TITLE PAGE

Protocol Title:

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

Protocol Number: SAMSON-1

Amendment Number: Original protocol

Product: HD204

Short Title:

Phase I, Double-blind, Randomized, Parallel Group Study to Demonstrate the Equivalent Pharmacokinetic Properties of a Single Intravenous Dose of HD204 and Avastin in Healthy Male Subjects

Study Phase: Phase I

Local Sponsor Name: IQVIA RDS Pty. Ltd

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Regulatory Agency Identifying Number(s):

EudraCT no. 2017-005174-19

Date of Protocol: 23 January 2019, Version 3.0

Sponsor Signatory:

I have read this protocol in its entirety and agree to conduct the study accordingly:

23 Jan 2019

Lisa Soyeon Park **Date**
Prestige Biopharma Chief Executive Officer

Medical Monitor name and contact information can be found in Appendix 2.

TABLE OF CONTENTS

TABLE OF TABLES....6

TABLE OF FIGURES....7

1.0 PROTOCOL SUMMARY....8
1.1 Synopsis....8
1.2 Schema....11
1.3 Schedule of Assessments....12

2.0 INTRODUCTION....17
2.1 Study Rationale....17
2.2 Background....17
2.3 Benefit/Risk Assessment....20

3.0 OBJECTIVES AND ENDPOINTS....21

4.0 STUDY DESIGN....22
4.1 Overall Design....22
4.2 Scientific Rationale for Study Design....24
4.3 Justification for Dose....25
4.4 End of Study Definition....25
4.5 Dose Escalation Criteria....25
4.6 Study Stopping Criteria....25
4.6.1 Stopping Criteria for Individual Subjects....25
4.6.2 Criteria for Stopping the Study....25

5.0 STUDY POPULATION....27
5.1 Inclusion Criteria....27
5.2 Exclusion Criteria....28
5.3 Lifestyle Considerations....30
5.3.1 Meals and Dietary Restrictions....30
5.3.2 Caffeine, Alcohol, and Tobacco....31
5.3.3 Activity....31
5.3.4 Avoidance of Pregnancy....31
5.4 Screen Failures....31
5.4.1 Repetition of Screening Assessment(s)....32
5.4.2 Rescreening of Subject(s)....32

6.0 STUDY TREATMENT....33
6.1 Study Treatment(s) Administered....33
6.2 Preparation/Handling/Storage/Accountability....34
6.3 Measures to Minimize Bias: Randomization and Blinding....34

6.3.1 Method of Assigning Subjects to Treatment Groups 34
6.3.2 Randomization Procedures 34
6.3.3 Maintenance of Randomization Codes 34
6.3.4 Unblinding 35
6.4 Study Treatment Compliance 35
6.4.1 Treatment Measures to Ensure Subject Safety 35
6.4.2 Warnings and Precautions 35
6.5 Concomitant Therapy 36
6.6 Dose Modification 36
6.7 Treatment After the End of the Study 36

7.0 DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL 37
7.1 Discontinuation of Study Treatment 37
7.2 Subject Discontinuation/Withdrawal from the Study 37
7.3 Lost to Follow-up 38

8.0 STUDY ASSESSMENTS AND PROCEDURES 39
8.1 Efficacy Assessments 39
8.2 Safety Assessments 39
8.2.1 Physical Examinations 39
8.2.2 Local Infusion Site Reactions 39
8.2.3 Immunogenicity 40
8.2.4 Vital Signs 41
8.2.5 Electrocardiograms 41
8.2.6 Clinical Safety Laboratory Assessments 41
8.3 Adverse Events 42
8.3.1 Time Period and Frequency for Collecting AE and SAE Information 42
8.3.2 Method of Detecting AEs and SAEs 43
8.3.3 Follow-up of AEs and SAEs 43
8.3.4 Regulatory Reporting Requirements for SAEs 43
8.3.5 Pregnancy 43
8.3.6 Adverse Events of Special Interest 44
8.4 Treatment of Overdose 44
8.5 Pharmacokinetics 44
8.5.1 Collection of Samples 44
8.5.2 Determination of Drug Concentration 44
8.5.3 Derivation of Pharmacokinetic Parameters 45
8.6 Pharmacodynamics 46
8.7 Genetics 46
8.8 Biomarkers 46

9.0 STATISTICAL CONSIDERATIONS 47
9.1 Statistical Hypotheses 47
9.2 Sample Size Determination 47

9.3 Populations for Analyses 47
9.4 Statistical Analyses 48
9.4.1 Primary Endpoint 48
9.4.2 Secondary Endpoints 48
9.4.3 Pharmacokinetic/Pharmacodynamic Analyses 48
9.4.4 Safety Analyses 49
9.4.5 Immunogenicity 49
9.4.6 Missing Data 49
9.5 Interim Analyses 50
9.5.1 Blinded Sample Size Re-evaluation 50
9.6 Safety Review Committee 50

10.0 REFERENCES 51

11.0 APPENDICES 52
Appendix 1 Abbreviations 53
Appendix 2 Regulatory, Ethical, and Study Oversight Considerations 55
Regulatory and Ethical Considerations 55
Adequate Resources 55
Financial Disclosure 56
Insurance 56
Informed Consent Process 56
Data Protection 56
Administrative Structure 57
Medical Monitor 58
Dissemination of Clinical Study Data 59
Data Quality Assurance 59
Source Documents 59
Study and Study Center Closure 60
Publication Policy 60
Appendix 3 Clinical Laboratory Tests 61
Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 63
Appendix 5 Contraceptive Guidance and Collection of Pregnancy Information 68
Appendix 6 Signature of Investigator 71

TABLE OF TABLES

Table 1 Schedule of Assessments 12
Table 2 Schedule of Assessments for Day 1 15
Table 3 Schedule of Pharmacokinetic Assessments 16
Table 4 Study Objectives and Endpoints 21
Table 5 Study Treatment Details 33
Table 6 Infusion Site Reaction Grading Scheme 40
Table 7 Serum Pharmacokinetic Parameters 46
Table 8 Analysis Sets 47
Table 9 Study Administrative Structure 57
Table 10 Protocol-required Safety Laboratory Assessments 61

TABLE OF FIGURES

Figure 1 Study Schema.....11
Figure 2 Study Design.....23

1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

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

Short Title:

Phase I, Double-blind, Randomized, Parallel Group Study to Demonstrate the Equivalent Pharmacokinetic Properties of a Single Intravenous Dose of HD204 and Avastin in Healthy Male Subjects

Rationale:

Prestige Biopharma Pte. Ltd is developing HD204, a biosimilar of the European Union (EU)-approved and US-licensed bevacizumab (Avastin®). Bevacizumab is a recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody that binds to vascular endothelial growth factor (VEGF) extracellularly to prevent interaction with VEGF receptors (VEGFRs). Avastin is licensed for clinical use in the US (US-Avastin) and the EU (EU-Avastin) for a variety of tumor types.

The purpose of this study is to compare the pharmacokinetics (PK) of HD204, US-Avastin, and EU-Avastin in healthy male subjects after intravenous (IV) administration of a single dose. As a First-in-Human study, the study will also evaluate the safety, tolerability, and immunogenicity of HD204, US-Avastin, and EU-Avastin in healthy subjects.

