STATISTICAL ANALYSIS PLAN

SPONSOR: PRESTIGE BIOPHARMA PTE. LTD.

PROTOCOL: SAMSON-1

A PHASE I, DOUBLE-BLIND, RANDOMIZED, PARALLEL GROUP STUDY TO DEMONSTRATE THE EQUIVALENT PHARMACOKINETIC PROPERTIES OF A SINGLE INTRAVENOUS DOSE OF HD204, US-AVASTIN® AND EU-AVASTIN® IN HEALTHY MALE SUBJECTS

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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MODIFICATION HISTORY

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Algorithm for Treatment Emergence of Adverse Events: **30**

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1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of pharmacokinetics (PK) and safety data for Protocol SAMSON-1. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed. This Statistical Analysis Plan (SAP) has been developed prior to database lock and final analysis. Any deviations from the planned analyses described in this SAP will be documented in the clinical study report, together with the reason for such changes.

This SAP is based on protocol Version 2.0, dated 23 August 2018.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

- The primary objective of the study is to establish pairwise PK similarity between HD204 (Prestige Biopharma Pte. Ltd bevacizumab), EU-Avastin, and US-Avastin after a single intravenous (IV) infusion of 1 mg/kg in healthy male subjects.

2.2. SECONDARY OBJECTIVE

- The secondary objectives are to evaluate the safety, tolerability, and immunogenicity, and to further characterize the PK of HD204, EU-Avastin, and US-Avastin after a single IV infusion of 1 mg/kg in healthy male subjects.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a Phase I, randomized, double-blind, single dose, 3-way parallel group study to compare the PK, and to evaluate the safety, tolerability, and immunogenicity, of HD204, EU-Avastin, and US-Avastin after a single IV infusion of 1 mg/kg in healthy adult male subjects.

Approximately 156 subjects will be screened to achieve a total of 120 evaluable subjects randomly assigned to 1 of 3 treatment groups in a 1:1:1 ratio to receive a single IV infusion of either HD204, EU-Avastin or US-Avastin. A total of 120 evaluable subjects are required.

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Initially, subjects will be administered the study drug in staggered groups; the first sentinel group will comprise 3 subjects (1 subject each in the 3 treatment groups), the second group 6 subjects and the third group 9 subjects. Within each group subjects will be randomized to ensure equal numbers of subjects receive each of the 3 treatments.

There will be at least 48 hours between administrations of study drug to each staggered group. Prior to administration of study drug to the next group, the blinded safety and tolerability findings of the preceding group will be reviewed by the Principal Investigator. The Principal Investigator will consult with the Investigator(s) when subjects have been enrolled over all sites. The next group will be administered study drug provided there are no serious or unexpected drug-related safety issues. Each subject will be required to remain in the study center for 48 hours after administration of study drug for safety evaluation.

Subjects who have signed the informed consent form (ICF) and meet all the eligibility criteria will be admitted to the study center on Day -1 (i.e., the day prior to dosing) and will be discharged 48 hours post-dose on Day 3. Thereafter, subjects will attend the study center on an outpatient basis on Day 4, Day 8, Day 15, Day 22, Day 29, Day 36, Day 43, Day 50, Day 64, Day 78, and Day 95.

Safety assessments include the evaluation of AEs, vital signs, electrocardiogram (ECG) parameters, clinical safety laboratory tests (hematology, clinical biochemistry, coagulation, urinalysis [including proteinuria], and urine microscopy where clinically indicated), physical examination, injection site reactions, and concomitant medication. Blood samples will be collected for PK evaluations, and measurement of antidrug antibodies (ADA) and neutralizing antibodies (NAb). For specific time points see **Error! Reference source not found.** of the study protocol.

The duration of participation for each enrolled subject is expected to be a maximum of 120 days comprising a 28-day screening period (from Visit 1 until admission), followed by administration of study drug (Visit 2) and a 95-day follow-up period (Visits 3 to 13).

3.2. SCHEDULE OF EVENTS

Schedule of events can be found in Table 1 of the protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

There are no meaningful changes in the analysis plans relative to the study protocol.

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4. PLANNED ANALYSES

The following sections specify all the planned analysis deliveries for the study. No formal interim analyses requiring multiplicity adjustment are planned for this study.

