STATISTICAL ANALYSIS PLAN

Protocol Name

A Randomized, Double-blind, Three-arm, Parallel Group, Single-dose Study to Compare the Pharmacokinetics and Safety of Three Formulations of Bevacizumab (CT-P16, EU-approved Avastin and US-licensed Avastin) in Healthy Male Subjects

Protocol No.

CT-P16 1.1 Version 1.0

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CT-P16

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Written By

[redacted]

[redacted]

Signature page

The Statistical Analysis Plan was written by [redacted] according to ICH guideline, Local regulation and a related SOP ([redacted]), after training related SOPs.

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The Statistical Analysis Plan was approved by Sponsor.

Approved by:

Date (DD-MMM-YYYY)	Name/Position	Signature

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Version	Effective Date	Prepared by Name	Details
V1.0	Sponsor's final approved date	[redacted]	First Version
V2.0	Sponsor's final approved date	[redacted]	Second Version

Abbreviation

Term	Definition
ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical code
AUC	Area Under the Concentration-time curve
$AUC_{0\text{-inf}}$	Area Under the Concentration-time curve from time zero to infinity
$AUC_{0\text{-last}}$	Area Under the Concentration-time curve from time zero to the last quantifiable concentration
BMI	Body Mass Index
CI	Confidence Interval
CL	Total Body Clearance
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
C_{max}	Maximum serum concentration
DRM	Data Review Meeting
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOI	End of Infusion
EOS	End of Study
EU	European Union
ICH	International Council for Harmonization
IMP	Investigational Medicinal Product
IRR	Infusion-Related Reaction
IV	Intravenous
IWRS	Interactive Web Response System
λ_z	Terminal elimination rate constant
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralizing Antibody
NCI	National Cancer Institute
PK	Pharmacokinetic (s)
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class

Term	Definition
SOI	Start of Infusion
SOP	Standard Operating Procedure
$t_{1/2}$	Terminal half-life
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
T_{max}	Time to C_{max}
US	United States
V_z	Volume of distribution during the terminal phase
WHODD	World Health Organization Drug Dictionary

Contents

1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of data collected within the scope of CELLTRION, Inc., protocol CT-P16 1.1 (A Randomized, Double-blind, Three-arm, Parallel-group, Single-dose Study to Compare the Pharmacokinetics and Safety of Three Formulations of Bevacizumab [CT-P16, European Union (EU)-approved Avastin and United States (US)-licensed Avastin] in Healthy Male Subjects) Version 1.0 dated 07 June 2017 and electronic case report form (eCRF) Version 3.0 dated 28 July 2017. The purpose of this plan is to provide specific guidelines for which the analyses will proceed. Any deviations from these guidelines will be documented in the clinical study report (CSR). The analyses described in this plan are considered a priori, in that they have been defined prior to database lock. Any analyses performed subsequent to database lock will be considered post-hoc and exploratory.

2. STUDY OBJECTIVES

2.1 Primary Objective

To demonstrate the similarity of the pharmacokinetics (PK) in terms of area under the concentration-time curve from time zero to infinity ($AUC_{0\text{-}inf}$), area under the concentration-time curve from time zero to the last quantifiable concentration ($AUC_{0\text{-}last}$), and maximum serum concentration (C_{max}) of CT-P16, EU-approved Avastin and US-licensed Avastin in healthy male subjects (CT-P16 to EU-approved Avastin, CT-P16 to US-licensed Avastin, and EU-approved Avastin to US-licensed Avastin).

2.2 Secondary Objective(s)

- To assess the additional PK parameters of CT-P16, EU-approved Avastin and US-licensed Avastin in healthy male subjects.

- To evaluate the safety and immunogenicity of CT-P16, EU-approved Avastin and US-licensed Avastin in healthy male subjects.

3. STUDY DESIGN

This study is a double-blind, three-arm, parallel group, single-dose study. A total of 141 healthy male subjects aged between 19 and 55 years will be enrolled; 47 subjects in each of the 3 arms of the clinical study. In each arm, all subjects will receive a single dose of CT-P16, EU-approved Avastin, or US-licensed Avastin by intravenous (IV) infusion for 90 min (±5 min) on Day 1 followed by 15 weeks during which the PK, safety and immunogenicity measurements will be made.

Subjects will be screened for eligibility within 21 to 2 days before the infusion of the Investigational Medicinal Product (IMP) after they have signed an informed consent. Multiple visits may be needed during the screening period to complete study-related assessment.

Eligible subjects will be admitted to the clinical unit on Day –1 to undergo baseline assessments and will be randomized on Day –1 to receive one of CT-P16, EU-approved Avastin, or US-licensed Avastin

once all eligibility criteria have been confirmed. Subjects will be confined to the clinical unit until completion of the 24-hour assessments after IMP administration. The consecutive study visits will be carried out on an out-patient basis. Blood for PK analysis will be collected up to Day 99. Safety will be assessed throughout the study by collection of information about AEs and concomitant medication, by clinical laboratory testing, measurement of vital signs, recording of 12-lead Electrocardiograms (ECGs), physical examination and assessment of the immunogenicity of CT-P16, EU-approved Avastin, and US-licensed Avastin. An end-of-study (EOS) examination will take place on Day 99.

The total duration of the participation will be up to 15 weeks for each individual subject who completes the entire clinical trial.

4. ENDPOINTS

4.1 Primary Endpoints

Pharmacokinetics

- Area under the concentration-time curve from time zero to infinity ($AUC_{0\text{-}inf}$)
- Area under the concentration-time curve from time zero to the last quantifiable concentration ($AUC_{0\text{-}last}$)
- Maximum serum concentration (C_{max})

4.2 Secondary Endpoints

Pharmacokinetics

- Time to C_{max} (T_{max})
- Volume of distribution during the terminal phase (V_z)
- Terminal elimination rate constant (λ_z)
- Terminal half-life ($t_{1/2}$)
- Total body clearance (CL)
- Percentage of $AUC_{0\text{-}inf}$ obtained by extrapolation ($\%AUC_{ext}$)

Safety and Immunogenicity

- Vital signs (blood pressure [BP], heart rate [HR], body temperature [BT], and respiratory rate [RR])
- Physical examination
- Clinical laboratory tests including hematology, chemistry, coagulation, and urinalysis
- 12-lead electrocardiogram (ECG)
- Adverse events (AEs) and concomitant medication
- Adverse event of special interest (AESI)
- Immunogenicity of CT-P16, EU-approved Avastin and US-licensed Avastin

5. GENERAL CONSIDERATIONS

5.1 General Considerations

Statistical analyses will be performed using [redacted].