Objectives and Endpoints:

Objectives	**Endpoints**
Primary	
• The primary objective of the study is to establish pairwise PK equivalence between HD204 (Prestige Biopharma Pte. Ltd bevacizumab), EU-Avastin, and US-Avastin after a single IV infusion of 1 mg/kg in healthy male subjects	• Area under the concentration-time curve (AUC) of the analyte in plasma over the time interval from time 0 (baseline) extrapolated to infinity ($AUC_{0\text{-}inf}$)

Secondary	
• The secondary objectives are to evaluate the safety and 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	• AUC from time 0 to the last quantifiable data point ($AUC_{0\text{-last}}$), maximum observed plasma concentration (C_{max}), time to maximum observed concentration (t_{max}), terminal half-life ($t_{1/2}$), terminal rate constant (λ_z), systemic clearance (CL), and volume of distribution at steady state (V_{ss}) • Pharmacokinetic equivalence of the EU and the US-Avastin will be evaluated • Immunogenicity will be assessed by the incidence of anti-bevacizumab antibodies (ADA), including neutralizing antibodies (NAb) (if ADA positive) from Day 1 through last subject last visit • Safety and tolerability will be assessed by clinical laboratory tests, vital signs, 12-lead electrocardiograms (ECGs), physical examinations, assessment of adverse events (AE), injection site reactions, and concomitant medications

Overall Design:

This is a 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 (bevacizumab) after a single IV infusion of 1 mg/kg in healthy adult male subjects. The PK of bevacizumab is independent of dose between 1 and 10 mg/kg, so the lowest possible dose is chosen for administration to healthy volunteers in this study. Healthy male subjects will be enrolled to minimize the variability in the PK data by minimizing the variability due to physiological factors. Initially, subjects will be administered the study treatment in staggered groups; the first sentinel group will comprise 3 subjects, the second group 6 subjects and the third group 9 subjects. 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. Subjects will be randomized to ensure equal numbers of subjects receive each of the 3 treatments. Safety assessments will include: adverse events (AE), vital signs, electrocardiograms (ECG) parameters, clinical safety laboratory tests (hematology, clinical biochemistry, coagulation, urinalysis [including proteinuria], and urine microscopy where clinically indicated), physical examination, injection site assessments, and concomitant medications. Blood samples will be collected for PK evaluations and measurement of antidrug antibodies (ADA) and neutralizing antibodies (NAb) will be conducted.

Number of Investigators and Study Centers:

Approximately 2 Investigators and study centers are expected to participate in this study.

Number of 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 (40 subjects per treatment arm).

Treatment Groups and Duration:

This study will have a screening period of up to 28 days. Subjects will be admitted to the study center on Day -1, receive a single IV infusion of 1 mg/kg of HD204 (Prestige Biopharma Pte. Ltd bevacizumab), EU-

sourced Avastin (bevacizumab) or US sourced Avastin (bevacizumab) on Day 1. Subjects will be resident until the Day 3 discharge procedures have been completed and then return to the study center for 10 ambulatory visits (Days 4, 8, 15, 22, 29, 36, 43, 50, 64, and 71 [end of study]).

Statistical Methods:

Pharmacokinetic Parameters:

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% confidence intervals (CIs) 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.

Similar analysis will be carried out for the secondary PK parameter $AUC_{0\text{-}last}$.

Safety Parameters:

All study subjects who have received the study treatment (partial or complete) will be included in the safety analysis.

Safety and tolerability will be assessed using reporting of AEs, concomitant medication, injection site reactions, physical examinations, vital signs, 12-lead ECGs, and laboratory parameters. Listings and descriptive statistics summary tables will be provided as appropriate.

Other Parameters:

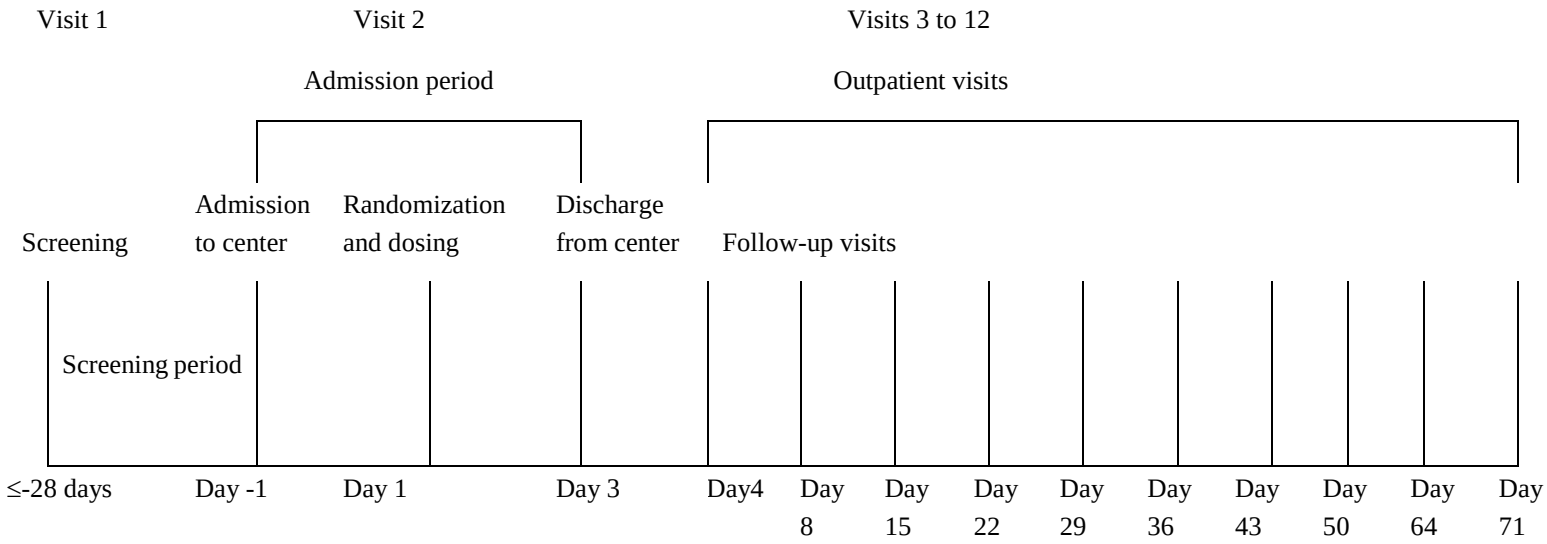
Proportion of subjects with ADA and with NAb will be summarized using descriptive statistics by visit for each parameter and presented in listings.

Safety Review Committee: Yes

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 next group will be dosed provided there are no serious or unexpected drug-related safety issues. The SRC will consist of the Principal Investigator, Investigator(s), Sponsor representative and IQVIA Medical Monitor.

1.2 Schema

Figure 1 Study Schema



The Day 71 visit will serve as the final follow-up visit for the study. However, subjects who are confirmed positive for anti-bevacizumab antibodies at the this visit or at and early termination visit (subjects who discontinue from the study following drug administration), will be followed up for up to 12 months or until 2 consecutive samples have been confirmed negative for anti-bevacizumab antibodies, whichever occurs earlier. These subjects will attend the clinical center at 6, 9, and 12 months after study completion post-dose for blood sampling to confirm their immunoglobulin status.

1.3 Schedule of Assessments

Table 1 Schedule of Assessments

Visit	**1**	**2**			**3 to 11**									**12**	
	Screen	**Treatment and in-patient stay**			**Outpatient visits**									**Final Follow-up/ Early termination**	**ADA FU (if required)**
Day (time windows are days unless specified otherwise)	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**8**	**15 ±1**	**22 ±1**	**29 ±1**	**36 ±1**	**43 ±2**	**50 ±2**	**64 ±3**	**71 ±4**	
Informed consent	X															
Inclusion/exclusion criteria	X	X														
Demographics	X															
Medical history	X	X														
Height and weight[c]	X	X														
Physical examination[a]	X	X	X[b]		X			X		X[c]		X[c]	X[c]	X[c]	X	
Viral serology[d]	X															
Drug, alcohol, and cotinine screen[e]	X	X														
Vital signs	X	X	X[f]	X[g]	X[g]	X	X	X	X[h]	X[h]	X[h]	X	X[h]	X[h]	X	
12-lead ECG	X	X	X[i]	X		X		X				X			X	
Clinical laboratory tests[j]	X	X			X	X		X				X		X	X	
Randomization			X													
Drug infusion			X													
Pharmacokinetic blood sampling[k]			X	X	X	X	X	X	X	X	X	X	X	X	X	
ADA/NAb test[l]			X[m]					X	X	X	X	X	X	X	X	X
Adverse events and infusion site assessment	X	X													X	X
Concomitant medications	X	X													X	X

ADA = antidrug antibodies; ECG = electrocardiogram; FU = follow-up; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; NAb = neutralizing antibodies; PK = pharmacokinetic

Where time points of clinical assessments and collection of biological samples coincide the order of priority will be:

- ECG
- Vital signs
- Pharmacokinetic samples
- Immunogenicity samples (ADA and NAb)
- Clinical laboratory samples

ECG will be conducted in time intervals of 15 minutes on either side of scheduled time point (ie ± 15 minutes) and vital signs will be collected in time interval of 10 minutes on either side of scheduled time point (ie ± 10 minutes). ECG and vital signs measurements performed outside of this window period will be considered protocol deviations. For PK sample collection, window period as specified in protocol will be followed.