4.1. SAFETY REVIEW COMMITTEE (SRC)

After the safety and tolerability data from the first 3 groups are available, a Safety Review Committee (SRC) meeting will be held to review the data and decide whether to proceed with continuous enrollment. The SRC will consist of the Principal Investigator, Investigator(s), Sponsor representative, and IQVIA Medical Monitor. IQVIA Biostatistics and PK are not supporting the SRC.

4.2. BLIND SAMPLE SIZE RE-EVALUATION

A blinded sample size re-evaluation (BSSR) will be performed after approximately 120 evaluable subjects (approximately 40 subjects per arm) have completed the study. If the BSSR results show that the study has achieved the planned total variability, it will be stopped. Otherwise, the required number of additional subjects will be recruited to yield up to a maximum of 282 evaluable subjects.

The BSSR will estimate the geometric coefficient of variation (CV) in the primary endpoint, ignoring any potential differences due to treatment. If the geometric CV is greater than 25%, the number of randomized subjects will be increased to yield up to a maximum of 282 evaluable subjects, which corresponds to a 39% CV. This procedure has been shown to preserve type I and type II errors below their nominal levels. If the CV is greater than 39%, the resulting power will fall below 80%, and the study will be halted or delayed.

If the CV ≤25% then the final analysis will be carried out.

4.3. INTERIM SAFETY REPORT

Analyses to support a blinded interim safety report (ISR) will be generated after completing Day 20 for the 60th study subject. The set of table, listings and figures (TLF) to be included in the ISR will be identified in the shell documents accompanying this SAP. ISR TLF will present treatment Overall only.

4.4. DRY RUN

A dry run analysis will precede final database lock. All TLF will be generated in the same format as for the final analysis, but instead using a dummy randomization.

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4.5. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics and Pharmacokinetics team following Sponsor authorization of this SAP, determination of analysis sets, database lock, and unblinding of treatment.

5. ANALYSIS SETS

Exclusions from analysis sets due to protocol violations or other events will be determined at the blinded data review meeting prior to database lock.

5.1. CONSENTED POPULATION

The consented population will include all subjects who provide informed consent. This set will be used for the disposition summary.

5.2. SAFETY ANALYSIS (SA) POPULATION

The SA population will include all subjects who receive the study drug (partial or complete). The SA population will be used for safety analysis. Immunogenicity will also be presented using the SA population.

5.3. PHARMACOKINETIC CONCENTRATION (PKC) POPULATION

The PKC population includes subjects with at least 1 valid postdose concentration, have received 1 dose of study drug without major protocol violations which may significantly affect the PK assessment. Subjects will be excluded from the PKC population if they have a significant protocol deviation that is likely to impact concentration. Exclusions from the PKC population due to major protocol violations will be decided before unblinding in the blinded data review meeting. Subjects who are confirmed positive post-dose for anti-bevacizumab antibodies will not be excluded from the PKC population. Serum bevacizumab concentrations summaries will be based on the PKC population.

5.4. PHARMACOKINETIC PARAMETER (PKP) POPULATION

The PKP population is a subpopulation of the PKC population, who have at least one evaluable primary or secondary PK parameter. Inclusion of incomplete/partial data into the PK analysis and descriptive

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statistics will be determined on a case-by-case basis. Pharmacokinetic parameter summary statistics and assessment of PK equivalence will be based on the PKP population.

5.5. PHARMACOKINETIC NON-NEUTRALIZING (PKNN) POPULATION

The PKNN population will include those members of the PKP population without sustained NAbs. Sustained NAbs occur when a patient has 2 consecutive visits with NAbs.

6. GENERAL CONSIDERATIONS

Derivation of the PK parameters for bevacizumab in serum will be the responsibility of the clinical pharmacokineticist at IQVIA, Overland Park, Kansas, United States. Safety and pharmacokinetic summary and individual figures, and data listings as well as the statistical analysis of the PK variables will be the responsibility of the study biostatistician at IQVIA.

Some minor modifications may be necessary to the planned design of tables, figures, and listings to accommodate data collected during the actual study conduct.

6.1. SUMMARY STATISTICS

For qualitative variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative variables will be summarized using descriptive statistics, including N, n, mean, standard deviation (SD), CV%, median, minimum, and maximum values. Geometric mean and Geometric CV% will be included for PK parameters, except time to maximum observed concentration (t_{max}). For t_{max}, only number of subjects, minimum, median, and maximum will be reported. Coefficient of variation will not be presented for change-from-baseline results.

