definitions

Definition of Baseline

In general, baseline will be defined for each subject and will be defined as the last available, non-missing assessment prior to first study drug administration. Unknown, Not Done, Not Applicable and other classifications of missing data will not be considered when calculating baseline observations. However, valid categorical observations will be considered for baseline calculations.

7.4 Missing Data

All withdrawals will be included in all summaries up to the time of withdrawal.

There will be no imputation for missing data, unless otherwise specified.

7.5 Visit Windows

All assessments will be included in the listings. No visit windows will be applied to assessments.

8. Interim Analyses

No formal interim analysis was planned in the protocol.

9. Study Population and Exposure

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

9.1 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

9.2 Protocol Deviations

The protocol deviations will be categorized and listed by subject.

9.3 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 population. All demographic characteristics will be listed by subject.

9.4 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).

Urine drug screen, cotinine test and alcohol breath test will be listed only.

9.5 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 Mar 2020, format B3 will be used to classify all medication reported during the study.

All prior and concomitant medications will be listed by subject.

9.6 Study Drug Administration

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

10. 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 signs and 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.

10.1 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 100 (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 population).

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.

10.2 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 or is deemed to be related to the study drug 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 23.0 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

SAEs will be listed separately by subjects.

10.3 Laboratory Parameters

Clinical laboratory (clinical chemistry, hematology, coagulation and urinalysis) results will be obtained at screening, Day -1 (check-in), Day 3, Day 8, Day 14, Day 21, Day 28, Day 42, Day 56, Day 78 and Day 100 (EOS).

Clinical chemistry parameters include the following: albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), Urea, 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 and Human immunodeficiency HIV antigen antibodies will be performed at screening.

Urinary drug screen including: Cotinine, Amphetamines/methamphetamines, Barbiturates, Benzodiazepines, Cocaine (metabolite), Methadone, Phencyclidine, Opiates, Tetrahydrocannabinol/cannabinoids, 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 representing the categorical change of laboratory results (normal, abnormal not clinically significant, or abnormal clinically significant) from baseline to each post baseline visit will be presented. 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.

If more than one clinical laboratory is used for the study, a formula that takes into consideration the relative normal ranges of each test of laboratories used will be applied to normalize these data. The conversion formula used will depend on the typical distribution of the normal range for each laboratory test; the two formula used are presented below:

- Hemoglobin, hematocrit, and platelet count test results are considered to have a normal distribution (Chuang-Stein, 1992) and the following formula will be used (Karvanen J., 2003):

$$s = L_s + (x - L_x)\frac{U_s - L_s}{U_x - L_x}$$

- The remaining hematology, biochemistry, and urinalysis test results are considered to have a non-normal distribution (Chuang-Stein, 1992) and the following formula will be used (Karvanen J., 2003):

$$s = \frac{x\ U_s}{U_x}$$

U= upper limit; L= lower limit; s= primary facility result; and x= secondary facility results.

Prior to applying these formulae, if required, units will be adjusted.

10.4 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 21, and Day 100 (EOS). Aural body temperature will be assessed at

screening, Day 2, Day 10, Day 21 and Day 100 (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.

10.5 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, Day 3, Day 8 and Day 100 (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 each time point and 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.

Furthermore, a shift table representing the categorical change of ECGs results (normal, abnormal not clinically significant, or abnormal clinically significant) from baseline to each post baseline visit will be presented.

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.

11. 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; Mean, and median will be presented with one more decimal place than the original values, and standard deviation, will be presented with two more decimal place than the original values.

12. 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.

13. 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).

14. Software to be Used

The safety data tables and listings will be created using SAS®, release 9.4. The study report text will be created using Microsoft® Office Word 2010, or a higher version.

15. 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.

Table/Figure/Listing Shells (Without PK and Immunogenicity analysis)

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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1. Tables, Figures and Data Listings Formatting

The table, figure, and data listing (TFL) shells are presented in order to provide a framework for displaying the study data. The shells may change due to unforeseen circumstances. The shells may not be truly representative of every aspect of the study (e.g., sampling time points, assessed laboratory parameters, calculated parameters, units), but are intended to illustrate the general layout of the tables, figures, and data listings that will be included in the final report.

The default tables, listings, and figures layout will be as presented in Table 1-1:

Table 1-1 Layout Specifications

Orientation	Portrait	Landscape
Paper Size	Letter	Letter
Margins	Top: 3.05 cm Bottom: 2.54 cm Left: 2.54 cm Right: 2.54 cm	Top: 3.05 cm Bottom: 2.2 cm Left: 1.9 cm Right: 1.9 cm
Font	Table text: Times new Roman 9 or 10 pts Table title: Times new Roman 12 pts Table legend: Times new Roman 9 or 10 pts	

The font size may be reduced as necessary to allow additional columns to be presented, but not at the expense of clarity. Also the orientation may be changed to portrait if appropriate.

1.1 Headers

- All output should have the following header at the top left of each page:
- mAbxience Research S.L.
- All output should have Page n of N at the top or bottom right corner of each page. TLFs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

2. Summary TFLs

Table 2-1 List of Table Shells

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	In-Text Table
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	Safety Data Summary Tables
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14.3.1-4	Number of Treatment-Emergent Adverse Events Summarized per Treatment and Severity – Safety Population
14.3.1-5	Frequency of Subjects Experiencing Treatment-Emergent Adverse Events Summarized per Treatment and Relationship – Safety Population
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14.3.4-1	Clinical Chemistry Summary Descriptive Statistics and Change from Baseline – Safety Population
14.3.4-2	Frequency of Subjects – Clinical chemistry Shifts from Baseline – Safety Population
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14.3.4-5	Urinalysis (pH and Specific Gravity) Summary Descriptive Statistics and Change from Baseline – Safety Population
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14.3.4-7	Coagulation Summary Descriptive Statistics and Change from Baseline – Safety Population
14.3.4-8	Frequency of Subjects – Coagulation Shifts from Baseline – Safety Population
14.3.4-9	Urinalysis Frequency Summary – Categorical Results – Safety Population
14.3.4-10	Frequency of Subjects – Urinalysis Shifts from Baseline – Categorical Results – Safety Population
14.3.4-11	Vital Signs Summary Descriptive Statistics and Change from Baseline – Safety Population
14.3.4-12	Electrocardiograms Summary Descriptive Statistics and Change from Baseline – Safety Population

14.3.4-13	Frequency of Subjects – Electrocardiograms Shifts from Baseline – Safety Population

Table 2-3 List of Data Listings Shells

Listing Number	Title
	Subject Characteristics Listings
16.2.1-1	Subjects Completion and Discontinuation Information
16.2.2-1	Protocol Deviations
16.2.4-1	Demographics
16.2.4-2	Medical History Findings at Screening
16.2.4-3	Prior and Concomitant Medications
16.2.4-4	Study Drug Administration
16.2.4-5	Interruption of IV Infusion
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16.2.8-1	Clinical Laboratory – Clinical chemistry
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16.2.8-6	Clinical Laboratory – Urine Drug Screen and Alcohol Breath Tests
16.2.8-7	Vital Signs Result
16.2.8-8	Pulse oximetry Results
16.2.8-9	Electrocardiogram Result
16.2.8-10	QT interval corrected for heart rate using QTcF > 500 msec
16.2.8-11	QTcF change from the baseline (predose) is > 60 msec
16.2.8-12	Physical Examination Findings by Subject