If clinical assessments are required for the immediate safety monitoring of the subject they will take priority over all other sample collection or clinical assessments.

Footnotes:

a Full physical examination will be performed at screening, admission to the study center (Day -1), discharge (Day 3), Day 15, and follow-up (Day 71).

b Infusion site check only.

c Physical examination will be performed if clinically indicated. Height will be measured at screening only. Body weight will be measured at admission (during the physical examination) as this measurement will be used to calculate the dose to be administered to the subject. Body weight at admission is required for the calculation of the dose to be administered to the subjects. Height will be only assessed at screening.

d Viral serology will include HIV 1 and 2, HBsAg and hepatitis C antibody screening.

e Urine screen for drugs of abuse, alcohol, and cotinine. The screen for alcohol may be performed by a breath test according to local procedures.

f Vital signs on Day 1 will be measured at the following times: pre-dose (within 1 hour prior to the start of the infusion) and 0.5 and 1 hour post start of infusion; 0.25, 0.5, 1, 2, 3, 5, 6, 8, and 12 hours post end of infusion.

g Vital signs are to be measured at 24 and 36 hours post-dose on Day 2 and at 48 hours post-dose on Day 3.

h Blood pressure and pulse rate measurements only.

i 12-lead ECG on Day 1 will be measured at the following times: pre-dose (within 1 hour prior to the start of the infusion) and 0.75 and 1.0 hours post start of infusion; 3 and 12 hours post end of infusion and according to the PK sample schedule below for any other visits. ECG assessments will be obtained after the subject has been in the semi-supine position for at least 5 minutes.

j Clinical laboratory tests include hematology, clinical chemistry, coagulation and urinalysis (urine microscopy will be performed if clinically indicated) (see Appendix 3). Subjects with a 1+ or greater dipstick reading should undergo further assessment as per the clinical judgement of the Investigator or delegate.

k PK blood samples will be collected as indicated in the Schedule of Pharmacokinetics Assessments (Table 3).

l Subjects who are confirmed positive for anti-bevacizumab antibodies at the follow-up visit (Day 71) or at and early termination visit (subjects who discontinue from the study following drug administration), will be followed up for up to 12 months or until 2 consecutive samples have been confirmed negative for anti-bevacizumab antibodies, whichever occurs earlier. These subjects will attend the clinical center at 6, 9, and 12 months after study completion post-dose for blood sampling to confirm their immunoglobulin status.

m Within 1 hour prior to the start of the infusion.

Table 2 Schedule of Assessments for Day 1

Hours post start of infusion	**Pre[a]**	**0**	**0.5**	**0.75**	**1.0**	**1.5[c]**									
Hours post end of infusion							**0.25**	**0.5**	**1.0**	**2.0**	**3.0**	**5.0**	**6.0**	**8.0**	**12.0**
Randomization	X														
Drug infusion		X----------X													
Vital signs	X		X		X		X	X	X	X	X	X	X	X	X
12-lead ECG	X			X	X						X				X
Pharmacokinetic blood sampling[b]	X			X		X					X		X		X
ADA/NAb test	X														
Adverse events	X----------														----------X
Concomitant medications	X----------														----------X

ADA = antidrug antibodies; NAb = neutralizing antibodies

a Within 1 hour prior to the start of the infusion.

b PK blood samples will be collected at pre-infusion (or 0 hour, collected within 1 hour prior to the start of the infusion), 0.75 hours from the start of infusion (± 2 min), the end of infusion (0 hour post end of infusion +≤ 2 min [which is approximately 1.5 hours from the start of infusion]), at 3 hours (± 5 min), 6 hours (± 15 min), and 12 hours (± 15 min) from the end of infusion on Day 1.

c On completion of the infusion.

Table 3 Schedule of Pharmacokinetic Assessments

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 71	1680 hours (post end of infusion)	±4 days

2.0 INTRODUCTION

2.1 Study Rationale

Prestige Biopharma Pte. Ltd is developing HD204, a biosimilar of the European Union (EU)-approved and United States of America (US) US-licensed bevacizumab (Avastin®). Bevacizumab is a recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody that binds to vascular endothelial growth factor (VEGF) extracellularly to prevent interaction with VEGF receptors (VEGFRs). Avastin is licensed for clinical use in the US (US-Avastin®) and the EU (EU-Avastin®) for a variety of tumor types.

The purpose of this study is to compare the pharmacokinetics (PK) of HD204, US-Avastin, and EU-Avastin in healthy male subjects after intravenous (IV) administration of a single dose. As a First-in-Human study, the study will also evaluate the safety, tolerability, and immunogenicity of HD204, US-Avastin, and EU-Avastin in healthy subjects.

2.2 Background

Since initial approval of bevacizumab (Avastin) in the US (2004) and in the EU (2005), for advanced colorectal cancer, bevacizumab has made anti-angiogenic therapy a fundamental pillar of cancer treatment. Avastin is approved in many countries for the treatment of advanced stages of colorectal cancer, metastatic non-squamous non-small cell lung cancer (NSCLC), metastatic renal cell cancer, breast cancer, epithelial ovarian cancer, and glioblastoma (1, 2).

However, the cost of biologic therapies has become increasingly prohibitive which can limit the therapeutic use of the drugs in patients. Moreover, globally, colorectal cancer is the third most common cancer in men and the second most common cancer in women (3). In the US, the National Cancer Institute estimates that 140 250 new cases will be reported in 2018, leading to the estimated deaths of 50 630 patients, or 8.3% of all cancer deaths (4). Overall, solid tumors constitute more than 94.4% and 96.8% of cancer-caused mortalities in males and females, respectively (2).

Angiogenesis is a physiological process in which new blood vessels are formed from pre-existing vessels. It occurs during normal growth and development, as well as during wound healing. Under physiological conditions, angiogenesis is tightly regulated. To date, many pro-angiogenic factors and their cognate receptors have been identified, including VEGF. Tumor angiogenesis is a hallmark of cancer and plays a crucial role in providing oxygen and nutrients to tumor cells during cancer progression and metastasis. Under pathological conditions, many pro-angiogenic factors and their receptors are upregulated; among these factors, VEGF is generally regarded as a key regulator of tumor angiogenesis (1).

Bevacizumab binds to VEGF and thereby inhibits the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. Neutralizing the biological

activity of VEGF regresses the vascularization of tumors, normalizes remaining tumor vasculature, and inhibits the formation of new tumor vasculature, thereby inhibiting tumor growth (5, 6).

HD204 is a biosimilar to Avastin being developed by Prestige Biopharma Pte. Ltd.

Bevacizumab is a monoclonal antibody recombinant humanized immunoglobulin of the human immunoglobulin G subclass 1, kappa light chain (IgG1κ). HD204 is produced in a mammalian cell (Chinese hamster ovary [CHO]) expression system and is subsequently purified and formulated.

Analytical assays have been conducted to compare the purity of multiple lots of HD204 and Avastin. The data indicate that HD204 is at least as pure as Avastin and that the molecular weight and binding affinity are consistent between HD204 and Avastin.

HD204 and Avastin have similar post translational modification in terms of glycan variant distribution, overall galactosylation, fucosylation, and distribution of glycan variants. Charge variant distribution, as measured by ion exchange chromatography, and capillary iso-electric focusing were also similar.

Biological functional assays showed very similar results. Overall, the data have demonstrated that HD204 is highly similar to the reference product, Avastin, in structure and function.

Nonclinical Studies Using HD204

In vitro assessments of antibody functionality (including Fab, Fc, and complement functions) of HD204 have been performed in comparison with Avastin. In addition, in vitro and in vivo pharmacodynamic (PD) studies have been performed in a variety of test systems. Toxicokinetic investigations in the non-human primate were performed in a single dose study and as part of the 4-week and 13-week repeated dose toxicity studies. In addition, the immunogenicity of the antibody was evaluated in the repeated dose toxicity studies. In all of these investigations, HD204 was compared against Avastin sourced in the EU (7).

The in vitro comparative analysis of HD204 and Avastin demonstrated:

- The binding affinities of 3 VEGF isomers ($VEGF_{121}$, $VEGF_{165}$, $VEGF_{189}$), which can bind to bevacizumab, were compared by enzyme-linked immunosorbent assay (ELISA). Relative binding affinity was measured using the in-house reference standard. The antigen binding affinity for HD204 excluding $VEGF_{189}$ was found to be similar to that of the reference drug value.