6.2. TREATMENT SUMMARIZATION

In general, data will be presented for each treatment group, unless otherwise specified. Data for all study subjects combined will also be presented when appropriate.

6.3. PRECISION

Safety variables, including derivations thereof, will be reported to the same precision as the source data.

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All PK concentrations will be reported and analyzed with the same precision as the source data provided by the bioanalytical laboratory regardless of how many significant figures or decimals the data carry. Derived PK parameters will be rounded for reporting purposes in by-subject listings. The rounded derived PK parameters will be considered the source data for the calculation of descriptive statistics and the statistical analysis. For most derived PK parameters, 3 significant digits will be used as the standard rounding procedure, with the following exceptions:

- Parameters directly derived from source data [e.g., maximum observed concentration (C_{max})] will be reported and analyzed with the same precision as the source data.
- Parameters derived from actual elapsed sample collection times (e.g., t_{max}) will be reported with 2 decimal places.

For the reporting of descriptive statistics, the mean, SD, standard error, and confidence intervals (CIs) associated with the means will be presented to one digit more precision than the source data. The minimum, median, and maximum will be presented to the same precision as the source data. Coefficient of variation will always be reported to 1 decimal place. Ratios of means for PK parameters and their associated CIs will be presented with two decimal places (as a percentage) to meet regulatory requirements. P-values, if any, shall be reported to four decimal places or as <0.0001.

6.4. REFERENCE START DATE AND STUDY DAY

Relative study day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.

Reference start date is defined as the first day of the study drug, (Day 1) and will appear in every listing where an assessment date or event date appears.

If the date of the event is on or after the reference date then: Study Day = (date of event – reference date) + 1.

If the date of the event is prior to the reference date then: Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day, and any corresponding durations will be presented based on the imputations specified in APPENDIX 2; Partial Date Conventions.

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6.5. BASELINE

Baseline, is defined as the last scheduled non-missing measurement taken prior to dosing. Baseline will correspond to Day -1 for clinical lab tests and physical exams, and to Day 1 predose for ADA/NAb assessments, vital signs and ECGs.

6.6. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

Unscheduled measurements will not be included in summary statistics but will contribute to the best/worst case value where required (e.g., shift tables) and assessment of clinical outliers. Early termination results will be recorded as such and included with the end-of-study time points, if the nominal or protocol time is not available.

In the case of a retest of a scheduled assessment, the earliest available measurement for that scheduled time (i.e., the original assessment) will be used for summaries unless flagged as invalid.

Listings will include all scheduled, unscheduled, retest, and early discontinuation data.

6.7. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as: Test Value (after baseline) – Baseline Value

6.8. SOFTWARE VERSIONS

All derivations, statistical analyses, summaries, and listings will be generated using SAS Version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina, United States). Non-compartmental PK parameter calculations will be performed using Phoenix® WinNonlin® Version 6.4 or higher (Certara, L.P., Princeton, New Jersey, United States). Graphics will be prepared using the same versions of SAS. Sample size re-assessment calculations will be performed using SAS.

7. STATISTICAL CONSIDERATIONS

7.1. MISSING DATA

Missing safety data will not be imputed. For handling of missing PK data, see Section 14.

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8. OUTPUT PRESENTATIONS

APPENDIX 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics.

9. DISPOSITION AND STUDY DRUG ADMINISTRATION

All subjects who are screened will be accounted for in this study and screen failures will be tabulated. Subject disposition will be tabulated for each study treatment and for all subjects combined with the number of subjects who are enrolled, randomly assigned to treatment, complete the study, prematurely discontinue, and the reason for early discontinuation. Number of subjects in each analysis set will also be summarized. A listing will present dates of completion or early withdrawal and the reason for early discontinuation, if applicable, for each subject.

Listings of unmet inclusion/exclusion criteria, treatment randomization, and study drug administration will be provided.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Individual subject demographics and baseline characteristics will be presented in listings.