Continuous data will be summarized by treatment group using descriptive statistics (number, mean, standard deviation, minimum, median and maximum), unless otherwise indicated. Minimum and maximum will be presented to the same number of decimal places as the raw data, mean and median will be presented to one more decimal place than the raw data, and standard deviation will be presented to two more decimal places than the raw data. If the geometric mean is to be presented, it will be set to the same precision as the mean. Percent Coefficient of Variance (CV) will be presented to two decimal places. Confidence Intervals (CIs) obtained from statistical procedures will be displayed to the same number of decimal places as the associated estimate is presented.

If minimum value from the data is zero, geometric mean will not be calculated.

Categorical data will be summarized by treatment group using frequency tables (number and percentage). Percentages will be suppressed when the count is zero. A row denoted "Missing" will be included in count tabulations where necessary to account for missing values. The denominator for all percentages will be the number of subjects within the randomized treatment group or the actual treatment group for the population of interest, unless otherwise indicated. Percentages will be presented to one decimal place.

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

EOS visit of early termination results will not be included in the summaries, but will be presented in data listings. Unscheduled results will not be included in the summary tables except for determining baseline, but will be presented in data listings.

Baseline will be the latest available measurement including unscheduled assessment prior to the administration of IMP, unless otherwise indicated.

This Statistical Analysis Plan (SAP) will be updated prior to unblinding after Data Review Meeting (DRM).

5.2 Sample Size

This study is powered to demonstrate PK equivalence of CT-P16, EU-approved Avastin and US-licensed Avastin in $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max}. Assuming a CV of 30% and ratio of geometric means of 1.03, 42 subjects for each arm are needed to achieve 90% power for a 90% CI for the ratio of $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max} to satisfy the equivalence margin of 80% to 125%. The sample size is calculated from two one-sided tests with each 5% significant level using geometric mean ratio. A 10% dropout rate is anticipated so approximately 141 subjects (47 subjects in each of 3 study arms; CT-P16, EU-approved

Avastin or US-licensed Avastin) will be enrolled. Sample size was calculated using [redacted].

5.3 Randomization, Stratification and Unblinding

Randomization will occur at Day -1 after all baseline assessments have been performed and eligibility for the study has been confirmed. Subjects will be randomly assigned to treatment groups (1:1:1 ratio to CT-P16, EU-approved Avastin, or US-licensed Avastin) using the Interactive Web Response System (IWRS). The randomization will be balanced by using permuted blocks and will be stratified by body weight (<70 kg vs ≥70 kg) and site.

The study will be performed in a double-blind manner. All IMPs will be diluted by a designated unblinded pharmacist, and will be supplied to the treating physician or designee in a blinded manner, in identical infusion bags, thereby enabling double-blind conditions.

The study blind should not be broken except in a medical emergency (where knowledge of the IMP administered would affect the treatment of the emergency) or regulatory requirement (e.g., for serious adverse events [SAEs] or death).

If a subject is unblinded, the subject must be withdrawn from the clinical study and procedures accompanying withdrawal are to be performed.

Suspected unexpected serious adverse reactions (SUSARs), which are subject to expedited reporting, should be unblinded before submission to the Competent Authorities.

The overall randomization code will be broken only for reporting purposes once all final clinical data have been entered into the database and all data queries have been resolved, and the assignment of subjects to the analysis sets has been completed. The randomization code will not be revealed to study subjects, parents or guardians, study site staff, or Investigators.

5.4 Analysis Populations

The following subject population are defined: all-randomized, safety, and PK. A summary table reflecting the numbers of subjects who comprised all-randomized, safety and PK population will be summarized by treatment group and overall. The number of subjects for all-randomized population is displayed using treatment to which they were randomized. For other populations, counts are based on the actual treatment they received. If a subject receives two or more kinds of IMPs including any dose of CT-P16 then the actual treatment of the subject will be CT-P16. A listing for analysis population will be provided.

- **All-randomized population**

  The all-randomized population is defined as all randomly assigned subjects. A subject will be considered to be assigned randomly if the subject is allocated a randomization number as recorded on the 'Randomization' eCRF page. Subjects in the all-randomized population will be

analyzed according to the treatment to which they were randomized and not according to what they actually received, in the event there will be a discrepancy between the actual treatment received and the randomized treatment.

- **Safety population**

The safety population will include all randomized subjects who received a complete or partial dose of IMP. A subject will be considered to have received IMP if the subject is recorded as having IMP administered (IMYN='Yes') on the 'Infusion of IMP' eCRF page. All subjects in the safety population will be analyzed according to the actual treatment they received. All safety analyses will be based on the safety population, unless otherwise specified.

- **Pharmacokinetic population**

The PK population will include all subjects who have received a complete dose of IMP with collection of at least one post-treatment PK sample with a concentration above the lower limit of quantification for bevacizumab. A subject, however, who has received two or more different kinds of IMPs, accidentally, will be excluded from the PK population. A subject will be considered to have received a complete dose of IMP if the subject is recorded as having IMP administered fully (IMFULL='Yes') on the 'Infusion of IMP' eCRF page. Subjects in the PK population will be analyzed according to the actual treatment they received, unless otherwise specified.

5.5 Protocol Deviation

The major protocol deviations are defined as follows:

- Protocol deviations thought to interfere with the absorption, distribution, metabolism, and excretion of the compound to be measured;
- Protocol deviations that may affect the interpretation of study results or the subject's rights, safety, or welfare.

A decision will be made during the blinded DRM to classify protocol deviations as major based on the underlying protocol deviations.
Major protocol deviations will be summarized by treatment group for the all-randomized population and they will also be presented in a listing.

5.6 General Comments

General Comments collected on eCRF will be presented in a listing for the all-randomized population.