- The binding affinity of 4 Fc receptors capable of binding to the Fc portion of the antibody was measured by the surface plasmon resonance method. Affinity for FcγRI, FcγRIIa, and FcγRIIIa receptors, which directly affect effector functions such as antibody-dependent cell-mediated cytotoxicity (ADCC), and FcRn receptors which are closely related to blood half-life was measured. A commercially available recombinant protein was used as a receptor for the assay. The analysis showed that the min/max values of the binding affinity measurements of all 4 HD204 samples in all Fc receptors were within the measurement range of the reference drug.
- The binding affinity to C1q, which binds to the hinge region of the antibody and is involved in complement-dependent cytotoxicity (CDC) activity, was measured by ELISA. HD204 and Avastin demonstrated similar binding activity.
- The degree of inhibition of cell activity was measured to confirm antigen binding affinity indirectly. Human umbilical vein endothelial cells (HUVEC) were used and the relative anti-proliferative effect of each sample was measured after $VEGF_{165}$ treatment using the in-house reference standard. The anti-proliferative effect of 2 HD204 clinical samples (BEA-14001, BEA-14002) was within the range of the reference drug. The third sample (HD204 BEA-14003) exceeded the upper limit of the reference drug's range.
- In the A549 lung cancer model, the efficacy of HD204 and the control agent on the size of the tumor when intraperitoneally administered twice weekly was comparable.
- No treatment-related adverse effects were observed in the animals treated with HD204 and Avastin.

Nonclinical Pharmacokinetics and Product Metabolism

The PK profile of HD204 was compared to that of Avastin in Cynomolgus monkeys (male and female), in a single subcutaneous dose study. HD204 and Avastin were administered by subcutaneous injection at a dose of 2 mg/kg. The result indicated comparable systemic clearance (CL) and concentration-time curve from time zero extrapolated to infinity ($AUC_{0\text{-}inf}$) between HD204 and Avastin.

Summary of Clinical Findings of HD204

At the time of preparation of this protocol, HD204 has not been administered to human subjects.

Additional information can be found in the Investigator's Brochure (IB).

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of HD204 may be found in the IB.

The subjects enrolled are not expected to gain any clinical benefit from participation in this clinical study. However, since a healthy subject population is most sensitive to product differences, such a population is expected to show a better response than patients to detect differences in PK profiles.

The safety procedures to be followed during the study have been selected to minimize the risk of harm to the subjects and to ensure the scientific integrity of the data collected during the study. All study treatment administrations will occur under medical supervision in the study center and subjects will remain at the study center for 48 hours following study treatment administration. The lowest dose of 1 mg/kg has been selected for the study to minimize exposure to healthy subjects and it is expected to be well tolerated in healthy subjects.

This study will be performed in compliance with the protocol, the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), European Union Good Manufacturing Practice (EU GMP) and applicable regulatory requirements.

The Sponsor will immediately notify the Principal Investigator if any additional safety or toxicology information becomes available during the study.

3.0 OBJECTIVES AND ENDPOINTS

Table 4 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• The primary objective of the study is to establish pairwise pharmacokinetic (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	• Area under the concentration-time curve (AUC) of the analyte in plasma over the time interval from time 0 (baseline) extrapolated to infinity ($AUC_{0\text{-}inf}$)
Secondary	
• 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	• AUC from time 0 to the last quantifiable data point ($AUC_{0\text{-}last}$), maximum observed plasma concentration (C_{max}), time to maximum observed concentration (t_{max}), terminal half-life ($t_{1/2}$), terminal rate constant (λ_z), systemic clearance (CL), and volume of distribution at steady state (V_{ss}) • Pharmacokinetic equivalence of the EU and the US-Avastin will be evaluated • Immunogenicity will be assessed by the incidence of anti-bevacizumab antibodies (ADA), including neutralizing antibodies (NAb) (if ADA positive) from Day 1 through last subject last visit • Safety and tolerability will be assessed by clinical laboratory tests, vital signs, 12-lead electrocardiograms (ECGs), physical examinations, assessment of adverse events (AE), injection site reactions and concomitant medications

4.0 STUDY DESIGN

4.1 Overall Design

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.

Initially, subjects will be administered the study treatment 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.

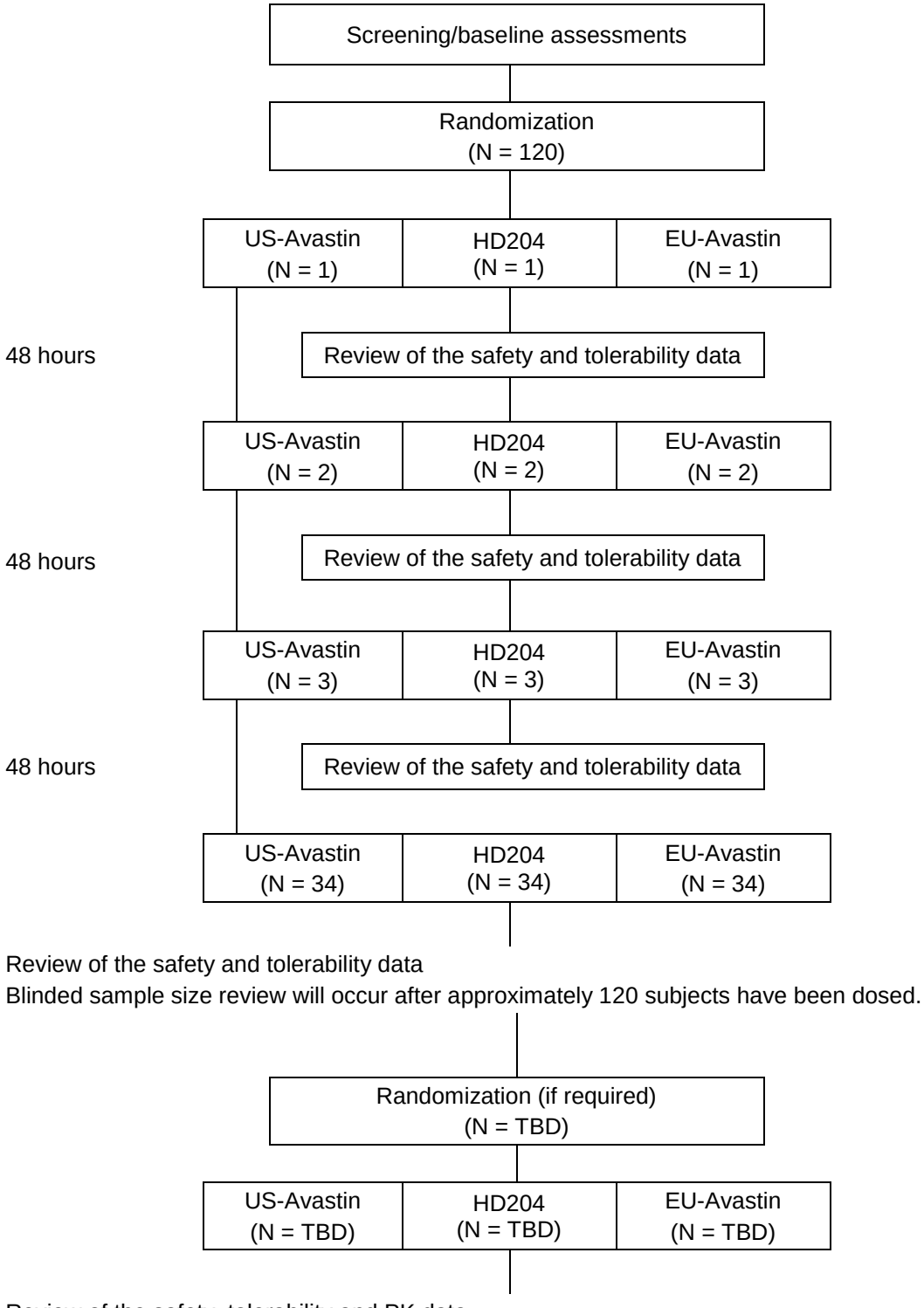
There will be at least 48 hours between administrations of study treatment to each staggered group. Prior to administration of study treatment to the next group, the blinded safety and tolerability findings of the preceding group will be reviewed by the Principal Investigator. The Principal Investigator will consult with the Investigator(s) when subjects have been enrolled over all sites. The next group will be administered study treatment 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 treatment for safety evaluation.