Demographic characteristics such as age, sex, race, ethnicity, height, weight, and body mass index (BMI) will be summarized and tabulated by treatment and for all subjects overall. Descriptive statistics will be presented for age, height, weight, and BMI. Frequency counts and percentages will be presented for sex, race, and ethnicity. No statistical testing will be carried out for demographic or other baseline characteristics.

11. PROTOCOL DEVIATIONS

11.1. DEVIATIONS RELATED TO STUDY CONDUCT

A protocol deviation is any noncompliance with the clinical study protocol, Good Clinical Practice, or Manual of Procedure requirements. The noncompliance may be either on the part of the subject, the site principal investigator, or the study site staff. Any subject enrolled who does not meet eligibility criteria will be considered an enrollment deviation. Protocol deviations will be listed including a classification, as determined by clinical staff.

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11.2. DEVIATIONS RELATED TO PK ANALYSIS

Changes to the procedures or events, which may impact the quality of the PK data, will be considered significant protocol deviations and will be described within the clinical study report body text. These changes or events will include any circumstances that will alter the evaluation of the PK. Examples include, but may not be limited to, sample processing errors that lead to inaccurate bioanalytical results and/or inaccurate dosing on the day of PK sampling. In the case of a significant protocol deviation or event, PK data collected during the affected treatment period will be excluded from the study results. Other changes to the procedures or events which do not impact the quality of the PK data will not be considered significant protocol deviations. A common example of a non-significant protocol deviation is a missed blood sample or deviations from blood collection times at collection times unlikely to affect the PK results. Exceptions to this are if a predose sample is taken after start of infusion or if the end of infusion sample is taken more than 5 minutes before the actual end of infusion or more than 5 minutes after the end of the infusion, each of which will result in careful evaluation if exclusion of the affected PK data (e.g., C_{max} and t_{max}) is warranted. If a predose sample is excluded due to being taken after start of infusion, the predose concentration will be taken as zero. For infusion, ± 5 minutes of deviation from 90 minutes of infusion duration is allowed and will not be considered as protocol deviation. This is not to be confused with, and is separate from, the +≤ 2 minute assessment window for the assessment at the end of infusion. Infusion durations outside 90 ± 5 minutes will be considered inaccurate dosing and a significant protocol deviation, and will lead to careful evaluation if exclusion of the affected PK data (e.g., C_{max} and t_{max}) is warranted. Infusion duration is defined as total elapsed time for the infusion, calculated as actual infusion end time minus actual infusion start time. Any interruption of infusion greater than 5 minutes will be considered a significant protocol deviation for dosing and will lead to exclusion of the affected PK data (e.g., C_{max} and t_{max}).

Protocol deviations will be reviewed by the study pharmacokineticist and biostatistician prior to unblinding to identify deviations which have the potential to affect the PK results.

12. MEDICAL HISTORY

Medical History will be coded using MedDRA Version 21.0 and will be listed and summarized by System Oran Class (SOC) and Preferred Term (PT).

13. MEDICATIONS

Medication usage will be coded using the WHO Drug Dictionary Version 01Mar2018 and presented for the safety analysis set.

- 'Prior' medications are medications which started and stopped prior to the study drug.

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- 'Concomitant' medications are medications which were taken during the treatment period, or specifically:
    - o started after the study drug or
    - o started prior to the study drug and were continued after the study drug

See APPENDIX 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case; i.e., concomitant.

A subject listing of all prior and concomitant medications will be provided. Since Anatomical Therapeutic Chemical (ATC) coding is not to be performed, no summarization of medications is planned.

14. PHARMACOKINETIC ANALYSIS

14.1. SERUM CONCENTRATION DATA

Pharmacokinetic blood samples will be collected from subjects to determine the serum concentration of bevacizumab, thus to evaluate the similarity of the PK of the three study drugs. The time points for sampling are as follows: prior to infusion of study drug, 45 minutes after the start of study drug infusion, at the end of infusion (i.e., at 90 minutes, with a ±2 minutes window), at 3h, 6h, and 12h after the end of infusion, at 24h (Day 2), 48h (Day 3), 72h (Day 4), 168h (Day 8), 336h (Day 15), 504h (Day 22), 672h (Day 29), 840h (Day 36), 1008h (Day 43), 1176h (Day 50), 1512h (Day 64), 1848h (Day 78), and 2256h (Day 95) after the end of infusion.