3. CSR In-text Tables

Table 10.1-1 Subject Disposition

Category	1 mg/kg MB02 - SP IV	1 mg/kg MB02 - DM IV	1 mg/kg US - Avastin® IV	Overall
Screened		-	-	xx
Screening Failures[1,2]		-	-	x (xx.x)
Not Enrolled[1,3]		-	-	x (xx.x)
Enrolled[1,4]		-	-	x (xx.x)
Safety Population	x (xx.x)	x (xx.x)	x (xx x)	x (xx.x)
Randomized	xx	xx	xx	xx
Dosed	xx	xx	xx	xx
Not Dosed	xx	xx	xx	xx
Completed Study[5,6]	x (xx.x)	x (xx.x)	x (xx x)	x (xx.x)
Number of Subjects Discontinued[7]	xx	xx	xx	xx
Primary Reason for Discontinuation[7, 8]				
Adverse Event	x (xx.x)	x (xx.x)	x (xx x)	x (xx.x)
Death	x (xx.x)	x (xx.x)	x (xx x)	x (xx.x)
Lost To Follow-up	x (xx.x)	x (xx.x)	x (xx x)	x (xx.x)
Physician Decision	x (xx.x)	x (xx.x)	x (xx x)	x (xx.x)
Protocol Deviation	x (xx.x)	x (xx.x)	x (xx x)	x (xx.x)
Study Terminated by Sponsor	x (xx.x)	x (xx.x)	x (xx x)	x (xx.x)
Informed Consent Withdrawn	x (xx.x)	x (xx.x)	x (xx x)	x (xx.x)
Withdrawal by Subject	x (xx.x)	x (xx.x)	x (xx x)	x (xx.x)
Other	x (xx.x)	x (xx.x)	x (xx x)	x (xx.x)

Programming Note:

[1] Percentage based on the number of screened subjects.

[2] Screening failures include subjects who did not meet project criteria.

[3] Not enrolled include subjects who were judged eligible but decided not to participate on study or who were not selected to participate in the study since there was already a sufficient number of subjects.

[4] Enrolled include subjects who were judged eligible and accepted to participate in the trial after having signed the approved final version of the study informed consent form and also those identified as standby who may replace subjects who withdraw from the study before dosing.
[5] Completed study include subjects who complete the study until follow-up visit without major protocol deviation.
[6] Percentage based on the number of dosed subjects for a given treatment.
[7] Overall, each subject could only contribute once to each reason for discontinuation, regardless of the number of occurrences.
[8] Percentage based on the number of discontinued subjects per treatment group or overall, as appropriate.

Data source: Listings 16.2.1-1 and 16.2.4-4.

4. Summary Tables

Table 14.1-1 Summary of Demographic Characteristics of Subjects Included in the Safety Population

Category	Statistic	1 mg/kg MB02 - SP IV	1 mg/kg MB02 - DM IV	1 mg/kg US - Avastin® IV
Age (years)	N	xx	xx	xx
	Mean	xx x	xx.x	xx x
	SD	xx x	xx.x	xx x
	Median	xx x	xx.x	xx x
	Min, Max	xx-xx	xx-xx	xx-xx
Gender				
Male	n (%)	x (xx x)	x (xx x)	x (xx.x)
Ethnicity				
Not Hispanic or Latino	n (%)	x (xx x)	x (xx x)	x (xx.x)
Hispanic or Latino	n (%)	x (xx x)	x (xx x)	x (xx.x)
Not Reported	n (%)	x (xx x)	x (xx x)	x (xx.x)
Unknown	n (%)	x (xx x)	x (xx x)	x (xx.x)
Race				
Am Indian:				
Asian	n (%)	x (xx x)	x (xx x)	x (xx.x)
Black	n (%)	x (xx x)	x (xx x)	x (xx.x)
Australian Aborigine/Torres Strait Islander	n (%)	x (xx x)	x (xx x)	x (xx.x)
Pacific Islander	n (%)	x (xx x)	x (xx x)	x (xx.x)
White	n (%)	x (xx x)	x (xx x)	x (xx.x)
Other	n (%)	x (xx x)	x (xx x)	x (xx.x)
Height (cm)	N	xx	xx	xx
	Mean	xx.xx	xx xx	xx.xx
	SD	xx.xx	xx xx	xx.xx
	Median	xx.xx	xx xx	xx.xx
	Min, Max	xx xx-xx xx	xx.xx-xx.xx	xx xx-xx xx
Weight (kg) Screening	N	xx	xx	xx
	Mean	xx.xx	xx xx	xx.xx
	SD	xx.xx	xx xx	xx.xx

	Median	xx.xx	xx xx	xx.xx
	Min, Max	xx xx-xx xx	xx.xx-xx.xx	xx xx-xx xx
Weight (kg) Day -1	N	xx	xx	xx
	Mean	xx.xx	xx xx	xx.xx
	SD	xx.xx	xx xx	xx.xx
	Median	xx.xx	xx xx	xx.xx
	Min, Max	xx xx-xx xx	xx.xx-xx.xx	xx xx-xx xx
Weight (≥50.0 to <72.5 kg) (kg)	N	xx	xx	xx
	Mean	xx.xx	xx xx	xx.xx
	SD	xx.xx	xx xx	xx.xx
	Median	xx.xx	xx xx	xx.xx
	Min, Max	xx xx-xx xx	xx.xx-xx.xx	xx xx-xx xx
Weight (≥72.5 to ≤95.0 kg) (kg)	N	xx	xx	xx
	Mean	xx.xx	xx xx	xx.xx
	SD	xx.xx	xx xx	xx.xx
	Median	xx.xx	xx xx	xx.xx
	Min, Max	xx xx-xx xx	xx.xx-xx.xx	xx xx-xx xx
BMI (kg/m^2)	N	xx	xx	xx
	Mean	xx xxx	xx xxx	xx xxx
	SD	xx xxx	xx xxx	xx xxx
	Median	xx xxx	xx xxx	xx xxx
	Min, Max	xx xx-xx xx	xx.xx-xx.xx	xx xx-xx xx

Programming Note:
1) Refer to the note below for additional instructions

N: Number of subjects dosed; n (%): Number and percent of subjects; SD: Standard Deviation.
Am Indian: American Indian or Alaskan Native; Black: Black or African American;
BMI: body mass index.

Last results (scheduled or unscheduled) obtained at screening were used to generate this table.
Data source: Listing 16.2.4-1

Table 14.1-2 Summary of Protocol Deviations – Safety Population

Protocol Deviation Category	1 mg/kg MB02 - SP IV (N= xxx)	1 mg/kg MB02 - DM IV (N= xxx)	1 mg/kg US - Avastin® IV (N= xxx)
Category 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Category 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Category 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
etc	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Programming Notes: Include categories as available in the source protocol deviation log.