5.7 Outlier

Any outliers that are detected during the blind review of the data will be investigated. In general, outliers will not be excluded unless they are considered to be erroneous values. Sensitivity analyses and exploratory analyses may be conducted using imputation or excluding outliers to ensure robustness of study conclusions.

6. SUBJECT DISPOSITION

6.1 Screening Failure

A listing of subjects reported as screening failures will be provided.

6.2 Subject Disposition

A summary table reflecting the number of subjects who were randomized, who initiated administration of IMP and who completed the study will be presented by treatment group and overall. This table will also present the number of subjects who did not complete the study, both overall and according to reasons for withdrawal from the study.

A subject will be considered to have been randomized if the subject is allocated a randomization number as recorded on the 'Randomization' eCRF page. A subject will be considered to have initiated treatment in the study if it is recorded that IMP was administered (IMYN='Yes') on the 'Infusion of IMP' page of the eCRF. A subject will be considered to have completed the study if it is recorded that they completed (DSCOMPL='Yes') on the 'End of Study' page of the eCRF. A subject will be considered to have discontinued the study if it is recorded that they did not complete (DSCOMPL='No') on the 'End of Study' page of the eCRF.

Subject disposition data will be summarized and listed by treatment group in all-randomized population.

6.3 Subject Disposition and Analysis Population by Study Site

The number and percentage of subjects who comprised all-randomized, safety and PK populations and who completed the study will be presented by treatment group and study site. This table will also present the number of subjects who did not complete the study, both overall and according to reasons for withdrawal from the study by study site.

Subject disposition by study site data will be summarized by treatment group in all-randomized population.

7. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

7.1 Demographics

Demographics and other background characteristics listed below will be presented in summary tables for the PK population and safety population.

The following continuous variables will be summarized by treatment group using descriptive statistics (number, mean, standard deviation, minimum, median and maximum):

- Age (years)
- Height (cm)
- Weight (kg)
- Body Mass Index (kg/m^2)

The following categorical data will be summarized by treatment group using frequency tables (number and percentage):

- Race
- Gender
- Weight (< 70 kg vs ≥ 70 kg)
- Smoking history
- Alcohol history
- Caffeine history
- (Abuse History) Drug
- (Abuse History) Alcohol

Subject demographics and baseline characteristics will be presented in a data listing for the safety population.

7.2 Medical History

Medical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1, and the version number will be shown as a footnote on the corresponding tables.

Medical history will be summarized for the safety population by treatment group, system organ class (SOC) and preferred term (PT) displaying the total number of medical history events, and the number and percentage of subjects with at least one medical history term. SOC and PT will be sorted by alphabetical order. At each level of summarization, a subject is counted once if he reported one or more medical histories.

A listing of medical history will also be provided by treatment group for the safety population.

7.3 Inclusion and Exclusion Criteria

Details of the inclusion and exclusion criteria can be found in sections 4.2 and 4.3 of the study protocol. A listing of the inclusion and exclusion criteria will be presented for each subject by treatment group for the all-randomized population.

7.4 Viral Serology

The following viral serology items will be listed by treatment group for the safety population:

- Hepatitis B surface antigen (HBsAg)
- Hepatitis B surface antibody (HBsAb)
- Hepatitis C virus antibody
- Human immunodeficiency virus-1 or -2 (HIV-1 or -2) antibodies
- Syphilis

7.5 Urine Drug Test

The following urine drug test items will be listed by treatment group for the safety population:

- Amphetamines
- Barbiturates
- Benzodiazepines
- Cocaine
- Opiates
- Cannabinoids

8. TREATMENTS AND MEDICATIONS

8.1 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the Anatomical Therapeutic Chemical (ATC) classification of World Health Organization Drug Dictionary (WHODD) version 01Sep2017, and the version number will be shown as a footnote on the corresponding tables.

All medications used within 30 days prior to screening visit until the EOS visit will be collected on the eCRF. Prior medication is defined as any medication with end date prior to the first administration of IMP date. Concomitant medication is defined as any medication that is ongoing, or has an end date that is on or after the date of IMP infusion. The start date of a concomitant medication can be before or after the date of first administration.

The total number of prior and concomitant medications and the number and percentage of subjects with at least one prior or concomitant medication will be tabulated for the safety population. Prior and concomitant medication data will be presented separately by treatment group, drug class and PT. Drug class will be displayed using ATC Level 2. ATC and PT will be sorted by alphabetical order. At each level of subject summarization, a subject is counted only once if one or more medication was reported at that level.

Additionally, prior and concomitant medications will be listed by treatment group for the safety population.

For the purpose of inclusion in prior or concomitant medication, incomplete medication start dates and end dates will be imputed respectively as described in Appendix 11.4.

8.2 Extent of Exposure

Extent of exposure table will be summarized for the safety population by treatment group with number and percentage of subjects who administered IMP and who received a complete dose or partial dose. Planned dose (mg), prescribed dose (mg) and administered dose (mg) of IMP (CT-P16, EU-approved Avastin, and US-licensed Avastin) will also be summarized for the safety population by treatment group using descriptive statistics (number, mean, standard deviation, minimum, median and maximum).
All IMP administration data will be presented in a data listing for the safety population.

9. PHARMACOKINETIC ANALYSIS

All pharmacokinetic analyses will be performed using all data on the PK population unless otherwise specified. Derivation of PK parameters will be the responsibility of [redacted] The PK parameters will be determined for analyte in serum following single dose administration.

9.1 Handling of Values Below the Limit of Quantification (BLQ)

The values below the limit of quantification values will be imputed in the PK concentration dataset used for serum concentration summarization, and the derivation of PK parameters.
The BLQ values prior to the IMP administration will be treated as zero. For the BLQ values after IMP administration, the following rules will be applied;

- The BLQ values at the beginning of a subject profile (i.e. before the first incidence of a measurable concentration) will be assigned to zero.
- The BLQ values at the end of a subject profile (i.e. after the last incidence of a measurable concentration) will be set to missing.
- Single BLQs which fall between two measurable concentrations will be set to missing.
- Consecutive BLQs which fall between measurable concentrations will be set to missing. Measurable concentrations after consecutive BLQs will also be set to missing.