Subjects with partial data will be evaluated on a case-by-case basis to determine if sufficient data are available for reliable estimation of PK parameters.

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided.

Serum concentrations will be summarized based on the PKC population using descriptive statistics for each treatment. Concentrations that are below the limit of quantification (BLQ) will be treated as zero for the computation of descriptive statistics. Concentrations assigned a value of missing will be omitted from the calculation of descriptive statistics.

The protocol-allowable PK sampling collection windows are described below and are generally within 5% of the scheduled time. Serum samples that are collected outside the protocol-specified time windows will be identified in the listings and included in the PK parameter calculations. To minimize loss of data, serum concentrations will be included in the concentration summary unless the elapsed time deviates more than 20% relative from the scheduled time. The protocol-specified PK sampling collection windows are as follows:

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Study Day	Hours Relative to Start/End of Infusion	Window Allowed
Day 1	0 hours (Pre-dose)	Within 1 hour
	0.75 (post start of infusion)	±2 min
	0 hours (post end of infusion) or 1.5 hours (post start of infusion)	+≤2 min
	3 hours (post end of infusion)	±5 min
	6 hours (post end of infusion)	±15 min
	12 hours (post end of infusion)	±15 min
Day 2	24 hours (post end of infusion)	±1 hour
Day 3	48 hours (post end of infusion)	±2 hours
Day 4	72 hours (post end of infusion)	±3 hours
Day 8	168 hours (post end of infusion)	±8 hours
Day 15	336 hours (post end of infusion)	±1 day
Day 22	504 hours (post end of infusion)	±1 day
Day 29	672 hours (post end of infusion)	±1 day
Day 36	840 hours (post end of infusion)	±1 day
Day 43	1008 hours (post end of infusion)	±2 days
Day 50	1176 hours (post end of infusion)	±2 days
Day 64	1512 hours (post end of infusion)	±3 days
Day 78	1848 hours (post end of infusion)	±3 days
Day 95	2256 hours (post end of infusion)	±4 days

A subject listing of all concentration-time data for each treatment will be presented. Figures of arithmetic mean concentration-time data (±SD, as appropriate) will be presented for each treatment on linear and semi-logarithmic scales. Individual subject concentration-time data will be graphically presented on linear and semi-logarithmic scales.

14.2. PHARMACOKINETIC PARAMETERS

For PK parameter calculations, predose samples that are BLQ or missing will be assigned a numerical value of zero. Any anomalous concentration values observed at predose will be identified in the study report and used for the computation of PK parameters. Pharmacokinetic parameters will be computed and the results will be included in the parameter summary and inferential analyses, if the anomalous predose concentration is not greater than 5% of the observed maximum concentration (C_{max}). If the

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anomalous predose concentration is greater than 5% of C_{max}, the PK parameters for the given subject will be calculated and reported in the listing but excluded from statistical summaries and analyses.

Any other BLQ concentrations will be assigned a value of zero if they precede quantifiable samples in the initial portion of the profile. A BLQ value that occurs between quantifiable data points, especially prior to C_{max}, will be evaluated to determine if an assigned concentration of zero makes sense, or if exclusion of the data is warranted. Following C_{max}, BLQ values embedded between 2 quantifiable data points will be treated as missing when calculating PK parameters. If a BLQ value occurs at the end of the collection interval (after the last quantifiable concentration), it will be set to zero. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantified values will be excluded from the PK analysis by setting them to missing, unless otherwise warranted by the concentration-time profile.

For calculation of AUCs, samples collected prior to dosing and designated as predose samples shall be assigned an actual sampling time of 0.00 hour. If concentration data are missing at the end of infusion, or associated with a large collection time deviation, the affected profile will be evaluated to whether AUC calculation may be performed by using the available concentration-time data or back-extrapolation to estimate the missing end-of-infusion concentration is warranted. If performed, analysis procedures will be following IQVIA SOPs and affected AUC values will be identified in the study report. Estimates for C_{max} and t_{max} will not be reported in such a situation.