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.

The Study Schema is presented in Figure 1 and a summary of the study design is presented in Figure 2.

The Schedule of Assessments (SoA) for the whole study is described in Table 1, and those for Day 1 in Table 2. The Schedule of Pharmacokinetic Assessments can be found in Table 3.

Figure 2 Study Design



TBD = To be determined

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 (ie, 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, and Day 71

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 Table 1.

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 treatment (Visit 2) and a 71-day follow-up period (Visits 3 to 12).

Subjects who are confirmed positive for anti-bevacizumab antibodies, including subjects who discontinue from the study following drug administration, will be followed up for up to 12 months. These subjects will attend the study center at 6, 9, and 12 months post-dose for blood sampling to confirm their immunoglobulin status or until 2 consecutive samples have been ‘confirmed negative’ for anti-bevacizumab antibodies, whichever occurs earlier.

A summary of study visits is presented in the study flow diagram in Figure 1. The start of the study is considered the date of the first subject providing informed consent and the end of the study will be the last subject’s last scheduled visit. Additional follow-up visits for subjects who are positive for anti-bevacizumab antibodies or have ongoing/resolving AEs will be conducted and reported separately.

Enrollment of Additional Subjects Following a Blinded 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.

If additional subjects are enrolled the Principal Investigator will decide on the timing and group size for enrollment according to the capability of the study center. The subjects will be 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 and will follow the study timeline and assessments described above.

4.2 Scientific Rationale for Study Design

A parallel group design is the preferred design for this study due to the long half-life (approximately 20 days) of bevacizumab and the potential development of immunogenicity.

The study design is expected to provide sufficient PK, immunogenicity and safety data to meet the study objectives. A healthy subject population was chosen as the recommended approach by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), to allow characterization of PK in the most homogenous population with the lowest variability.

The safety of the subjects will be ensured by means of regular medical supervision and assessment throughout their residential stay at the study center, and periodic health assessments thereafter throughout the study.

Additionally, as a safety measure, subjects will be administered the study treatment in separate staggered groups starting with a sentinel group of 3 subjects (1 subject per treatment). The second group will comprise 6 subjects and the third group 9 subjects. After the first 3 groups have been evaluated, the SRC will decide whether to proceed with continuous enrollment according to the study center's capability.

4.3 Justification for Dose

The PK of bevacizumab is independent of dose between 1 and 10 mg/kg, so the lowest possible dose is chosen for administration to healthy subjects in this study.

4.4 End of Study Definition

A subject is considered to have completed the study if he/she has completed all phases of the study including the last visit.

The end of the study is defined as the date of the last visit of the last subject in the study.

4.5 Dose Escalation Criteria

Not applicable.

4.6 Study Stopping Criteria

4.6.1 Stopping Criteria for Individual Subjects

The infusion will be stopped at any time if the subject experiences a severe infusion reaction (Table 6) or a serious adverse event (SAE) during the infusion period. The subject will be followed up until resolution of the SAE and then withdrawn from the study.

4.6.2 Criteria for Stopping the Study

The study may be stopped if any of the following occur:

- ≥ 1 subject experiences SAEs considered to have a reasonable possibility of relationship to the study treatment.
- ≥ 1 subject experiences a drop in absolute neutrophil count to below 1.0×10^9/L on repeat measurement and for which there is no other likely cause.

- ≥ 1 subject experiences a drop in platelet count to below 100×10^9/L.
- ≥ 2 subjects experience non-tolerable AEs that are considered to have a reasonable possibility of relationship to the study treatment.
- ≥ 2 subjects who receive study treatment have a QTc prolongation defined as QTcF > 500 ms, or an increase of QTcF > 60 ms above baseline on the 12-lead ECG, confirmed (persistent for > 5 minutes) on repeated 12-lead ECGs.
- ≥ 1 subject who receives study treatment fulfils Hy's law, defined as an increase in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 × the upper limit of normal (ULN) and total bilirubin ≥ 2 × ULN, where no other reason can be found to explain the combination of increases.
- ≥ 2 subjects have > 3 × ULN of either ALT, AST, bilirubin, or alkaline phosphatase (ALP)
- The occurrence of significant safety events (as judged by the Investigator) other than those described above that in the opinion of the Principal Investigator requires evaluation before any further subjects are dosed.

5.0 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

1. Adult healthy male subjects aged 18 to 50 years (inclusive) and body mass index 18.0 to 30.0 kg/m^2 (inclusive) and body weight ≥ 60 kg to ≤ 100 kg.
2. Subjects who are healthy as determined by pre-study medical history, physical examination, vital signs, and 12-lead ECG at screening and admission on Day -1.
3. Subjects whose clinical laboratory test results are normal, or where outside the reference range is judged as not clinically relevant by the Investigator.
4. Have systolic blood pressure ≥ 90 and ≤ 140 mmHg, diastolic blood pressure ≥ 50 and ≤ 90 mmHg and heart rate ≥ 40 and ≤ 90 bpm at screening and admission on Day -1. For single measurements in the 141 to 160 mmHg range (systolic) or in the 91 to 100 mmHg range (diastolic), a single repetition on the same day is allowed and, in this case, the mean of both measurements will guide eligibility. The mean of both the measurements should be ≤ 140 mmHg (systolic) and ≤ 90 mmHg (diastolic).
5. Have physical examination results without clinically relevant findings at screening and admission on Day -1.
6. Have 12-lead ECG results without clinically relevant findings at screening and admission on Day -1.
7. Subjects who are non-smokers and have not regularly used tobacco or nicotine containing products for at least 3 months prior to screening and have a < 10 pack year smoking history.
8. Males must be willing to use a medically acceptable method of contraception from the time of the administration of study treatment, throughout the study and for a period of 6 months after the administration of the study treatment (see Appendix 5). This requirement may be waived if the Principal Investigator or delegate is satisfied that the subject or subject's female partner is sterile ie, if female has undergone a hysterectomy or tubal ligation at least 3 months prior to screening or is postmenopausal (defined as no menses for 12 months without an alternative medical cause) or if the subject has undergone a vasectomy at least 6 months prior to screening.
9. Must agree not to donate sperm for at least 6 months after the administration of study treatment.
10. Must be willing and able to comply with scheduled visits, laboratory tests, and other study procedures.

11. Must be able to provide informed consent which must be obtained prior to any study-related procedures.
12. Subjects who are willing to comply with the study restrictions, and comply with the scheduled visits from screening and throughout the study.

5.2 Exclusion Criteria

1. Have a history of hypersensitivity or allergic reactions (either spontaneous or following drug administration) to bevacizumab or VEGF targeted treatment or to any other excipients.
2. Have a history of or presence of current clinically significant gastrointestinal (including diverticulitis, stomach ulcers, inflammatory intestinal disease, gastrointestinal perforations/fistulae/intra-abdominal abscess), any other internal, non-gastrointestinal fistulae that is at an increased risk of bleeding, renal, hepatic, cardiovascular, hematological (including pancytopenia, aplastic anemia or blood dyscrasia), pulmonary, neurologic, metabolic (including known diabetes mellitus), psychiatric or allergic disease excluding mild asymptomatic seasonal allergies.
3. Have a history of and/or current cardiac disease defined as one of the following:
    - History of congestive heart failure;
    - Angina pectoris requiring antianginal medication;
    - Evidence of transmural infarction on ECG;
    - History of sustained hypertension (systolic > 180 mmHg and/or diastolic > 100 mmHg) or hypertensive crisis or hypertensive encephalopathy;
    - Clinically significant valvular heart disease; or
    - Severe arterial thromboembolic events.
4. Have a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus, or human immunodeficiency virus (HIV) I and II at screening.
5. Have any history of malignancy including lymphoma, leukemia, and skin cancer (even resected basal cell carcinoma or squamous cell carcinoma).
6. Have an illness within 30 days prior to screening, or prior to Day -1, that is considered as clinically significant by the Investigator.
7. Prior exposure to any investigational monoclonal antibody within 12 months of Day -1. Prior investigational exposure to Avastin > 12 month is acceptable.
8. Any clinically significant infection, in the opinion of the Investigator, ongoing at screening or admission on Day -1.