9.2 Serum Concentration

Venous blood samples will be collected from each subject during this study for the determination of the PK of bevacizumab administered as CT-P16, EU-approved Avastin, and US-licensed Avastin. Blood samples for PK analysis will be drawn according to the following schedule:

Day of study period	Time point	Window
Day 1	Pre-dose	Before IMP infusion
	End of infusion	Immediately end of infusion (Within +5 minutes after EOI)
	1 hour after EOI	± 15 minutes
	4 hours after SOI	
	8 hours after SOI	
	12 hours after SOI	
Day 2	24 hours after SOI	
Day 3	48 hours after SOI	± 1 hour
Day 4	72 hours after SOI	
Day 8	168 hours after SOI	± 4 hours
Day 15	336 hours after SOI	
Day 29	672 hours after SOI	± 1 day
Day 43	1,008 hours after SOI	
Day 57	1,344 hours after SOI	
Day 71	1,680 hours after SOI	± 3 days
Day 85	2,016 hours after SOI	
Day 99	2,352 hours after SOI	

Serum samples will be analyzed to determine the concentrations of bevacizumab using a validated immunoassay.

Serum concentrations, serum collection times, and deviations from scheduled collection times of bevacizumab will be listed for safety population. Serum concentrations of bevacizumab will be summarized for PK population by treatment group and scheduled sampling time point using descriptive statistics (number, mean, geometric mean, standard deviation, CV, minimum, median, and maximum).

The individual serum concentration versus time profiles for bevacizumab, as well as the mean serum concentration versus time profiles will be presented graphically in both linear and semi-logarithmic scales by treatment group. The individual serum concentration versus time profiles for bevacizumab will be presented by treatment group as spaghetti plots showing all data from subjects in the same treatment group. The individual serum concentration versus time profiles for each subject will also be

presented. For ease of presentations, scheduled sampling times will be used to present results in mean figures. For individual figures, actual times will be used.

9.3 Serum Pharmacokinetic Parameters

The following serum PK parameters will be calculated for bevacizumab administered as CT-P16, EU-approved Avastin, and US-licensed Avastin by [redacted] with following guidelines:

- Actual sampling times relative to dosing rather than nominal times will be used in the calculation of all derived PK parameters.
- There will be no imputation of missing data.
- Any subjects with missing concentration data will be included in the PK population provided that at least C_{max} and $AUC_{0\text{-}last}$ can be reliably calculated.

The serum PK parameters are defined as the following table.

Parameter	Definition
$AUC_{0\text{-}inf}$	AUC from time zero extrapolated to infinity
$AUC_{0\text{-}last}$	AUC from time zero to the time of the last quantifiable concentration
C_{max}	Maximum observed serum concentration
T_{max}	Time corresponding to occurrence of C_{max}
V_z	Volume of distribution during terminal phase (after IV)
λ_z	Terminal elimination rate constant
$t_{½}$	Apparent terminal elimination half life
CL	Total body clearance
$\%AUC_{ext}$	Percentage of $AUC_{0\text{-}inf}$ obtained by extrapolation

PK parameters will be estimated according to the following guidelines:

- C_{max} will be obtained directly from the concentration-time data.
- T_{max} is the time at which C_{max} is observed.
- λ_z will be estimated at terminal phase by linear regression after log-transformation of the concentrations:
  - Only those data points that are judged to describe the terminal log-linear decline will be used in the regression.
  - A minimum number of three data points in the terminal phase will be used in calculating

λ_z with the line of regression starting at any post-C_{max} data point (C_{max} should not be part of the regression slope). The adjusted coefficient of determination (R^2 adjusted) in general should be greater than 0.85. Any value < 0.85 will be flagged but may be used at the PK Scientist's best knowledge and judgment. All the derived parameters (i.e. λ_z, $t_{½}$, $AUC_{0\text{-}inf}$, CL, V_z, and $\%AUC_{ext}$) will need to be flagged in the individual data listing and excluded from statistical analysis and descriptive summary accordingly.

- The interval used to determine λ_z should be equal or greater than 1.5-fold the estimated half-life or otherwise flagged and used at the PK Scientist's best knowledge and judgment. All the derived parameters (i.e. $t_{½}$, $AUC_{0\text{-}inf}$, CL, V_z, and $\%AUC_{ext}$) will need to be flagged in the individual data listing and excluded from statistical analysis and descriptive summary accordingly.

- $t_{½}$ will be calculated as $\ln 2/\lambda_z$.
- AUC is calculated by the linear up/log down method (linear method will be employed for all incremental trapezoids arising from increasing concentrations and the logarithmic method will be used for those arising from decreasing concentrations.
  - $AUC_{0\text{-}t} = \int_0^t \mathbf{C(t)dt}$
  - $AUC_{0\text{-}inf} = \int_0^t \mathbf{C(t)dt} + \int_t^\infty \mathbf{C(t)dt} = AUC_{0\text{-}last} + C_{last}/\lambda_z$.
  - C_{last} is last observed quantifiable concentration.
  - If a subject withdraws after the IMP infusion but before last planned PK sampling time then the calculated PK parameters will be flagged (i.e. $AUC_{0\text{-}last}$) and used at the PK Scientist's best knowledge and judgment. This kind of $AUC_{0\text{-}last}$ will be flagged in individual data listing and excluded from statistical analysis and descriptive summary accordingly.
- $\%AUC_{ext}$ will be calculated as $(1 - [AUC_{0\text{-}last}/AUC_{0\text{-}inf}]) \times 100$. The $\%AUC_{ext}$ should not exceed 20% for each individual profile. If the $\%AUC_{ext}$ is more than 20%, the individual result should be flagged and mentioned in the report and all derived parameters (i.e. $AUC_{0\text{-}inf}$ and CL) will be flagged in the individual data listing and excluded from statistical analysis and descriptive summary accordingly.
- CL will be calculated as $dose/AUC_{0\text{-}inf}$.
- V_z will be calculated as $dose/(\lambda_z * AUC_{0\text{-}inf})$.

PK parameters will be presented in data listings and summarized in tables for PK population by treatment group, using descriptive statistics (number, mean, standard deviation, CV, geometric mean, minimum, median, and maximum). The decimal places of the raw data for each PK parameter will be considered as following table.