The following PK parameters will be estimated for bevacizumab in serum by non-compartmental methods using actual elapsed time relative to the start of the infusion. A minimum of 3 quantifiable concentration-time data points will be required for calculation of PK parameters. The following PK parameters will be estimated:

C_{max}	Maximum concentration in serum (µg/mL), obtained directly from the observed concentration versus time data.
t_{max}	Time of maximum concentration (h), obtained directly from the observed concentration versus time data.
λ_z	Terminal rate constant (1/h), determined by linear regression of the terminal points of the log-linear concentration-time curve. Visual assessment will be used to identify the terminal linear phase of the concentration-time profile.
$t_{1/2}$	Terminal half-life (h), determined as $\ln 2/\lambda_z$.

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$AUC_{0\text{-last}}$	Area under the serum concentration-time curve from time zero to the time of last quantifiable analyte concentration (µg·h/mL), calculated by linear up/log down trapezoidal summation. $AUC_{0\text{-last}}$ will be listed only and excluded from summaries/inferential analysis if PK samples were not collected up to and including at least Day 43, which exceeds 2x the reported $t_{1/2}$. A sensitivity analysis may be performed excluding $AUC_{0\text{-last}}$ estimates for subjects with missing terminal samples at times later than Day 43.
$AUC_{0\text{-inf}}$	Area under the concentration-time curve in serum from zero (predose) extrapolated to infinite time (µg·h/mL), calculated by linear up/log down trapezoidal summation and extrapolated to infinity by addition of the last quantifiable concentration divided by the terminal rate constant: $AUC_{0\text{-last}} + C_{last}/\lambda_z$.
CL	Total systemic clearance (L/h), calculated as the administered dose (in mg) divided by $AUC_{0\text{-inf}}$.
V_{ss}	Apparent volume of distribution at steady state (L), calculated as $$\left[\frac{AUMC_{0-inf}}{AUC_{0-inf}} - \frac{TI}{2}\right] \cdot CL$$ where TI is the length of infusion.
V_z	Volume of distribution following intravenous dosing (L), calculated as dose divided by $\lambda_z \cdot AUC_{0\text{-inf}}$

The following PK parameters will be calculated for diagnostic purposes and listed, but will not be summarized.

$t_{1/2}$, Interval	The time interval (h) of the log-linear regression to determine λ_z.
$t_{1/2}$, N	Number of data points included in the log-linear regression analysis to determine λ_z. A minimum of 3 data points will be used for determination.

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R_{sq}	Goodness-of-fit statistic for calculation of λ_z (Regression coefficient). Lambda_z and related parameters will be listed but excluded from summaries/inferential statistics if R_{sq} is less than 0.800.
$\%AUC_{ex}$	Percentage of $AUC_{0\text{-inf}}$ obtained by extrapolation, calculated as $[(C_{last}/\lambda_z)/AUC_{0\text{-inf}}\times 100]$.

No dose adjustment will be made for any molecular conversions between administered drug product and analyte measure for calculation of PK parameters.

Due to collection of a blood sample at the end of the infusion, no additional calculation of a concentration at the end of infusion will be performed unless the sample is reported as missing or associated with a large collection time deviation. Any decision to impute a missing end-of-infusion value will be made on a case-by-case basis and documented in the study report. If the end-of-infusion value is imputed, C_{max} and t_{max} will not be reported. Any imputed end-of-infusion values will be provided in the data listings.

Pharmacokinetic parameters will be summarized based on the PKP population by treatment using descriptive statistics. A subject listing of individual PK parameters for each treatment will be provided.

Scatter plots of individual and geometric mean PK parameters ($AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max}) versus treatment will be presented.

The primary PK variable is $AUC_{0\text{-inf}}$. $AUC_{0\text{-last}}$, C_{max}, t_{max}, $t_{½}$, λ_z, V_{ss}, V_z, and CL are secondary variables.

The primary statistical null hypothesis is that $AUC_{0\text{-inf}}$ is not equivalent between HD204 and the reference products within 80.00% to 125.00% limits, against the alternative that HD204 is equivalent to the reference products.

The primary PK parameter, $AUC_{0\text{-inf}}$, will be compared using an analysis of variance (ANOVA) model with treatment as a fixed effect. The data will be natural log transformed prior to the analysis. Transformed back to the original scale, the geometric mean together with the 2-sided 95% CI for each treatment will be estimated and presented. Also, ratios of geometric means together with CIs (2-sided 90%) for treatment comparisons (HD204 versus EU-Avastin, HD204 versus US-Avastin, EU-Avastin versus US-Avastin) will be estimated and presented.