Table 14.3.1-1 Overview of Treatment-Emergent Adverse Events – Safety Population

MedDRA® System Organ Class MedDRA® Preferred Term	Statistic	1 mg/kg MB02 - SP IV	1 mg/kg MB02 - DM IV	1 mg/kg US - Avastin® IV	Overall (N=XX)
Subjects with TEAEs	n (%)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)
Number of TEAEs	[E]	[x]	[x]	[x]	[x]
Subjects with SAEs	n(%)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)
Total number of SAEs	[E]	[x]	[x]	[x]	[x]
Subjects discontinued due to TEAEs	n(%)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)
Total number of TEAEs leading to discontinuation	[E]	[x]	[x]	[x]	[x]
All TEAEs by Severity					
Grade 1: Mild	n (%)[E]	x (xx x) [x]	x (xx.x) [x]	x (xx x) [x]	x (xx x) [x]
Grade 2: Moderate	n (%)[E]	x (xx x) [x]	x (xx.x) [x]	x (xx x) [x]	x (xx x) [x]
Grade 3: Severe	n (%)[E]	x (xx x) [x]	x (xx.x) [x]	x (xx x) [x]	x (xx x) [x]
Grade 4: Life Threatening	n (%)[E]	x (xx x) [x]	x (xx.x) [x]	x (xx x) [x]	x (xx x) [x]
Grade 5: Death	n (%)[E]	x (xx x) [x]	x (xx.x) [x]	x (xx x) [x]	x (xx x) [x]
Total	n (%)[E]	x (xx x) [x]	x (xx.x) [x]	x (xx x) [x]	x (xx x) [x]
Related TEAEs (possible, probable, related) by severity					
Grade 1: Mild	n (%)[E]	x (xx x) [x]	x (xx.x) [x]	x (xx x) [x]	x (xx x) [x]
Grade 2: Moderate	n (%)[E]	x (xx x) [x]	x (xx.x) [x]	x (xx x) [x]	x (xx x) [x]
Grade 3: Severe	n (%)[E]	x (xx x) [x]	x (xx.x) [x]	x (xx x) [x]	x (xx x) [x]
Grade 4: Life Threatening	n (%)[E]	x (xx x) [x]	x (xx.x) [x]	x (xx x) [x]	x (xx x) [x]
Grade 5: Death	n (%)[E]	x (xx x) [x]	x (xx.x) [x]	x (xx x) [x]	x (xx x) [x]
Total	n (%)[E]	x (xx x) [x]	x (xx.x) [x]	x (xx x) [x]	x (xx x) [x]

E: Number of TEAEs; N: Number of subjects dosed; n (%): Number and percent of subjects with TEAE; MedDRA®: Medical Dictionary for Regulatory Activities, version 23.0; TEAEs: Treatment-Emergent Adverse Events.
Each subject could only contribute once to each of the incidence rates, regardless of the number of occurrences.
Overall: Included results from all treatment groups.
Data source: Listing 16.2.7-2

Table 14.3.1-2 Frequency of Subjects Experiencing Treatment-Emergent Adverse Events and Number of Events Summarized per Treatment – Safety Population

MedDRA® System Organ Class MedDRA® Preferred Term	Statistic	1 mg/kg MB02 - SP IV (N=XX)	1 mg/kg MB02 - DM IV (N=XX)	1 mg/kg US - Avastin® IV (N=XX)	Overall (N=XX)
Number of TEAEs	E	xx	xx	xx	xx
Number of Subjects with TEAEs	n (%)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)
MedDRA® System Organ Class 1	n(%) [E]	x (xx x) [x]	x (xx.x) [x]	x (xx x) [x]	x (xx x) [x]
MedDRA® Preferred Term 1	n(%) [E]	x (xx x) [x]	x (xx.x) [x]	x (xx x) [x]	x (xx x) [x]
MedDRA® Preferred Term 2	n(%) [E]	x (xx x) [x]	x (xx.x) [x]	x (xx x) [x]	x (xx x) [x]
MedDRA® System Organ Class 2	n(%) [E]	x (xx x) [x]	x (xx.x) [x]	x (xx x) [x]	x (xx x) [x]
MedDRA® Preferred Term 1	n(%) [E]	x (xx x) [x]	x (xx.x) [x]	x (xx x) [x]	x (xx x) [x]
MedDRA® Preferred Term 2	n(%) [E]	x (xx x) [x]	x (xx.x) [x]	x (xx x) [x]	x (xx x) [x]
MedDRA® System Organ Class 3	n(%) [E]	x (xx x) [x]	x (xx.x) [x]	x (xx x) [x]	x (xx x) [x]
MedDRA® Preferred Term 1	n(%) [E]	x (xx x) [x]	x (xx.x) [x]	x (xx x) [x]	x (xx x) [x]
MedDRA® Preferred Term 2	n(%) [E]	x (xx x) [x]	x (xx.x) [x]	x (xx x) [x]	x (xx x) [x]

Programming Notes:
1) 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.
2) Refer to footnotes for additional instructions.

E: Number of TEAEs; N: Number of subjects dosed; n (%): Number and percent of subjects with TEAE; MedDRA®: Medical Dictionary for Regulatory Activities, version 23.0; TEAEs: Treatment-Emergent Adverse Events.
Each subject could only contribute once to each of the incidence rates, regardless of the number of occurrences.
Overall: Included results from all treatment groups.
Data source: Listing 16.2.7-2

Table 14.3.1-3 Frequency of Subjects Experiencing Treatment-Emergent Adverse Events Summarized per Treatment and Severity – Safety Population

MedDRA® System Organ Class MedDRA® Preferred Term	1 mg/kg MB02 - SP IV (N=XX)						1 mg/kg MB02 - DM IV (N=XX)					
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total TEAEs	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total TEAEs
MedDRA® System Organ Class 1	x (xx.x)	x (xx.x)	x (xx x)	x (xx x)	x (xx x)	x (xx x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)
MedDRA® Preferred Term 1	x (xx.x)	x (xx.x)	x (xx x)	x (xx x)	x (xx x)	x (xx x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)
MedDRA® Preferred Term 2	x (xx.x)	x (xx.x)	x (xx x)	x (xx x)	x (xx x)	x (xx x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)
MedDRA® System Organ Class 2	x (xx.x)	x (xx.x)	x (xx x)	x (xx x)	x (xx x)	x (xx x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)
MedDRA® Preferred Term 1	x (xx.x)	x (xx.x)	x (xx x)	x (xx x)	x (xx x)	x (xx x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)
MedDRA® Preferred Term 2	x (xx.x)	x (xx.x)	x (xx x)	x (xx x)	x (xx x)	x (xx x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)

Programming Notes:

1) *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.*
2) *If the distribution of treatments is presented on more than one page, preserve the order of the SOC and PT as defined in the generation of the global table without severity.*
3) *Refer to footnotes for additional instructions.*

N: Number of subjects dosed; n (%): Number and percent of subjects with treatment-emergent adverse events; MedDRA®: Medical Dictionary for Regulatory Activities, version 23.0.

Each subject could only contribute once to each of the incidence rates, regardless of the number of occurrence; the highest severity is presented.

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.

Total TEAEs: Includes results from all severities per treatment and overall.

Overall: Included results from all treatment groups.

Data source: Listing 16.2.7-2

Table 14.3.1-3 Frequency of Subjects Experiencing Treatment-Emergent Adverse Events Summarized per Treatment and Severity – Safety Population (cont.)