PK parameter	Unit	The decimal places of the raw data
$AUC_{0\text{-}inf}$	h・μg/mL	1
$AUC_{0\text{-}last}$	h・μg/mL	1
C_{max}	μg/mL	1
T_{max}	h	2
V_z	L	2
λ_z	1/h	5
$t_{½}$	h	1
CL	L/h	4
$\%AUC_{ext}$	%	1

9.4 Statistical Analysis of Pharmacokinetic Data

The statistical analysis of the log-transformed primary endpoints ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and C_{max}) will be based on an analysis of covariance (ANCOVA) model with treatment as a fixed effect and body weight (<70kg vs ≥70kg) assessed on day -1 and study site as covariates. The difference in least squares means between the CT-P16 and EU-approved Avastin, CT-P16 and US-licensed Avastin, and EU-approved Avastin and US-licensed Avastin, and the associated 90% CIs will be determined. Back transformation will provide the ratio of geometric means and 90% CIs for these ratios.

Similarity of systemic exposure ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and C_{max}) will be determined if 90% CI for the ratio of geometric means is within the acceptance interval of 0.8 to 1.25 for the following comparisons:

- CT-P16 vs EU-approved Avastin
- CT-P16 vs US-licensed Avastin
- EU-approved Avastin vs US-licensed Avastin

10. SAFETY ANALYSIS

This section provides details of safety analysis. All analyses of safety data will be conducted using the safety population, unless otherwise specified.

10.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this product. Concomitant illnesses, which existed prior to entry into the clinical study, will not be considered as AEs unless they worsen during the treatment period. Pre-existing conditions will be recorded in the eCRF on the Medical History. All AEs will be collected from the date the informed consent form is signed and will continue until the end of the subject's participation in the

study. A treatment-emergent adverse event (TEAE) is defined as an AE that begins or that worsens in severity after administration of the IMP.

A SAE is defined in the protocol as any event that: results in death; is life threatening; requires at least 24-hour hospitalization or prolongation of expected length of stay; results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; is a congenital anomaly or birth defect, or is another important medical event other than listed above which may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

An AESI is defined as AE classified as an infusion-related reaction (IRR)/ hypersensitivity, which is checked (AEIRR='Yes') on the 'Adverse Events' eCRF page.

Adverse events will be coded to SOC and PT according to the MedDRA version 20.1. AEs will be graded for intensity according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

A summary table of overall AEs will be presented with the number and percentage of subjects with at least one AE, TEAE, SAE, treatment-emergent serious adverse event (TESAE), TEAE leading to permanent discontinuation of IMP, AE leading to death and TEAE of special interest.

For summarization of TEAEs, a subject will be counted only once if one or more events are reported and only the worst intensity will be counted at each level of summarization. The summary of TEAEs will be presented in alphabetical order of SOC. Within each SOC, the PTs will be also presented in alphabetical order.

AEs will be considered to be related if relationship is possible, probable or definite for IMP. AEs with no relationship or intensity recorded will be summarized separately under a missing category.

The following TEAE summary tables will include the total number of each corresponding TEAEs and the number and percentage of subjects experiencing TEAEs by treatment group, SOC, PT, relationship, and maximum intensity.

- Treatment-emergent Adverse Events
- Treatment-emergent Serious Adverse Events
- Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of IMP
- Treatment-Emergent Adverse Events of Special Interest (Infusion-related reaction/hypersensitivity)

The following TEAE summary tables will include the total number of each corresponding TEAEs and the number and percentage of subjects experiencing TEAEs by treatment group, SOC, PT, and maximum intensity regardless of relationship.

- Treatment-emergent Adverse Events
- Treatment-emergent Serious Adverse Events
- Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of IMP

Listings for AE, SAE, TEAE leading to permanent discontinuation of IMP and TEAE of special interest will be provided by actual treatment received. The listings will include the following information from the eCRF: SOC, reported term and PT; start and end date; outcome (recovered, recovered with sequelae, recovering, not recovered, fatal, unknown); severity/intensity (Grade 1 [mild], Grade 2 [moderate], Grade 3 [severe], Grade 4 [life-threatening], Grade 5 [death]); relationship/causality to IMP (unrelated, possible, probable, definite); action taken with study treatment (no action taken, IMP interrupted, IMP withdrawn, not applicable); other treatment (no treatment, medication treatment, non-medication treatment, specify, both medication and non-medication treatment, specify), and whether a subject was discontinued from study due to AE (no, yes) . For IRR only, start time and end time will also be included in the listing. Additionally, following listings will be provided; signs and symptoms of infusion-related reaction/hypersensitivity, additional AEs with an outcome of "Death", and additional information on SAEs.

10.2 Clinical Laboratory Tests

Clinical laboratory tests (hematology, clinical chemistry, coagulation, and urinalysis) will be summarized by laboratory test type, treatment group using descriptive statistics (number, mean, standard deviation, minimum, median and maximum) at each scheduled collection time. For continuous parameters, change from baseline will also be summarized for all post infusion scheduled collection times. For neutrophil, lymphocyte, monocyte, eosinophil, and basophil, minimum and maximum will be presented to three decimal places, mean and median will be presented to four decimal places, and standard deviation will be presented to five decimal places. For all other items except neutrophil, lymphocyte, monocyte, eosinophil, and basophil, minimum and maximum will be presented to the two decimal places, mean and median will be presented to three decimal places, and standard deviation will be presented to four decimal places. A shift table comparing the categorical results classified as either "Normal", "Abnormal, not clinically significant", "Abnormal, clinically significant" or "Not done" at each scheduled post-baseline visit with those at baseline will be summarized by treatment group and visit except for urinalysis. It is considered as "Not done" if it is recorded that the sample was not collected (LBYN='No') on the 'Clinical Laboratory Assessment-Hematology', 'Clinical Laboratory Assessment-Clinical Chemistry', 'Clinical Laboratory Assessment-Coagulation', or 'Clinical Laboratory Assessment-Urinalysis' page of the eCRF or the actual result of the item has been not collected at each scheduled collection time. For summaries using shift tables, 'Not done' will also be regarded as a baseline value. All laboratory results will be listed by treatment group. If any continuous parameter of clinical laboratory tests is collected with inequality signs (>, <) the inequality signs will be removed and the numeric values will be used for analyses (e.g., [>3, ≥3, <3, ≤3] will be analyzed as 3).