The 90% CI of the ratio of geometric means of log-transformed $AUC_{0\text{-inf}}$ will be used to assess bioequivalence between the test and reference using the bioequivalence interval of 80.00% to 125.00%. Bioequivalence will be declared if the 90% CI for the ratio falls within 80.00% and 125.00% for the primary PK parameter $AUC_{0\text{-inf}}$ for the comparisons: HD204 versus EU-Avastin, HD204 versus US-Avastin. The analysis will be repeated for the PKNN population and for secondary parameters C_{max} and $AUC_{0\text{-last}}$.

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If $AUC_{0\text{-}inf}$ is extrapolated by more than 20% in more than 20% of the subjects, a sensitivity analysis will be performed and the above described ANOVA will be repeated for the PKP population plus the $AUC_{0\text{-}inf}$ values which were excluded due to a greater than 20% extrapolation but which are otherwise evaluable.

For the BSSR, PK parameters will be estimated using nominal (scheduled) times if actual times are not available at that stage. Protocol deviations, adverse events, concomitant medications plus other relevant study data available will be reviewed to determine if subjects should be excluded from the analysis. Descriptive statistics will be generated to summarize across all evaluable subject treatment arms and estimate the overall geometric CV.

15. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the Safety Analysis Population.

There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

15.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using the MedDRA coding dictionary, Version 21.0.

Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after study drug.

Pretreatment AEs are defined as AEs occurring prior to dosing. These events will be presented in the listings only and are not included in the tabular summary of AEs.

See APPENDIX 2 for handling of partial dates for AEs. In the rare case where it is not possible to assess treatment emergence, the AE will be classified as treatment emergent (i.e., the worst case).

Severity

AE Severity will be classified as mild, moderate, or severe. TEAEs starting after the study drug with a missing severity will be classified as severe. If a subject reports a TEAE more than once within that SOC/ PT, the AE with the worst case severity will be used in the corresponding severity summaries.

Relationship to Study Medication

Relationship to study medication, as indicated by the Investigator, is classified as "definitely related", "probably related", "possibly related", "unlikely related", "unrelated" and "unable to determine". A "related" TEAE is defined as a TEAE with a relationship to study medication as "definitely related" or

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"probably related" or "possibly related" to study medication. TEAEs with a missing relationship to study medication will be regarded as "probably related" to study medication. If a subject reports the same AE more than once within that SOC/ PT, the AE with the worst case relationship to study medication will be used in the corresponding relationship summaries.

All AE tabulations will be will include the number and percentage of subjects. Incidence of TEAEs will be tabulated by the following:

- By SOC and PT
- By SOC, PT and Severity
- By SOC and PT for AEs Related to study medication only

15.1.1. TEAEs Leading to Discontinuation of Study

TEAEs leading to discontinuation of study, as recorded on AE panel, will be listed.

15.1.2. Infusion Site Reactions

The number and percentage of subjects with infusion site reactions will be summarized by SOC and PT. Infusion site reaction checks (Yes/No) will be listed.

15.1.3. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the (e)CRF and will be listed separately. Deaths, if any, will be included on this listing. SAEs will only be summarized if warranted.

15.2. Laboratory Evaluations

Central laboratory results will be included in the reporting of this study for Hematology, Blood Chemistry, Coagulation and Urinalysis. A list of laboratory assessments to be included in the outputs is included in the protocol, Appendix 3. Presentations will use SI Units.

Protocol-specified clinical laboratory tests will be summarized using descriptive statistics. Clinical laboratory data collected during study conduct, which were not required per protocol, such as for special testing to evaluate an AE, will be listed separately and not summarized.

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Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

The following summaries will be provided for laboratory data:

- Actual and change from baseline by visit (for quantitative measurements)
- Tabulation of results relative to reference ranges

Corresponding figures or individual profiles with out of range values flagged may be generated, if deemed beneficial for interpretation of results.

Screening lab test results (viral serology, drug and alcohol screening) will be listed only.

15.2.1. Laboratory Reference Ranges

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges by the lab vendors and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

Clinical laboratory reference/normal ranges will be listed.

15.3. ECG Evaluations

Results of the ECG assessments will be included in the reporting of this study.