MedDRA® System Organ Class MedDRA® Preferred Term n (%)	1 mg/kg US - Avastin® IV (N=XX)						Overall (N=XX)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total TEAEs	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total TEAEs
MedDRA® System Organ Class 1	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx x)	x (xx x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)	x (xx x)
MedDRA® Preferred Term 1	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx x)	x (xx x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)	x (xx x)
MedDRA® Preferred Term 2	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx x)	x (xx x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)	x (xx x)
MedDRA® System Organ Class 2	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx x)	x (xx x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)	x (xx x)
MedDRA® Preferred Term 1	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx x)	x (xx x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)	x (xx x)
MedDRA® Preferred Term 2	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx x)	x (xx x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)	x (xx x)

Programming Notes:

1) *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.*
2) *If the distribution of treatments is presented on more than one page, preserve the order of the SOC and PT as defined in the generation of the global table without severity.*
3) *Refer to footnotes for additional instructions.*

N: Number of subjects dosed; n (%): Number and percent of subjects with treatment-emergent adverse events; MedDRA®: Medical Dictionary for Regulatory Activities, version 23.0

Each subject could only contribute once to each of the incidence rates, regardless of the number of occurrence; the highest severity is presented.

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.

Total TEAEs: Includes results from all severities per treatment and overall.

Overall: Included results from all treatment groups.

Data source: Listing 16.2.7-2

Table 14.3.1-4 Number of Treatment-Emergent Adverse Events Summarized per Treatment and Severity – Safety Population

MedDRA® System Organ Class MedDRA® Preferred Term		1 mg/kg MB02 - SP IV (N=XX)						1 mg/kg MB02 - DM IV (N=XX)					
	E	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total TEAEs	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total TEAEs
Total Number of TEAEs													
MedDRA® System Organ Class 1	x	x	x	x	x	x	x	x	x	x	x	x	x
MedDRA® Preferred Term 1	x	x	x	x	x	x	x	x	x	x	x	x	x
MedDRA® Preferred Term 2	x	x	x	x	x	x	x	x	x	x	x	x	x
MedDRA® System Organ Class 2	x	x	x	x	x	x	x	x	x	x	x	x	x
MedDRA® Preferred Term 1	x	x	x	x	x	x	x	x	x	x	x	x	x
MedDRA® Preferred Term 2	x	x	x	x	x	x	x	x	x	x	x	x	x

Programming Notes:

1) *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.*
2) *If the distribution of treatments is presented on more than one page, preserve the order of the SOC and PT as defined in the generation of the global table without severity.*

E: Number of treatment-emergent adverse event; N: Number of subjects dosed; MedDRA®: Medical Dictionary for Regulatory Activities, version 23.0.
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.
Total TEAEs: Includes results from all severities per treatment and overall.
Overall: Included results from all treatment groups.
Data source: Listing 16.2.7-2

Table 14.3.1-4 Number of Treatment-Emergent Adverse Events Summarized per Treatment and Severity – Safety Population (cont.)

MedDRA® System Organ Class MedDRA® Preferred Term E	1 mg/kg US - Avastin® IV (N=XX)						Overall (N=XX)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total TEAEs	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total TEAEs
Total Number of TEAEs												
MedDRA® System Organ Class 1	x	x	x	x	x	x	x	x	x	x	x	x
MedDRA® Preferred Term 1	x	x	x	x	x	x	x	x	x	x	x	x
MedDRA® Preferred Term 2	x	x	x	x	x	x	x	x	x	x	x	x
MedDRA® System Organ Class 2	x	x	x	x	x	x	x	x	x	x	x	x
MedDRA® Preferred Term 1	x	x	x	x	x	x	x	x	x	x	x	x
MedDRA® Preferred Term 2	x	x	x	x	x	x	x	x	x	x	x	x

Programming Notes:

1) *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.*
2) *If the distribution of treatments is presented on more than one page, preserve the order of the SOC and PT as defined in the generation of the global table without severity.*
3) *Refer to footnotes for additional instructions.*

E: Number of treatment-emergent adverse event; N: Number of subjects dosed; MedDRA®: Medical Dictionary for Regulatory Activities, version 22.1.
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.
Total TEAEs: Includes results from all severities per treatment and overall.
Overall: Included results from all treatment groups.
Data source: Listing 16.2.7-2

Table 14.3.1-5 Frequency of Subjects Experiencing Treatment-Emergent Adverse Events Summarized per Treatment and Relationship – Safety Population

MedDRA® System Organ Class MedDRA® Preferred Term n (%)	1 mg/kg MB02 - SP IV (N=XX)						1 mg/kg MB02 - DM IV (N=XX)					
	Not related	Unlikely related	Possibly related	Probably related	Related	Total related TEAEs (possibly + probably + related)	Not related	Unlikely related	Possibly related	Probably related	Related	Total related TEAEs (possibly + probably + related)
MedDRA® System Organ Class 1	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)
MedDRA® Preferred Term 1	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)
MedDRA® Preferred Term 2	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)
MedDRA® System Organ Class 2	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)
MedDRA® Preferred Term 1	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)
MedDRA® Preferred Term 2	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)

Programming Notes:

1) *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.*
2) *If the distribution of treatments is presented on more than one page, preserve the order of the SOC and PT as defined in the generation of the global table without relationship.*
3) *Refer to footnotes for additional instructions.*

N: Number of subjects dosed; n (%): Number and percent of subjects with treatment-emergent adverse event; MedDRA®: Medical Dictionary for Regulatory Activities, version 23.0

Each subject could only contribute once to each of the incidence rates, regardless of the number of occurrences; the highest relationship is presented.

Total related TEAEs: Includes results from possibly, probably and related relationships per treatment and overall.

Overall: Included results from all treatment groups.

Data source: Listing 16.2.7-2

Table 14.3.1-5 Frequency of Subjects Experiencing Treatment-Emergent Adverse Events Summarized per Treatment and Relationship – Safety Population

MedDRA® System Organ Class MedDRA® Preferred Term n (%)	1 mg/kg US - Avastin® IV (N=XX)						Overall (N=XX)					
	Not related	Unlikely related	Possibly related	Probably related	Related	Total related TEAEs (possibly + probably + related)	Not related	Unlikely related	Possibly related	Probably related	Related	Total related TEAEs (possibly + probably + related)
MedDRA® System Organ Class 1	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)
MedDRA® Preferred Term 1	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)
MedDRA® Preferred Term 2	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)
MedDRA® System Organ Class 2	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)
MedDRA® Preferred Term 1	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)
MedDRA® Preferred Term 2	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)

Programming Notes:

1) *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.*
2) *If the distribution of treatments is presented on more than one page, preserve the order of the SOC and PT as defined in the generation of the global table without relationship.*
3) *Refer to footnotes for additional instructions.*

Table 14.3.1-6 Number of Treatment-Emergent Adverse Events Summarized per Treatment and Relationship – Safety Population

MedDRA® System Organ Class MedDRA® Preferred Term		1 mg/kg MB02 - SP IV (N=XX)						1 mg/kg MB02 - DM IV (N=XX)					
	E	Not related	Unlikely related	Possibly related	Probably related	Related	Total related TEAEs (possibly + probably + related)	Not related	Unlikely related	Possibly related	Probably related	Related	Total related TEAEs (possibly + probably + related)
MedDRA® System Organ Class 1		x	x	x	x	x	x	x	x	x	x	x	x
MedDRA® Preferred Term 1		x	x	x	x	x	x	x	x	x	x	x	x
MedDRA® Preferred Term 2		x	x	x	x	x	x	x	x	x	x	x	x
MedDRA® System Organ Class 2		x	x	x	x	x	x	x	x	x	x	x	x
MedDRA® Preferred Term 1		x	x	x	x	x	x	x	x	x	x	x	x
MedDRA® Preferred Term 2		x	x	x	x	x	x	x	x	x	x	x	x