9. Have had major surgery within 3 months prior to screening, or will have an operation between screening and the end of study visit, or still has an unhealed wound, including wound dehiscence and wound healing complications requiring medical intervention. Major Surgery would include any surgery which is invasive, and allows access to body cavities beyond the skin, superficial tissues or mucous membranes, requires beyond local anesthesia, or requires in house hospitalization.
10. Have received live vaccine(s) within 3 months prior to screening or will require a live vaccine(s) between screening and the end of study visit.
11. Have an intake of alcoholic beverages of more than 14 units per week (1 unit = 250 mL of beer, 25 mL of spirits or 1 glass [125 mL] of wine).
12. Have reasonable evidence (in the opinion of the Investigator) of drug abuse as indicated by a positive urinary drug test at screening or admission on Day -1.
13. Have taken medication with a half-life of > 24 hours within 30 days or less than 10 half-lives of the medication prior to Day -1 as determined by the Investigator.
14. Have donated blood and blood products within 3 months prior to Day -1. Blood donation and blood products are not permitted throughout study.
15. Have participated in another clinical study of an investigational drug within 90 days or 5 half-lives of the investigational drug (whichever is longer) prior to Day -1, or are currently participating in another clinical study of an investigational drug, or intending to participate in another clinical study of an investigational drug before completion of all scheduled evaluations in this clinical study.
16. Subjects who, in the opinion of the Investigator, are not likely to complete the study for whatever reason.
17. The Investigator or any sub-investigator, research assistant, pharmacist, study coordinator, other staff directly involved in the conduct of the clinical study or any of their immediate family members (parents, siblings or spouses).
18. Abnormal or irregular bowel movements eg, less than 1 bowel movement every 3 days.
19. Any history of non-traumatic hemorrhage (ie, any hemorrhage requiring medical intervention) or any condition which may increase bleeding risk including clotting disorders, thrombocytopenia (platelet count < 150, 000 per µL) or an international normalized ratio higher than 1.5 at screening.

20. Impaired liver function as determined by:
    - Serum ALT and/or AST > 1.5 × ULN at screening or admission. Subjects with values between ULN and 1.5 × ULN may be included in the study if considered not clinically significant by the Investigator.
21. Any intake of a non-steroidal anti-inflammatory drug (NSAID) including any dose of aspirin in the 30 days before Day -1 (NSAIDs are not allowed for the duration of the study).
22. Intake of herbal drugs or dietary supplements excluding routine vitamins but including megadose (intake of 20 to 600 times the recommended daily dose) vitamin therapy within 30 days prior to Day -1, unless agreed as not clinically relevant by the Investigator and Sponsor.
23. Strenuous exercise or activity within 96 hours prior to admission on Day -1 and has a creatinine kinase value > 2.5 × ULN.
24. Subjects with unsuitable veins for infusion or venipuncture.
25. Subjects with a non-healing wound or hematoma of a clinically relevant size as assessed by the Investigator, or a clinically significant current fracture.
26. Presence of proteinuria (other than trace amounts ie, +, ++/+++) at screening or admission on Day -1.
27. Known personal or family history of venous thromboembolic events or idiopathic venous thromboembolic events in first degree relatives.
28. Inability to refrain from contact or collision sport until Day 30.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

1. Study treatment administration will occur on Day 1 after a fast of at least 8 hours. Water will be permitted as required. The study treatment will be administered intravenously to the subjects in bed in the semi-supine position. Subjects will remain fasting until 1 hour following completion of the study treatment infusion after which a meal will be served on completion of the scheduled assessments.
2. Subjects will receive a standard diet while resident in the study center and will only consume food and beverages provided by the study center.
3. Subjects will refrain from consumption of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, and Seville orange juice or other products containing grapefruit or Seville oranges from 30 days prior to admission on Day -1 and for the duration of the residential period.

4. Subjects should refrain from consumption of any foods containing poppy seeds within 48 hours prior to screening and admission to the study center on Day -1.

5.3.2 Caffeine, Alcohol, and Tobacco

1. Subjects should refrain from smoking for the duration of the study (through Day 71).
2. Subjects should refrain from alcoholic beverages from 48 hours prior to Day 1 until discharge on Day 3 and for 24 hours prior to each outpatient visit; at other times alcohol intake should be limited to ≤ 2 units per day (1 unit = 250 mL of beer, 25 mL of spirits or 1 glass [125 mL] of wine).
3. Subjects should refrain from taking drugs of abuse during the study (up to the final follow-up visit).

5.3.3 Activity

1. Subjects should refrain from strenuous exercise or activity from admission on Day -1 until Day 10 of the study. Subjects should not participate in contact/collision sports until Day 30.
2. Subjects should adhere to study requirements for contraceptives.
3. Subjects should adhere to the concomitant medication restrictions.
4. Subjects should refrain from blood or blood product donation for the duration of the study (through Day 71).

5.3.4 Avoidance of Pregnancy

1. Female subjects will not be enrolled on this clinical study.
2. The use of contraception will not be required if the female partner of the subject has undergone a hysterectomy or tubal ligation at least 3 months prior to screening or is postmenopausal (defined as no menses for 12 months without an alternative medical cause).
3. As a precaution, all male subjects should avoid fathering a child by either true abstinence or, in conjunction with their partner (if the partner is of childbearing potential), the use of 2 acceptable means of contraception from the time of the administration of the study treatment, throughout the study and for a period of 6 months after the administration of the study treatment (see details in Appendix 5).

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomly assigned to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

5.4.1 Repetition of Screening Assessment(s)

Repetition of a screening assessment would be allowed if there is evidence of a laboratory error or if there is reason to believe that the result is not an accurate reflection of the subject's clinical status. One repeat test will be permitted to re-assess a subject's eligibility. The Investigator is encouraged to discuss or seek advice with the Medical Monitor if needed.

5.4.2 Rescreening of Subject(s)

Subjects may only be rescreened with the approval of the Medical Monitor in case a permanent change has occurred in eligibility criteria (medical status or laboratory findings) that previously led to screen failure. If a subject is rescreened, all screening assessments will be repeated.

6.0 STUDY TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a subject according to the study protocol.

6.1 Study Treatment(s) Administered

Table 5 Study Treatment Details

Study Treatment Name	HD204 (bevacizumab)	EU-Avastin (bevacizumab)	US-Avastin (bevacizumab)
Dosage Formulation	Sterile solution	Sterile solution	Sterile solution
Unit Dose Strength(s)/Dosage Level(s)	100 mg/4 mL, a single dose of 1 mg/kg will be administered	100 mg/4 mL, a single dose of 1 mg/kg will be administered	100 mg/4 mL, a single dose of 1 mg/kg will be administered
Route of Administration	IV infusion	IV infusion	IV infusion
Dosing Instructions	Individual subject treatments will be dispensed by the unblinded pharmacist in IV infusion bags, diluted with 0.9% sodium chloride. Subjects will receive a single administration 90-minute IV infusion. All dose administrations will be performed in the study center under the supervision of appropriately trained staff.	Individual subject treatments will be dispensed by the unblinded pharmacist in IV infusion bags, diluted with 0.9% sodium chloride. Subjects will receive a single administration 90-minute IV infusion. All dose administrations will be performed in the study center under the supervision of appropriately trained staff.	Individual subject treatments will be dispensed by the unblinded pharmacist in IV infusion bags, diluted with 0.9% sodium chloride. Subjects will receive a single administration 90-minute IV infusion. All dose administrations will be performed in the study center under the supervision of appropriately trained staff.
Packaging and Labeling	Study treatment will be provided in glass vials. Each vial will be labeled as required per country requirement.	Study treatment will be provided in glass vials. Each vial will be labeled as required per country requirement.	Study treatment will be provided in glass vials. Each vial will be labeled as required per country requirement.
Manufacturer	Prestige Biopharma Pte. Ltd	Roche	Genetech
First-in-Human	For the purpose of the first human dose study, drug product will be prepared at the study center, diluted to the required volume using 0.9% sodium chloride solution.	For the purpose of the first human dose study, drug product will be prepared at the study center, diluted to the required volume using 0.9% sodium chloride solution.	For the purpose of the first human dose study, drug product will be prepared at the study center, diluted to the required volume using 0.9% sodium chloride solution.