The items will be summarized as following:

- Hematology: Hemoglobin, Hematocrit, Red Blood Cell, White Blood Cell, Neutrophil,

Lymphocyte, Monocyte, Eosinophil, Basophil, absolute neutrophil count, and Platelets

- Clinical Chemistry: Albumin, Alkaline phosphatase, Alanine aminotransferase, Aspartate aminotransferase, Blood urea nitrogen, Calcium, Chloride, Total cholesterol, Creatine phosphokinase, Creatine kinase–myocardial band isoenzyme, Creatinine, Creatinine clearance, C reactive protein, Gamma-glutamyl transferase, Glucose, Lactate dehydrogenase, Magnesium, Phosphate, Potassium, Sodium, Total bilirubin, Direct bilirubin, Total protein, Uric acid, Triglyceride, and Troponin I
- Coagulation: Fibrinogen, International normalized ratio, Prothrombin time, and Activated partial thromboplastin time
- Urinalysis: Color, pH, Specific gravity, Ketones, Protein, Glucose, Bilirubin, Nitrite, Urobilinogen, and Occult blood

All numeric parameters will be labeled with a CTCAE term and grading will be applied to post-baseline values for all numeric parameters where possible according to CTCAE v 4.03. Grades that require clinical input only will not be assigned to these parameters. Grades which are part numeric and part clinical input will be assigned based on the numeric portion only. The CTCAE terms and ranges for applicable parameters are listed in Appendix 11.3. The CTCAE grades for this analysis will be Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe) and Grade 4 (Life threatening). The CTCAE Grade 5 (Death) will not be applied in this analysis since death cannot be determined from a numeric laboratory result. If the post-baseline result for a subject does not satisfy any CTCAE grade, it will be classified as "No Grade". The number and percentage of subjects with a result for each grade will be summarized by CTCAE term, visit (overall period and all post-baseline scheduled visits), and treatment group for safety population. In addition, a listing will be provided showing the CTCAE results for each subject by treatment group in the safety population.

A listing showing only subjects with abnormal values will be provided.

10.3 Hypersensitivity Monitoring

Hypersensitivity monitoring in vital signs of systolic and diastolic BP, HR, BT, RR will be summarized by treatment group at each scheduled collection time using descriptive statistics (number, mean, standard deviation, minimum, median and maximum). Change from baseline will also be summarized for all scheduled collection times. The baseline value on the 'Vital Signs' page of the eCRF for each corresponding item will be used as the baseline of hypersensitivity monitoring in vital signs.

The number and percentage of subjects who have a clinically significant vital sign hypersensitivity will be presented by treatment group and parameter.

The criteria for clinically notable results are defined as follows:

Parameter	Low	High
Systolic blood pressure (mmHg)	≤ 90	≥ 160
Diastolic blood pressure (mmHg)	≤ 50	≥ 90
Respiratory rate (breaths per minute)	≤ 12	≥ 20
Heart rate (beats per minute)	≤ 50	≥ 100
Body temperature (°C)	≤ 35.0	≥ 38.0

Hypersensitivity monitoring finding in 12-lead ECG will be classified as either "Normal", "Abnormal, not clinically significant", "Abnormal, clinically significant", "Not Done", or "Missing". It is considered as "Not done" if it is recorded that the ECG was not performed (HGYN='No') on the 'Hypersensitivity Monitoring-12-lead ECG' page of the eCRF. It is considered as "Missing" if it is recorded that the ECG was performed (HGYN='Yes') on the 'Hypersensitivity Monitoring-12-lead ECG' page of the eCRF but the actual result has been not collected. Results will be summarized by treatment group, in the form of a shift table comparing the categorical results of hypersensitivity monitoring finding in 12-lead ECG with ECG at baseline. The baseline value on the '12-lead ECGs' page of the eCRF will be used as the baseline of hypersensitivity monitoring in 12-lead ECG.
All hypersensitivity monitoring results in vital signs, 12-lead ECG, and continuous monitoring will be listed by treatment group.

10.4 Vital Signs

Vital signs of systolic and diastolic BP, HR, BT, RR will be listed and summarized by treatment group at each scheduled collection time using descriptive statistics (number, mean, standard deviation, minimum, median and maximum). Change from baseline will also be summarized for all post-infusion scheduled collection times.

10.5 12-Lead Electrocardiogram

12-lead electrocardiograms (ECGs) findings will be classified as either "Normal", "Abnormal, not clinically significant", "Abnormal, clinically significant", "Not done", or "Missing". A subject will be considered "Not done" if 'No' was recorded for the question, 'Was the ECG performed?' in the '12-lead ECG' page of the eCRF. A subject will be considered "Missing" if 'Yes' was recorded for the question, 'Was the ECG performed?' in the '12-lead ECG' page of the eCRF but the actual result was not collected. Results will be listed and summarized by treatment group and visit, in the form of a shift table comparing the categorical results at each scheduled post-baseline visit with those at baseline. For summaries using shift tables, 'Not done' and 'Missing' will also be regarded as a baseline value.

10.6 Physical Examination

Physical examinations should be based on the following body systems: general appearance,

head/ears/eyes/nose/throat, urogenital system, skin, cardiovascular system, respiratory system, abdominal system, neurological system, musculoskeletal system and lymph nodes. Findings will be classified as either "Normal", "Abnormal, not clinically significant", "Abnormal, clinically significant", "Not done", or "Missing". A subject will be considered "Not done" if 'No' was recorded for the question, 'Was the physical examination performed?' or if 'Not done' was recorded for 'Interpretation' for each body system in the 'Physical Examinations' page of the eCRF. A subject will be considered "Missing" if 'Yes' was recorded for the question, 'Was the physical examination performed?' in the 'Physical Examinations' page of the eCRF but the actual result for each body system has been not collected. A shift table comparing the categorical results at each scheduled post-baseline visit with those at baseline will be summarized by treatment group and visit. For summaries using shift tables, 'Not done' and 'Missing' will also be regarded as a baseline value. All physical examination findings will be presented in a data listing.