Programming Notes:

1) *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.*
2) *If the distribution of treatments is presented on more than one page, preserve the order of the SOC and PT as defined in the generation of the global table without relationship.*

E: Number of treatment-emergent adverse event; N: Number of subjects dosed; MedDRA®: Medical Dictionary for Regulatory Activities, version 23.0
Total related TEAEs: Includes results from possibly, probably and related relationships per treatment and overall.
Overall: Included results from all treatment groups.
Data source: Listing 16.2.7-2

Table 14.3.1-6 Number of Treatment-Emergent Adverse Events Summarized per Treatment and Relationship – Safety Population

MedDRA® System Organ Class MedDRA® Preferred Term	1 mg/kg US - Avastin® IV (N=XX)						Overall (N=XX)					
E	Not related	Unlikely related	Possibly related	Probably related	Related	Total related TEAEs (possibly + probably + related)	Not related	Unlikely related	Possibly related	Probably related	Related	Total related TEAEs (possibly + probably + related)
MedDRA® System Organ Class 1	x	x	x	x	x	x	x	x	x	x	x	x
MedDRA® Preferred Term 1	x	x	x	x	x	x	x	x	x	x	x	x
MedDRA® Preferred Term 2	x	x	x	x	x	x	x	x	x	x	x	x
MedDRA® System Organ Class 2	x	x	x	x	x	x	x	x	x	x	x	x
MedDRA® Preferred Term 1	x	x	x	x	x	x	x	x	x	x	x	x
MedDRA® Preferred Term 2	x	x	x	x	x	x	x	x	x	x	x	x

Programming Notes:

1) *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.*
2) *If the distribution of treatments is presented on more than one page, preserve the order of the SOC and PT as defined in the generation of the global table without relationship*

E: Number of treatment-emergent adverse event; N: Number of subjects dosed; MedDRA®: Medical Dictionary for Regulatory Activities, version 22.1.
Total related TEAEs: Includes results from possibly, probably and related relationships per treatment and overall.
Overall: Included results from all treatment groups.
Data source: Listing 16.2.7-2

Table 14.3.1-7 Frequency of Subjects Experiencing Treatment-Emergent Adverse Events Leading to Discontinuation Summarized per Treatment – Safety Population

MedDRA® System Organ Class MedDRA® Preferred Term	Statistic	1 mg/kg MB02 - SP IV (N=XX)	1 mg/kg MB02 - DM IV (N=XX)	1 mg/kg US - Avastin® IV (N=XX)	Overall (N=XX)
Number of Subjects with TEAEs	n (%)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)
MedDRA® System Organ Class 1	n(%)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)
MedDRA® Preferred Term 1	n(%)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)
MedDRA® Preferred Term 2	n(%)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)
MedDRA® System Organ Class 2	n(%)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)
MedDRA® Preferred Term 1	n(%)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)
MedDRA® Preferred Term 2	n(%)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)
MedDRA® System Organ Class 3	n(%)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)
MedDRA® Preferred Term 1	n(%)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)
MedDRA® Preferred Term 2	n(%)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)

Programming Notes:
1) 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.
2) Refer to footnotes for additional instructions.

N: Number of subjects dosed; n (%): Number and percent of subjects with TEAE; MedDRA®: Medical Dictionary for Regulatory Activities, version 23.0; TEAEs: Treatment-Emergent Adverse Events.
Each subject could only contribute once to each of the incidence rates, regardless of the number of occurrences.
Overall: Included results from all treatment groups.
Data source: Listing 16.2.7-2

Table 14.3.1-8 Frequency of Subjects Experiencing Serious Treatment-Emergent Adverse Events Summarized per Treatment – Safety Population

MedDRA® System Organ Class MedDRA® Preferred Term	Statistic	1 mg/kg MB02 - SP IV (N=XX)	1 mg/kg MB02 - DM IV (N=XX)	1 mg/kg US - Avastin® IV (N=XX)	Overall (N=XX)
Number of Subjects with TEAEs	n (%)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)
MedDRA® System Organ Class 1	n(%)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)
MedDRA® Preferred Term 1	n(%)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)
MedDRA® Preferred Term 2	n(%)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)
MedDRA® System Organ Class 2	n(%)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)
MedDRA® Preferred Term 1	n(%)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)
MedDRA® Preferred Term 2	n(%)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)
MedDRA® System Organ Class 3	n(%)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)
MedDRA® Preferred Term 1	n(%)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)
MedDRA® Preferred Term 2	n(%)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)

Programming Notes:
1) 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.
2) Refer to footnotes for additional instructions.

N: Number of subjects dosed; n (%): Number and percent of subjects with TEAE; MedDRA®: Medical Dictionary for Regulatory Activities, version 23.0; TEAEs: Treatment-Emergent Adverse Events.
Each subject could only contribute once to each of the incidence rates, regardless of the number of occurrences.
Overall: Included results from all treatment groups.
Data source: Listing 16.2.7-2

Table 14.3.4-1 Clinical Chemistry Summary Descriptive Statistics and Change from Baseline – Safety Population

Parameter (unit)	Visit	Statistic	1 mg/kg MB02 - SP IV (N=XX)	1 mg/kg MB02 - DM IV (N=XX)	1 mg/kg US - Avastin® IV (N=XX)
Parameter 1 (unit)	Screening	n	xx	xx	xx
xx-xx		Mean	xx.x	xx x	xx x
		SD	xx.x	xx x	xx x
		Median	xx.x	xx x	xx x
		Min, Max	xx-xx	xx-xx	xx-xx
	Day -1	n	xx	xx	xx
		Mean	xx.x	xx x	xx x
		SD	xx.x	xx x	xx x
		Median	xx.x	xx x	xx x
		Min, Max	xx-xx	xx-xx	xx-xx
	Baseline	n	xx	xx	xx
		Mean	xx.x	xx x	xx x
		SD	xx.x	xx x	xx x
		Median	xx.x	xx x	xx x
		Min, Max	xx-xx	xx-xx	xx-xx
	Day 3	n	xx	xx	xx
		Mean	xx.x	xx x	xx x
		SD	xx.x	xx x	xx x
		Median	xx.x	xx x	xx x
		Min, Max	xx-xx	xx-xx	xx-xx
	Day3 - CFB	n	xx	xx	xx
		Mean	xx.x	xx x	xx x
		SD	xx.x	xx x	xx x
		Median	xx.x	xx x	xx x
		Min, Max	xx-xx	xx-xx	xx-xx
	Day 8	n	xx	xx	xx
		Mean	xx.x	xx x	xx x
		SD	xx.x	xx x	xx x
		Median	xx.x	xx x	xx x
		Min, Max	xx-xx	xx-xx	xx-xx

Table 14.3.4-1 Clinical Chemistry Summary Descriptive Statistics and Change from Baseline – Safety Population