EU: European Union; IV: intravenously; US: Unites States

6.2 Preparation/Handling/Storage/Accountability

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only subjects enrolled in the study may receive study treatment and only authorized study center staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study center staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual.

The Investigator, a member of the study center staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study medication using the Drug Accountability Form. These forms must be available for inspection at any time.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Method of Assigning Subjects to Treatment Groups

At screening, potential study subjects will be assigned a screening number. Following confirmation of eligibility, prior to study treatment administration, subjects will be assigned a subject number in the order in which they are enrolled in the study.

6.3.2 Randomization Procedures

The randomization list will be generated using a validated system by an unblinded statistician who will not be involved in the analysis of the study data before unblinding. The unblinded statistician will provide the independent pharmacist of the study center with the subject randomization.

Subjects will be randomly assigned to one of the study treatments in a 1:1:1 ratio. The subject number will determine the allocation of treatment, per the randomization schedule with the subject numbers starting with X001, where ‘X’ would be the study center number.

6.3.3 Maintenance of Randomization Codes

Randomization codes will be provided to the independent pharmacist, and an unblinded Medical Monitor as a list. Individual treatment disclosure envelopes (code break) will be kept by the independent pharmacist at the study center and the Investigator will be able to access these during the study if required for safety reasons. The independent pharmacist will use the randomization

code list for preparing subject doses throughout the study. The individual disclosure envelopes will be used if it is necessary to break the blind for an individual subject.

The unblinded/independent study center pharmacist (or an appropriately qualified designee) will be responsible for preparation of the blinded study treatment infusion bags for each subject according to the instructions in the Pharmacy Manual.

6.3.4 Unblinding

Unblinding can only take place for the purpose of managing an SAE if deemed necessary by the Investigator. If the code for a subject is broken, the Investigator must withdraw the subject from the study, document the details of the event and the reason for unblinding in the subject's case report form (CRF) and promptly inform the Sponsor's study physician/Medical Monitor and the Ethics Committee. Additionally, the Sponsor and/or designee may be required to unblind the subject if the AE meets criteria of a suspected unexpected serious adverse reaction (SUSAR) in order to fulfil expedited regulatory reporting requirements.

After completion of the study, all code break envelopes will be returned to the Sponsor or a delegate.

6.4 Study Treatment Compliance

The prescribed dose, timing, and mode of administration may not be changed. Any departures from the intended regimen must be recorded in the CRF.

All dose administrations will be performed in the study center under the supervision of appropriately trained staff.

6.4.1 Treatment Measures to Ensure Subject Safety

The clinical staff is responsible for the ongoing safety and wellbeing of the subjects in this First-in-Human study while they are in the study center. There is a paging system to alert the clinical staff to any area in the center where a subject may need medical attention. In the case of an emergency, cardiac resuscitation trolleys are found in the main ward areas of the study center. These trolleys contain drugs, equipment for airway insertion, circulation lines, defibrillation etc, together with oxygen cylinders and portable suction machines. There is a physician on site 24 hours a day. In addition, if necessary the clinical staff can contact further on-call physicians or public emergencies services in the event of a serious medical event. Equipment and emergency drugs are available to treat common medical emergencies that might occur in a Phase 1 study.

6.4.2 Warnings and Precautions

As this is the first administration of HD204 to man, all effects cannot be reliably predicted. The preclinical data suggest an acceptable safety margin. Facilities and staff for resuscitation and the treatment of other medical emergencies will be provided.

6.5 Concomitant Therapy

Subjects are not allowed to take the following medications except for management of AEs as advised by the Principal Investigator:

- Any prescription or over-the-counter medication with a half-life of > 24 hours within 30 days or less than 10 half-lives of the medication prior to Day 1 and for the duration of the study (except paracetamol as detailed below)
- Any herbal remedies or dietary supplements within 30 days prior to Day 1 and for the duration of the study, unless agreed as not clinically relevant by the Investigator and Sponsor
- Any NSAIDs (including aspirin) within 30 days prior to Day 1 and for the duration of the study
- Any live virus vaccination within 30 days before screening and during study participation until the final follow-up visit

In the interests of subject safety and acceptable standards of medical care the Investigator will be permitted to prescribe treatment(s) at his/her discretion. All treatments must be recorded in the subjects' CRF (medication, dose, treatment duration and indication).

Paracetamol, up to 2 g per day, will be allowed.

6.6 Dose Modification

Dose modifications are not planned or allowed in this study.

6.7 Treatment After the End of the Study

The Sponsor will not provide any additional care to subjects after they leave the study.

7.0 DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

The infusion will be stopped at any time if the subject experiences a severe infusion reaction (Table 6) or a SAE during the infusion period. The subject will be followed up until resolution of the SAE and then withdrawn from the study.

If a subject who does not meet enrollment criteria is inadvertently enrolled, that subject must be discontinued from study treatment and the Sponsor or Sponsor designee must be contacted. An exception may be granted in rare circumstances for which there is a compelling safety reason to allow the subject to continue. In these rare cases, the Investigator must obtain documented approval from the Sponsor or Sponsor designee to allow the subject to continue in the study.

Subjects who discontinue study treatment will not be replaced.

7.2 Subject Discontinuation/Withdrawal from the Study

- A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the study center study records.
- See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. Should a subject request or decide to withdraw from the study, all efforts must be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. Subjects withdrawing due to an AE should be followed up according to the follow-up visit.
- Subjects who voluntarily withdraw are termed dropouts. Dropouts and subjects withdrawn due to protocol violations may be replaced following discussion with the Principal Investigator and Sponsor.
- Subjects withdrawn due to an AE will not be replaced.

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study center.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The study center must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

8.0 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (see Section 1.3).

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor and SRC upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

The number of samples collected and the volume required for each analysis may be changed during the study (eg, if additional samples are collected for repeat or additional safety assessments at the request of the Investigator).

The total volume of blood to be collected per subject during the study will not exceed 400 mL.

8.1 Efficacy Assessments

Not applicable.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (see Section 1.3).

8.2.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Any clinically significant changes from admission will be recorded as treatment-emergent AEs (TEAEs).

8.2.2 Local Infusion Site Reactions

Infusion site evaluations will be made by clinical staff during the administration of the infusion and during Day 1 as described below; if an infusion site reaction is observed, a physician will characterize and document the reaction as an AE. Review of the infusion site will continue until the AE is resolved.

If infusion site reactions are observed after Day 1 the same grading system may be used and the site reaction recorded as an AE and review of the infusion site will continue until the AE is resolved.

The infusion sites will be monitored for pain, tenderness, erythema and swelling. Each infusion site reaction will be categorized using the intensity grading scheme presented in Table 6; the intensity of each resulting AE will be categorized (eg, a moderate intensity infusion site reaction may be recorded as a mild AE if considered appropriate according to the Investigator's judgement).

Table 6 Infusion Site Reaction Grading Scheme

	Intensity Grading				
Reaction	**Absent (0)**	**Mild [a] (1)**	**Moderate [a] (2)**	**Severe [a] (3)**	**Potentially Life-threatening (4)**
Pain	Absent	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Hospital visit (A and E) or hospitalization
Tenderness	Absent	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Hospital visit (A and E) or hospitalization
Erythema/ redness	Absent	2.5 to 5.0 cm	5.1 to 10.0 cm	> 10.0 cm	Necrosis or exfoliative dermatitis
Induration/ swelling	Absent	2.5 to 5.0 cm and does not interfere with activity	5.1 to 10.0 cm or interferes with activity	> 10.0 cm or prevents daily activity	Necrosis
Other [b]	Absent	Present			

A and E = accident and emergency department; AE = adverse event.

[a] Measurements refer to the reaction at the greatest single diameter.

[b] Any other reactions such as bruising, itching or ulceration will be recorded as absent or present and will be recorded as AEs; AEs will be categorized according to the Investigator's judgement.

Reference:

http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm074775.htm

8.2.3 Immunogenicity

Blood samples for analysis of the incidence and titer of antibodies to bevacizumab and the incidence of any NAbs in serum will be collected as indicated in the SoA (see Section 1.3).

Subjects who are confirmed positive for anti-bevacizumab antibodies at the follow-up visit (Day 71) or at an early termination visit (subjects who discontinue from the study following drug

administration), will be followed up for up to 12 months or until 2 consecutive samples have been confirmed negative for anti-bevacizumab antibodies, whichever occurs earlier. These subjects will attend the study center at 6, 9, and 12 months after study completion post-dose for blood sampling to confirm their immunoglobulin status.