The following ECG parameters will be reported for this study (ms): PR, QRS, RR, QT, QTcB, QTcF and HR (bpm).

Overall assessment of ECG (Investigator's judgment) will be recorded as following:

- o Normal
- o Abnormal, Not Clinically Significant (ANCS)
- o Abnormal, Clinically Significant (ACS)

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ECG parameter data and clinical interpretation of ECG findings will be presented in data listings. In addition, ECG monitoring results at Day 1 will be listed for all subjects.

The following summaries will be provided for ECG data:

- Actual and change from baseline by visit (for quantitative measurements)

15.4. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

- Systolic and Diastolic Blood Pressure (mmHg) and Pulse Rate (bpm)
- Temperature (^{o}C)

The following summaries will be provided for vital signs data:

- Actual and change from baseline

15.5. PHYSICAL EXAMINATION

Physical exam results will be listed including specification of any abnormalities observed.

15.6. IMMUNOGENICITY EVALUATION

Immunogenicity will be evaluated in terms of incidence of positive rate of anti-drug antibody (ADA), ADA titration, and neutralizing antibodies of ADA (NAb). All immunogenicity data will be listed and the proportion of subjects with ADA or NAb present will be summarized.

16. DATA NOT SUMMARIZED OR PRESENTED

The other domains not summarized or presented are:

- Comments

These domains and/or variables will not be summarized or presented, but will be available in the clinical study database, SDTM and/or ADaM datasets.

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17. REFERENCES

Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product. US FDA; 2016. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf

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APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

OUTPUT CONVENTIONS

Outputs will be presented according to the IQVIA Global Biostatistics Standard Output Conventions, which is available upon request.

DATES & TIMES

Depending on data available, dates and times will take the format yyyy-mm-dd; times will take the format hh:mm:ss; combined dates and times will take the format yyyy-mm-ddThh:mm:ss.

SPELLING FORMAT

English US.

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in that order:

For Tables, Listings and Graphs
HD204
EU-Avastin
US-Avastin

PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order:

Long Name (default)	Short Name
Screening	Scr
Day -1	D -1

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Long Name (default)	Short Name
Baseline	BL
Day 1	D1
Day X	DX
Day 43	D43
Day 50	D50
Day 64	D64
Day 78	D78
Day 95/ET	D95/ET
ADA Follow-Up	ADAFU

PRESENTATION OF NOMINAL TIMES

Nominal times will be presented in order in the units of hour(s) relative to start or end of infusion, as applicable.

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- randomized treatment group (or treatment received if it's a safety or PK output)
- center-subject ID
- date (where applicable)

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APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study drug start date, then not TEAE If start date >= study drug start date, then TEAE
	Partial	If start date < study drug start date, then not TEAE If start date >= study drug start date, then TEAE
	Missing	If start date < study drug start date, then not TEAE If start date >= study drug start date, then TEAE
Partial, but known components show that it cannot be on or after study drug start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study drug start date	Known	If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE

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START DATE	STOP DATE	ACTION
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study drug start date, assign as prior If start date < study drug start date and stop date >= study drug start date, assign as concomitant If start date >= study drug start date and stop date >= study drug start date, assign as concomitant

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START DATE	STOP DATE	ACTION
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If start date < study drug start date and stop date >= study drug start date, assign as concomitant If start date >= study drug start date and stop date >= study drug start date, assign as concomitant
	Missing	If stop date is missing could never be assumed a prior medication If start date < study drug start date, assign as concomitant If start date >= study drug start date, assign as concomitant
Partial	Known	Impute start date as earliest possible date (i.e., first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study drug start date, assign as prior If start date < study drug start date and stop date >= study drug start date, assign as concomitant If start date >= study drug start date and stop date >= study drug start date, assign as concomitant
	Partial	Impute start date as earliest possible date (i.e., first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If start date < study drug start date and stop date >= study drug start date, assign as concomitant If start date >= study drug start date and stop date >= study drug start date, assign as concomitant
	Missing	Impute start date as earliest possible date (i.e., first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date < study drug start date, assign as concomitant If start date >= study drug start date, assign as concomitant
Missing	Known	If stop date < study drug start date, assign as prior If stop date >= study drug start date, assign as concomitant

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START DATE	STOP DATE	ACTION
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date, assign as concomitant
	Missing	Assign as concomitant

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