Parameter (unit)	Visit	Statistic	1 mg/kg MB02 - SP IV (N=XX)	1 mg/kg MB02 - DM IV (N=XX)	1 mg/kg US - Avastin® IV (N=XX)
	Day - CFB	n	xx	xx	xx
		Mean	xx.x	xx x	xx x
		SD	xx.x	xx x	xx x
		Median	xx.x	xx x	xx x
		Min, Max	xx-xx	xx-xx	xx-xx
	…				
	End of Study (Day 100)	n	xx	xx	xx
		Mean	xx.x	xx x	xx x
		SD	xx.x	xx x	xx x
		Median	xx.x	xx x	xx x
		Min, Max	xx-xx	xx-xx	xx-xx
	End of Study (Day 100) - CFB	n	xx	xx	xx
		Mean	xx.x	xx x	xx x
		SD	xx.x	xx x	xx x
		Median	xx.x	xx x	xx x
		Min, Max	xx-xx	xx-xx	xx-xx

CFB: Change from baseline; N: Number of subjects dosed; n: Number of subjects; SD: Standard Deviation.
Baseline is defined as the last results (scheduled or unscheduled) obtained prior to the study drug administration.
Data source: Listing 16.2.8-1

Note: This table will be repeated for Tables 14.3.4-3, 14.3.4-5, 14.3.4-7, 14.3.4-11 and 14.3.4-12. Please adapt title and footnotes accordingly.

Table 14.3.4-2 Frequency of Subjects – Clinical Chemistry Shifts from Baseline – Safety Population

Treatment Parameter (unit)	Baseline Flag: Post-Baseline Flag: Visit	Normal Normal n (%)	Normal Abnormal NCS n (%)	Normal Abnormal CS n (%)	Abnormal NCS Normal n (%)	Abnormal NCS Abnormal NCS n (%)	Abnormal NCS Abnormal CS n (%)	Abnormal CS Normal n (%)	Abnormal CS Abnormal NCS n (%)	Abnormal CS Abnormal CS n (%)
1 mg/kg MB02 - SP IV (N=XX)										
Parameter 1	Day 3	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)
	Day 8	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)
	Day 14	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)
	Day 21	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)
	Day 28	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)
	Day 42	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)
	Day 56	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)
	Day 78	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)
	Day 100 (End of Study)	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)
Parameter 2	Day 3	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)
	Day 8	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)
	Day 14	x (xx x)	x (xx x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx x)	x (xx.x)	x (xx x)	x (xx x)
	…									
…										
Add for all other Treatments and Parameters										

Programming Notes:

1) *Preserve parameters, scheduled visits and sorting defined in Summary Descriptive Statistics Table*
2) *Refer to footnotes for additional instructions.*
3) *Adapt Data Source to the appropriate laboratory category listing.*

N: Number of subjects dosed; n: Number and percent of subjects.
Baseline is defined as the last results (scheduled or unscheduled) obtained prior to the study drug administration.
Percentage based on the number of subjects having available results at baseline and at the specific post-baseline timepoint.
Data source: Listing 16.2.8-1

Note: This table will be repeated for Tables 14.3.4-4, 14.3.4-6, 14.3.4-8, and 14.3.4-13 please adapts title and footnotes accordingly.

Table 14.3.4-9 Urinalysis Frequency Summary – Categorical Results – Safety Population

Parameter (unit) Normal Range	Visit	Result n (%)	1 mg/kg MB02 - SP IV (N=XX)	1 mg/kg MB02 - DM IV (N=XX)	1 mg/kg US - Avastin® IV (N=XX)
Parameter 1 (unit)	Screening	Negative	x (xx x)	x (xx x)	x (xx x)
XX-XX		Trace	x (xx x)	x (xx x)	x (xx x)
	Day -1	Negative	x (xx x)	x (xx x)	x (xx x)
		Trace	x (xx x)	x (xx x)	x (xx x)
	Baseline	Negative	x (xx x)	x (xx x)	x (xx x)
		Trace	x (xx x)	x (xx x)	x (xx x)
	Day 8	Negative	x (xx x)	x (xx x)	x (xx x)
		Trace	x (xx x)	x (xx x)	x (xx x)
	Day 14	Negative	x (xx x)	x (xx x)	x (xx x)
		Trace	x (xx x)	x (xx x)	x (xx x)
	Day 21	Negative	x (xx x)	x (xx x)	x (xx x)
		Trace	x (xx x)	x (xx x)	x (xx x)
	…				
	Day 100 (End of Study)	Negative	x (xx x)	x (xx x)	x (xx x)
		Trace	x (xx x)	x (xx x)	x (xx x)
…					

Programming Notes:

1) *Urine Microscopy parameters will not presented in this table.*
2) *Evaluate if the units must be added to parameter name if a numeric result was observed. Remove (units) from column header if no numeric results were observed.*
3) *For each parameter provide normal range of primary facility and, for gender specific parameters, use the same sorting of gender from demographic table.*
4) *Independently for each parameter, sort results by gradation.*
5) *Refer to footnotes for additional instructions.*

N: Number of subjects dosed; n (%): Number and percent of subjects.
Baseline is defined as the last results (scheduled or unscheduled) obtained prior to the study drug administration.
Percentage based on the number of subjects having available result at each timepoint, independently for each parameter.
Data source: Listing 16.2.8-3

Table 14.3.4-10 Frequency of Subjects – Urinalysis Shifts from Baseline – Categorical Results – Safety Population

Treatment Parameter (unit)	Visit	Baseline Flag: Post-Baseline Flag:	Normal Normal n (%)	Normal Abnormal n (%)	Abnormal Normal n (%)	Abnormal Abnormal n (%)
1 mg/kg MB02 - SP IV (N=XX)						
Parameter 1	Day 3		x (xx x)	x (xx.x)	x (xx x)	x (xx x)
	Day 8		x (xx x)	x (xx.x)	x (xx x)	x (xx x)
	Day 14		x (xx x)	x (xx.x)	x (xx x)	x (xx x)
	Day 21		x (xx x)	x (xx.x)	x (xx x)	x (xx x)
	Day 28		x (xx x)	x (xx.x)	x (xx x)	x (xx x)
	Day 42		x (xx x)	x (xx.x)	x (xx x)	x (xx x)
	Day 56		x (xx x)	x (xx.x)	x (xx x)	x (xx x)
	Day 78		x (xx x)	x (xx.x)	x (xx x)	x (xx x)
	Day 100 (End of Study)		x (xx x)	x (xx.x)	x (xx x)	x (xx x)
Parameter 2	Day 3		x (xx x)	x (xx.x)	x (xx x)	x (xx x)
	Day 8		x (xx x)	x (xx.x)	x (xx x)	x (xx x)
	Day 14		x (xx x)	x (xx.x)	x (xx x)	x (xx x)
	Day 21		x (xx x)	x (xx.x)	x (xx x)	x (xx x)
	Day 28		x (xx x)	x (xx.x)	x (xx x)	x (xx x)
	Day 42		x (xx x)	x (xx.x)	x (xx x)	x (xx x)
	Day 56		x (xx x)	x (xx.x)	x (xx x)	x (xx x)
	Day 78		x (xx x)	x (xx.x)	x (xx x)	x (xx x)
	Day 100 (End of Study)		x (xx x)	x (xx.x)	x (xx x)	x (xx x)
Add for all other Treatments and Parameters						

Programming Notes:

1) *Preserve parameters, scheduled visits and sorting defined in Summary Descriptive Statistics Table*
2) *Refer to footnotes for additional instructions.*
3) *Adapt Data Source to the appropriate laboratory category listing.*

N: Number of subjects dosed; n: Number and percent of subjects.