10.7 Immunogenicity Analysis

Immunogenicity assessment consists of both anti-drug antibody (ADA) and neutralizing antibody (NAb) assay. The test outcome will be reported as "Positive" or "Negative" and the titer values will be reported as the reciprocal of the dilution able to yield a background just at or above the cut point. ADA assay result will be considered as "Positive" only when the confirmatory assay result using CT-P16 as inhibition drug is "Positive". NAb assay result will be summarized only when the ADA result is considered as "Positive".

ADA Screening/Confirmatory assay results				ADA Result	NAb Result
Screening	Confirmatory				
	CT-P16	EU-Approved Avastin	US-Licensed Avastin		
Negative	N/A	N/A	N/A	Negative	N/A
Positive	Positive	Positive/Negative	Positive/Negative	Positive	The result will be summarized as reported.
Positive	Negative	Positive/Negative	Positive/Negative	Negative	The result will not be summarized.

The number and percentage of subject will be presented by treatment group and visit for the safety population. A listing showing immunogenicity test results for each subject will be provided by treatment group and visit. The ADA result will involve both a screening and a confirmatory assay using 3 Inhibition drugs (CT-P16, EU-approved Avastin and US-licensed Avastin) and the NAb result will involve a screening assay. The listing will also include actual results of ADA titer and NAb titer and

transformed results of ADA titer for each visit. ADA titer, NAb screening assay, and NAb titer results will be listed when any of 3 drug inhibition results is positive in ADA confirmatory assay. The ADA titer values will be transformed using a logarithmic transformation. Transformed ADA titer values can be obtained using $\left[\log_2\left(\frac{X}{20}\right)\right]+1$ transformation. If the values in the data are in inequality forms, the sign of inequality will be removed and then the values will be transformed.

10.8 Restriction Assessment

Restriction assessment should be based on the following categories: alcohol, caffeine, nicotine, meals, activity, medications, and contraception. Compliance of restriction for each category will be classified as either "Yes" or "No". A listing showing restriction assessment results for each subject will be provided by treatment group and visit.

11. APPENDICES

11.1 Schedule of Assessments

Assessments	Screening	In-House Stay			Out-patient Visits									EOS[1]
Day of Study Period	Day -21 to -2	Day -1	Day 1	Day 2	Day 3[2]	Day 4[2]	Day 8	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85	Day 99
Visit window (day)			-	-	-	-	-	-	± 1	± 1	± 1	± 3	± 3	± 3
Informed consent	X													
Medical and medication history	X	X												
Demographics	X													
Inclusion / exclusion criteria[3]	X	X												
Body weight & Height[4]	X	X												X
Physical examination	X	X			X									X
Viral serology test[5]	X													
Drugs of abuse / alcohol / nicotine check[6]	X	X												
Randomization		X												
Clinical laboratory tests[7]	X	X			X		X	X		X		X		X
Vital signs[8]	X	X	X		X	X	X	X	X	X	X	X	X	X
12-lead electrocardiogram[9]	X				X		X	X		X		X		X
Infusion of IMP			X											
Pharmacokinetic sampling[10]			X[11]	X	X	X	X	X	X	X	X	X	X	X
Hypersensitivity monitoring[12]			X											

Immunogenicity[13]			X[11]					X		X		X		X
Restriction assessment	X	X											
Concomitant medication[14]	X	X											
Adverse events	X	X											

Abbreviations: ECG, electrocardiogram; EOS, end of study; IMP, investigational medicinal product; PK, pharmacokinetic;

1. End-of-study visit procedures will be performed for subjects who completed the study as well as subjects who terminated the clinical study prematurely. After the EOS visit, serious adverse drug reactions will be reported to the Sponsor or its designee.
2. Assessments on Day 3 and 4 can be carried out either during the In-House Stay or on an out-patient basis according to Investigator decision.
3. Inclusion and exclusion criteria should be checked before randomization.
4. Height will be measured at screening only.
5. Serology tests will be performed at the screening visit for human immunodeficiency virus (HIV) -1 or -2 antibodies, hepatitis B surface antigen (HBsAg) and hepatitis B surface antibody (HBsAb), hepatitis C antibody and syphilis.
6. Drug abuse testing includes the followings: amphetamines, barbiturates, benzodiazepines, cocaine, opiates, and cannabinoids during the screening period only. The history of Drug abuse, alcohol and nicotine will be checked by medical history taking by Investigator during the screening period and Day -1.
7. Clinical laboratory tests will be carried out at screening, on Day –1, Day 3, 8, 15, 43, 71, and 99; **Hematology** (hematocrit, hemoglobin, red blood cell count, white blood cell count with differential, absolute neutrophil count, and platelets), **Clinical chemistry** (albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, calcium, chloride, total cholesterol, creatine phosphokinase, creatine kinase–myocardial band isoenzyme, creatinine, creatinine clearance [estimated by Modification of Diet in Renal Disease [MDRD]], C reactive protein, gamma-glutamyl transferase, glucose, lactate dehydrogenase, magnesium, phosphate, potassium, sodium, total bilirubin, direct bilirubin, total protein, uric acid, triglyceride, and Troponin I), **Urinalysis** (color, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, occult blood, and microscopic examination), **Coagulation** (Fibrinogen, international normalized ratio, prothrombin time, and activated partial thromboplastin time)
8. Vital signs will be measured at screening, on Day –1, before dosing on Day 1, on Day 3, 4, 8, 15, 29, 43, 57, 71, 85, and 99.
9. Twelve-lead ECG will be performed at the screening visit, on Day 3, 8, 15, 43, 71, and 99.
10. Blood samples for PK analysis will be collected as specified in CT-P16 1.1 SAP section 9.2.
11. Pre-dose blood sample for PK and immunogenicity assessment will be collected before start of infusion on Day 1.

12. For hypersensitivity monitoring, vital signs measurement and 12-lead ECG will be done as specified in CT-P16 1.1 Protocol Table 3.
13. Immunogenicity will be assessed on before dosing on Day 1, on Day 15, 43, 71 and 99.
14. Prior and concomitant medication use will be recorded for the 30 days prior to the screening visit until the EOS visit.

11.2 CTCAE Grades

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL[1])
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL[2]
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Source: CTCAE Version 4.03

Note: a semicolon indicates "or" within each description.

1. Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
2. Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

11.3 Laboratory Grades

CTCAE Term	Laboratory Parameter	Level	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	Hemoglobin	Low	<LLN - 10.0 g/dL; <LLN - 100 g/L	<10.0 - 8.0 g/dL; <100 - 80 g/L	<8.0 g/dL; <80 g/L;	-
Alanine aminotransferase increased	Alanine Aminotransferase (ALT)	High	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Alkaline phosphatase increased	Alkaline phosphatase	High	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Aspartate aminotransferase increased	Aspartate Aminotransferase (AST)	High	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Blood bilirubin increased	Total Bilirubin	High	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
CPK increased	Creatine Phosphokinase (CPK)	High	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN
Creatinine increased	Creatinine	High	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN

CTCAE Term	Laboratory Parameter	Level	Grade 1	Grade 2	Grade 3	Grade 4
GGT increased	Gamma Glutamyl Transferase	High	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Hemoglobin increased	Hemoglobin	High	Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	-
Hypercalcemia	Calcium	High	>ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L	>11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L	>12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L	>13.5 mg/dL; >3.4 mmol/L
Hyperkalemia	Potassium	High	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
Hypernatremia	Sodium	High	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L;	>160 mmol/L
Hyperuricemia	Uric acid	High	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	-	>10 mg/dL; >0.59 mmol/L; life-threatening consequences
Hypoalbuminemia	Albumin	Low	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	-

CTCAE Term	Laboratory Parameter	Level	Grade 1	Grade 2	Grade 3	Grade 4
Hypocalcemia	Calcium	Low	<LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L	<8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L	<7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L	<6.0 mg/dL; <1.5 mmol/L
Hypoglycemia	Glucose	Low	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L
Hypokalemia	Potassium	Low	<LLN - 3.0 mmol/L	-	<3.0 - 2.5 mmol/L	<2.5 mmol/L
Hyponatremia	Sodium	Low	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L
Lymphocyte count decreased	Lymphocytes	Low	<LLN - 800/mm^3; <LLN - 0.8 x $10e^9$/L	<800 - 500/mm^3; <0.8 - 0.5 x $10e^9$ /L	<500 - 200/mm^3; <0.5 - 0.2 x $10e^9$ /L	<200/mm^3; <0.2 x $10e^9$ /L
Lymphocyte count increased	Lymphocytes	High	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3	-
Neutrophil count decreased	Total Neutrophils	Low	<LLN - 1500/mm^3; <LLN - 1.5 x $10e^9$ /L	<1500 - 1000/mm^3; <1.5 - 1.0 x $10e^9$ /L	<1000 - 500/mm^3; <1.0 - 0.5 x $10e^9$ /L	<500/mm^3; <0.5 x $10e^9$ /L

CTCAE Term	Laboratory Parameter	Level	Grade 1	Grade 2	Grade 3	Grade 4
Platelet count decreased	Platelet count	Low	<LLN - 75,000/mm^3; <LLN - 75.0 x $10e^9$ /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x $10e^9$ /L	<50,000 - 25,000/mm^3; <50.0 - 25.0 x $10e^9$ /L	<25,000/mm^3; <25.0 x $10e^9$ /L
White blood cell decreased	White Blood Cells	Low	<LLN - 3000/mm^3; <LLN - 3.0 x $10e^9$ /L	<3000 - 2000/mm^3; <3.0 - 2.0 x $10e^9$ /L	<2000 - 1000/mm3; <2.0 - 1.0 x $10e^9$ /L	<1000/mm^3; <1.0 x $10e^9$ /L

Note: The LLN and ULN values will be the normal ranges as provided by the central laboratory at each relevant transfer.

A Semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a grade is not available.

11.4 Date Imputation for Prior and Concomitant Medication

Prior and concomitant medications will be coded using the WHO Drug Dictionary version 01Sep2017 or later. For the purpose of inclusion in prior and/or concomitant medication tables, incomplete medication start and end dates will be imputed as follows:

- Missing day: Assume the day is 1st of the month. If the partial date and the date of IMP infusion (defined as the date recorded on 'Infusion of IMP' eCRF page) lie within the same month and year, set to the date of first infusion, if not after the end date for the medication, otherwise set to end date of the medication.

- Missing day and month: Assume 1st January. If the partial date and the date of first infusion lie within the same year, set to the date of first infusion, if not after the end date for the medication, otherwise set to end date of the medication.

- Missing day, month and year: Assume date of first infusion, if not after the end date for the medication, otherwise set to the end date for the medication.

For the missing day imputation, the following examples should be used for reference:

- Example 1:
  Medication start: JUN2015
  Medication end: 20OCT2015
  Date of first infusion: 16OCT2015
  Medication start imputed: 01JUN2015

- Example 2:
  Medication start: OCT2015
  Medication end: 20OCT2015
  Date of first infusion: 16OCT2015
  Medication start imputed: 16OCT2015

- Example 3:
  Medication start: OCT2015
  Medication end: 20OCT2015
  Date of first infusion: 24OCT2015
  Medication start imputed: 20OCT2015

Partial end dates will be imputed as follows:

- Missing day: Assume the last day of the month
- Missing day and month: Assume December 31st
- Missing day, month and year: Assume that the medication is continuing.

In the case of the death of a subject, and the imputed end date is after the date of death, the end date will be imputed as the date of death.

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Listing 16.2.9.4	Physical Examination	Safety Population
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Figure 14.2.1.1	Mean (+/-SD) Serum Concentrations of Bevacizumab by Treatment	Pharmacokinetic Population
Figure 14.2.1.2	Individual Serum Concentrations of Bevacizumab Versus Time (Spaghetti Plot)	Pharmacokinetic Population

Figure 14.2.1.3	Individual Serum Concentrations of Bevacizumab Versus Time	Pharmacokinetic Population

12. ROLE & RESPONSIBILITIES

Role	Name	Responsibilities
Biostatistician	[redacted]	Responsible for conducting statistical analysis and managing all the relevant tasks
Biostatistician	[redacted]	Responsible for reviewing the statistical analysis results conducted by the Project Biostatistician
Biostatistician	[redacted]	Responsible for reviewing the statistical analysis results conducted by the Project Biostatistician
Biostatistician	[redacted]	Responsible for conducting double programming for statistical analysis

13. APPLIED SOPs

SOP No.	SOP Version_Effective date	SOP Name
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]