Baseline is defined as the last results (scheduled or unscheduled) obtained prior to the study drug administration.

Percentage based on the number of subjects having available results at baseline and at the specific post-baseline timepoint.

Data source: Listing 16.2.8-3

5. Listings

Listing 16.2.1-1 Subjects Completion and Discontinuation Information

Subject	Treatment	Date ICF signed	Completion/ Discontinuation Date and Time	Date of Last Contact With The Subject	Primary Reason for Discontinuation	Comment
001	1 mg/kg MB02 - SP IV		DD-MM-YYYYTHH:MM	DD-MM-YYYY	XXX	XXX

Listing 16.2.2-1 Protocol Deviations

Subject	Treatment	Category	Deviation
	1 mg/kg MB02 - SP IV		

Listing 16.2.4-1 Demographics

Subject	Visit	Treatment	Age (years)	Race	Ethnicity	BMI (kg/m^2)	Height (cm)	Weight (kg)
001	Screening	1 mg/kg MB02 - SP IV						

BMI: Body Mass Index.
Last results (scheduled or unscheduled) obtained at screening were used to generate this listing.

Listing 16.2.4-2 Medical History Findings at Screening

Subject	Treatment	Finding	MedDRA® Preferred Term	MedDRA® System Organ Class	Onset Date	Resolution Date (or Ongoing)
	1 mg/kg MB02 - SP IV	FINDING 1	Preferred Term 1	SOC 1	YYYY-MM-DDTHH:MM	YYYY-MM-DDTHH:MM
		FINDING 2	Preferred Term 2	SOC 2	YYYY-MM-DDTHH:MM	ONGOING

Programming Notes

1) SOC and Finding will be presented in uppercase. The Preferred Term will be presented in "propcase". The SAS coding "/~n" between terms will generate the break line.
2) The SAS coding "/~n" between dates will generate the break line.
3) If finding is ongoing, replace missing resolution date per ONGOING.
4) Sort events per Subject, Start Date, Stop Date, SOC and PT.
5) For incomplete date display, refer to CDISC SDTM Implementation Guide according to ISO 8601 format.

MedDRA®: Medical Dictionary for Regulatory Activities; MedDRA® Version 23.0.

Listing 16.2.4-3 Prior and Concomitant Medications

Subject	Treatment	Prior/ Concomitant	WHO DDE ATC / WHO DDE Preferred Term / Medication	Dose (unit)/ Frequency	Route	Onset Date and Time/ Resolution Date and Time (or Ongoing)	Indication (Condition or AE No.)
		Prior	ATC 1/ Preferred Term 1/ MEDICATION 1/	20 (mg) QID	ORAL	YYYY-MM-DDTHH:MM/ YYYY-MM-DDTHH:MM	
	1 mg/kg MB02 - SP IV	Concomitant	ATC 2/ Preferred Term 2/ MEDICATION 2/			YYYY-MM-DDTHH:MM/ ONGOING	

Programming Notes:

1) ATC and Medication will be presented in uppercase. The Preferred Term will be presented in "propcase". The SAS coding "/~n" between terms will generate the break line.

2) The SAS coding "/~n" will generate the break line between treatment sequence and treatment, dose with units and frequency. In the same way apply a break line between dates.

3) If medication is ongoing, replace missing resolution date per ONGOING.

4) Sort events per Subject, Onset Date, Resolution Date, ATC and PT.

5) For incomplete date display, refer to CDISC SDTM Implementation Guide according to ISO 8601 format.

ATC: Anatomic Therapeutic Chemical; WHO DDE: World Health Organization Drug Dictionary Enhanced Version Mar 2020, format B3.

Listing 16.2.4-4 Study Drug Administration

Subject	Treatment	Drug Taken/ If No, Reason"	Infusion Start Date and Time	Infusion End Date and Time	Duration of infusion (hh: min)	Total Dose per subject Weight (mg)	Was the total volume administered?	Infusion Rate (unit)	Volume infused (mL)	Location of study drug administration	Fasting Status	Was the infusion interrupted?
	1 mg/kg MB02 - SP IV		YYYY-MM-DDTHH:MM:SS	YYYY-MM-DDTHH:MM:SS								

Listing 16.2.4-5 Interruption of IV Infusion

Subject	Treatment	Drug Interruption Date and Time	Restart Date and Time	Reason for interruption	If Adverse event, please select corresponding AE No.	Was the infusion restarted?
	1 mg/kg MB02 - SP IV	YYYY-MM-DDTHH:MM:SS	YYYY-MM-DDTHH:MM:SS			

Listing 16.2.4-6 Assignment to Analysis Populations

Subject	Treatment	Included in Safety Population
101	1 mg/kg MB02 - SP IV	Yes

Listing 16.2.4-7 Cotinine Test

Subject	Treatment	Visit	Test Performed/ If No, Reason	Date/Time of Sample Collection	Result
xxxxx	1 mg/kg MB02 - SP IV	Screening	Yes	ddmmmyyyy / hh mm	Negative
		Day -1	Yes	ddmmmyyyy / hh mm	Positive
xxxxx		Screening	No		
		Day -1	Yes	ddmmmyyyy / hh mm	Negative
etc.					

Listing 16.2.4-8 Urine Drug Screen

Subject	Treatment	Visit	Test Performed/ If No, Reason	Date/Time of Sample Collection	Result	Test Name If Positive Results
xxxxx	1 mg/kg MB02 - SP IV	Screening	Yes	ddmmmyyyy / hh mm	Negative	
		Day -1	Yes	ddmmmyyyy / hh mm	Positive	
xxxxx		Screening	No			
		Day -1	Yes	ddmmmyyyy / hh mm	Negative	
etc.						

Listing 16.2.4-9 Alcohol Breath Test

Subject	Treatment	Visit	Test Performed/ If No, Reason	Date/Time of Sample Collection	Result
xxxxx	1 mg/kg MB02 - SP IV	Screening	Yes	ddmmmyyyy / hh mm	Negative
		Day -1	Yes	ddmmmyyyy / hh mm	Positive
xxxxx		Screening	No		
		Day -1	Yes	ddmmmyyyy / hh mm	Negative
etc.					

Listing 16.2.4-10 Randomization

Subject	Treatment	Subject Was Randomized / If No, Reason	Randomization Date	Randomization Number.
101	1 mg/kg MB02 - SP IV		ddmmmyyyy	

Listing 16.2.7-1 Non-Treatment-Emergent Adverse Events

Subject	AE Number	MedDRA® System Organ Class/ MedDRA® Preferred Term/ Adverse Event Description	Onset Date and Time/ Resolution Date and Time (or Ongoing)	Severity/ Relationship	Other causal relationship	Serious (Yes/No)	Action taken		Outcome
							Study Drug	Other	
		SOC 1/ Preferred Term 1/ DESCRIPTION 1	YYYY-MM-DDTHH:MM/ YYYY-MM-DDTHH:MM	Severe/ Unrelated		Yes			
		SOC 2/ Preferred Term 2/ DESCRIPTION 2	YYYY-MM-DDTHH:MM/ ONGOING	Mild/		No			

Programming Notes

1) SOC and AE Description will be presented in uppercase. The Preferred Term will be presented in "propcase". The SAS coding "/~n" between terms will generate the break line.
2) The SAS coding "/~n" will generate the break line between dates and between Severity and Relationship.
3) If needed, hardcode OUTCOME and ACTIONS in order to introduce break line (~n) between answer elements.
4) If medication is ongoing, replace missing resolution date per ONGOING.
5) Sort events per Subject, Onset Date/time, Resolution Date/time, SOC and PT.
6) For incomplete date display, refer to CDISC SDTM Implementation Guide according to ISO 8601 format.
7) Please update' MedDRA® System Organ Class' footnote by keeping only those SOC terms referred in table.

MedDRA®: Medical Dictionary for Regulatory Activities (MedDRA®); MedDRA® Version 23.0

MedDRA® System Organ Class (SOC): Cardiac disorders (Card); Eye disorders (Eye); Gastrointestinal disorders (Gastr); General disorders and administration site conditions (Genrl); Infections and infestations (Infec); Injury, poisoning and procedural complications (Inj&P); Investigations (Inv); Musculoskeletal and connective tissue disorders (Musc); Nervous system disorders (Nerv); Psychiatric disorders (Psych); Respiratory, thoracic and mediastinal disorders (Resp); Skin and subcutaneous tissue disorders (Skin) Vascular disorders (Vasc).

Note: The list of MedDRA® SOC will be updated according to the AEs observed for the study.

Listing 16.2.7-2 Treatment-Emergent Adverse Events

Subject	Treatment	AE Number	MedDRA® System Organ Class/ MedDRA® Preferred Term/ Adverse Event Description	Onset Date and Time/ Resolution Date and Time (or Ongoing)	Severity/ Relationship	Other causal relationship	Serious (Yes/No)	Action taken		Outcome
								Study Drug	Other	
001	1 mg/kg MB02 - SP IV		SOC 1/ Preferred Term 1/ DESCRIPTION 1	YYYY-MM-DDTHH:MM/ YYYY-MM-DDTHH:MM	Grade 1/ Unrelated		Yes			
			SOC 2/ Preferred Term 2/ DESCRIPTION 2	YYYY-MM-DDTHH:MM/ ONGOING	Grade 2/ Remote		No			

Programming Notes:

1) SOC and AE Description will be presented in uppercase. The Preferred Term will be presented in "propcase". The SAS coding "/~n" between terms will generate the break line.
2) The SAS coding "/~n" will generate the break line between dates and between Severity and Relationship.
3) If needed, hardcode OUTCOME and ACTIONS in order to introduce break line (~n) between answer elements.
4) If medication is ongoing, replace missing resolution date per ONGOING.
5) Sort events per Subject, Onset Date/time, Resolution Date/time, SOC and PT.
6) For incomplete date display, refer to CDISC SDTM Implementation Guide according to ISO 8601 format.
7) Please update' MedDRA® System Organ Class' footnote by keeping only those SOC terms referred in table.

MedDRA®: Medical Dictionary for Regulatory Activities (MedDRA®); MedDRA® Version 23.0

MedDRA® System Organ Class (SOC): Cardiac disorders (Card); Eye disorders (Eye); Gastrointestinal disorders (Gastr); General disorders and administration site conditions (Genrl); Infections and infestations (Infec); Injury, poisoning and procedural complications (Inj&P); Investigations (Inv); Musculoskeletal and connective tissue disorders (Musc); Nervous system disorders (Nerv); Psychiatric disorders (Psych); Respiratory, thoracic and mediastinal disorders (Resp); Skin and subcutaneous tissue disorders (Skin) Vascular disorders (Vasc).

Note: The list of MedDRA® SOC will be updated according to the AEs observed for the study.

Note: Similar layout will be used for Listing 16.2.7-3, 16.2.7-4 and 16.2.7-5 please adapt title and footnotes accordingly.

Listing 16.2.8-1 Clinical Laboratory – Clinical chemistry

Subject	Treatment	Laboratory Visit	Collection Date and Time	Parameter(unit)	Result	Normalized Result	Normal Range	Flag	Interpretation
001	1 mg/kg MB02 - SP IV		YYYY-MM-DDTHH:MM				XX.X-XX.X	H	Abnormal NCS

Programming Notes:

1) *Sort assessments per Subject, Timepoint/Date and parameters. Sorting for parameter should be as defined in Summary Descriptive Statistics Table.*
2) *For each parameter provide normal range of primary facility and, for gender specific parameters, use the same sorting of gender from demographic table.*
3) *If multiple laboratories involved, display standard and normalised results. Display the ranges in the same way. The SAS coding "/~n" between results or ranges will generate the break line. Take care to use the same precision of both, standard and normalised results/ranges.*

Laboratory facilities could be abbreviated with appropriation description on footnote; BML: Biron Medical Laboratory).

H: Above normal range; L: Below normal range; N: Normal Range.

Note: Similar layout will be used for Listings 16.2.8-2, 16.2.8-3, 16.2.8-4, 16.2.8-5, and 16.2.8-6. Please adapt title and footnotes accordingly.

Listing 16.2.8-7 Vital Signs Result

Subject	Treatment	Visit/ Timepoint	Measurement Date and Time	Parameter(unit)	Result
001	1 mg/kg MB02 - SP IV	Screening	YYYY-MM-DDTHH:MM		

Programming Notes:

1) Sort assessments per Subject, Timepoint/Date and parameter. Parameters for each subject to be sorted as defined in Summary Descriptive Statistics Table.

*The medical judgement for abnormal ECG interpretation is also presented in this column as CS: Clinically significant or NCS: Not clinically significant.

Listing 16.2.8-8 Pulse Oximetry Results

Subject	Treatment	Visit	Start Date and Time	Test (unit)	Result	Reason, if Test is Not Performed
001	1 mg/kg MB02 - SP IV	Screening	YYYY-MM-DDTHH:MM			

Listing 16.2.8-9 Electrocardiogram Result

Subject	Treatment	Visit/Timepoint	Assessment Date and Time	Parameter(unit)	Result	Interpretation*
	1 mg/kg MB02 - SP IV		YYYY-MM-DDTHH:MM			

Programming Notes:

1) *Sort assessments per Subject, timepoint/Date and parameter. Parameters for each subject to be sorted as defined in Summary Descriptive Statistics Table.*

*The medical judgement for abnormal ECG interpretation is also presented in this column as CS: Clinically significant or NCS: Not clinically significant.

Note: Similar layout will be used for Listings 16.2.8-10, and 16.2.8-11. Please adapt title and footnotes accordingly

Listing 16.2.8-12 Physical Examination Findings by Subject

Subject/Age	Treatment	Timepoint	Examination Date and Time	Site/System	Results
101/29	1 mg/kg MB02 - SP IV	Screening	YYYY-MM-DDTHH:MM	General Appearance	Normal
				Eye/Ear/Nose/Throat	Normal
				Oral	Normal
				Head and Neck	Normal
				Chest/Lungs	Normal
				Abdomen	Normal
				Lymphatic	Normal
				Neurologic	Normal
				Extremities	NE
				Psychiatric	NE
				Other	NE
				…	
…					

NE: not evaluated.