Blood sample processing and handling details will be presented in a separate Laboratory Manual.

8.2.4 Vital Signs

Aural temperature, pulse rate, blood pressure, and respiratory rate will be assessed.

Blood pressure and pulse measurements will be assessed in the semi-supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (eg, television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 1 blood pressure measurements (one repeat measurement may be taken if out of range).

8.2.5 Electrocardiograms

A single 12-lead ECG will be obtained at time points indicated in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

ECG assessments will be obtained after the subject has been in the semi-supineposition for at least 5 minutes.

The ECGs will be reviewed by the Investigator, or a designee, to assess for any abnormalities. Refer to Section 4.6.2 for QTcF-related stopping criteria and any additional QTcF readings that may be necessary.

8.2.6 Clinical Safety Laboratory Assessments

See Appendix 3 for the list of clinical laboratory tests to be performed and to the SoA (see Section 1.3) for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the subject's health status, unless judged by the Investigator to be more severe than expected for the subject's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 3, must be conducted in accordance with the Laboratory Manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.3 Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the subject to discontinue the study (see Section 7.0).

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 1.3).

All AEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

8.3.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences. All study assessments results (eg, laboratory tests, vital signs, ECGs, etc) will be reviewed by the Investigator for determination of AE occurrence.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 4.

8.3.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of all pregnancies in female partners of male subjects will be collected after the start of study treatment and until 6 months after the last dose.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Adverse Events of Special Interest

Not applicable.

8.4 Treatment of Overdose

For this study, any dose of study treatment greater than 1 mg/kg within a 24-hour time period will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the subject for any AE/SAE and laboratory abnormalities until study treatment can no longer be detected systemically.
3. Obtain a plasma sample for PK analysis within 1 day from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

8.5 Pharmacokinetics

8.5.1 Collection of Samples

Venous blood samples of approximately 2.5 mL will be collected for measurement of serum concentrations of bevacizumab at times as specified in the SoA. Instructions for the collection and handling of biological samples will be provided by the Sponsor. Blood samples will be taken either by direct venipuncture or an indwelling cannula inserted in a forearm vein. Blood samples for PK will not be collected from the arm used for the IV infusion for at least 24 hours after administration. The actual date and time (24-hour clock time) of each sample will be recorded in the CRF. The time and date of study treatment administration including infusion start and stop times and any infusion interruptions will also be recorded in the CRF. Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

Pre-dose samples may be collected within 1 hour of dose administration. The post-dose sample windows are specified in the SoA (see Section 1.3).

8.5.2 Determination of Drug Concentration

Samples for the determination of bevacizumab in serum will be analyzed on behalf of CPR Pharma using appropriate validated bioanalytical methods. Full details of the bioanalytical methods will be described in a separate Bioanalytical Report.

All samples still within the known stability of the analyte of interest at the time of receipt by the bioanalytical laboratory will be analyzed.

Remaining serum samples may be subjected to further analysis by the Sponsor or designee for the purpose of the development of additional bioanalytical assays and/or to investigate the presence of analytes of interest. Samples collected for analyses of bevacizumab serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained. At visits during which serum samples for the determination of biosimilarity of HD204 will be taken, 1 sample of sufficient volume can be used.

8.5.3 Derivation of Pharmacokinetic Parameters

Pharmacokinetic parameters will be derived using noncompartmental methods with Phoenix® WinNonlin® Version 6.4 or higher (Certara, L.P. Princeton, New Jersey, US) and/or SAS® Version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina, US). Actual elapsed time from dosing will be used for the final serum PK parameter calculations. In cases where the actual sampling time is missing, calculations will be performed using the scheduled time. Otherwise, there will be no further imputation of missing data. Interim PK analyses will be performed by using scheduled time post-dose for all calculations.

Serum Pharmacokinetic Parameters

The PK parameters in Table 7 will be determined for bevacizumab when possible. A minimum of 3 quantifiable post-dose concentrations will be required for all calculations.

Table 7 Serum Pharmacokinetic Parameters

Primary Pharmacokinetic Parameter	**Definition**
$AUC_{0\text{-inf}}$	Area under the concentration-time curve from time 0 extrapolated to infinity
Secondary Pharmacokinetic Parameters	**Definition**
$AUC_{0\text{-last}}$	Area under the concentration-time curve from time 0 to the last quantifiable data point
C_{max}	Maximum observed concentration
t_{max}	Time to maximum observed concentration
$t_{½}$	Terminal half-life
λ_z	Terminal rate constant
V_{ss}	Volume of distribution at steady state
CL	Systemic clearance

The calculation of AUCs will be performed using the mixed log-linear trapezoidal method (linear up/log down). The pre-dose samples will be considered as if they had been taken immediately before the administration. Concentrations below the lower limit of quantification (BLQ) will be taken as zero for calculating the AUC of single dose profiles. The PK parameters will be evaluated and listed for all subjects who provide sufficient concentration-time data.

Other parameters may be added as appropriate. Final PK parameters reported will be detailed in the Statistical Analysis Plan (SAP).

8.6 Pharmacodynamics

Pharmacodynamics are not evaluated in this study.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary statistical null hypothesis is that $AUC_{0\text{-inf}}$ is not equivalent between HD204 and the reference products within 80% to 125% limits, against the alternative that HD204 is equivalent to the reference products.

9.2 Sample Size Determination

Based on historical data, an inter-subject variability of 25% and a proportion of 20% of non-PK evaluable subjects have been assumed for sample size determination. Assuming an inter-subject geometric coefficient of variation (CV) of 25% and a geometric mean ratio of 1.05, 40 evaluable subjects per arm are required for the 2-sided 90% confidence interval (CI) of the geometric mean ratio being completely contained within 80% to 125% with 80% overall power and at least 90% power for each pairwise comparison (HD204 versus EU-Avastin, HD204 versus US-Avastin, and EU-Avastin versus US-Avastin). To allow for a proportion of 20% non-PK evaluable subjects, 150 subjects (50 subjects per arm) are planned to be enrolled.

9.3 Populations for Analyses

For purposes of analysis, the analysis sets are defined in Table 8.

Table 8 Analysis Sets

Analysis Set	Description
Pharmacokinetic Concentration (PKC) Population	The PKC population includes subjects with at least 1 valid post-dose concentration and includes all subjects who have received 1 dose of study treatment and completed the study assessments without major protocol violations which may significantly affect the pharmacokinetic (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 will be summarized based on the PKC population. Serum bevacizumab concentrations will be listed and summarized using descriptive statistics in tables and graphs, as appropriate.
Pharmacokinetic Parameter (PKP) Population	The PKP population is a subpopulation of the PKC population, which includes all subjects in 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 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.
PK Non-Neutralizing (PKNN) Population	The PKNN population will include those members of the PKP population without sustained neutralizing antidrug antibodies (ADAs). Sustained neutralizing antibodies occur when a patient has 2 consecutive visits with neutralizing antibodies. Pharmacokinetic analyses will be repeated on the PKNN population to assess robustness of results.

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

9.4 Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the subject analysis sets to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1 Primary Endpoint

The primary PK parameter for assessment of PK equivalence is $AUC_{0\text{-inf}}$.

9.4.2 Secondary Endpoints

The secondary PK parameters are: $AUC_{0\text{-last}}$, C_{max}, t_{max}, $t_{½}$, λ_z, V_{ss} and CL. In addition, the PK similarity of the EU and the US-Avastin will be evaluated to provide the bridging data justifying the use of a single reference product in further comparative clinical studies in patient populations.

Immunogenicity will be assessed by the incidence of anti-bevacizumab antibodies, including NAbs from Day 1 through last subject last visit. NAbs will only be assessed in those subjects in whom positive ADA antibodies are detected.

The safety and tolerability will be assessed by clinical laboratory tests, vital signs, 12-lead ECGs, physical examinations, assessment of AEs, injection site reactions, and concomitant medications.

9.4.3 Pharmacokinetic/Pharmacodynamic Analyses

9.4.3.1 Serum Bevacizumab Concentration Data

All analyses of PK endpoints will be performed using the PKP population. A subject listing of all concentration-time data for each treatment will be presented.

Concentration data of bevacizumab will be summarized by treatment and nominal time point using appropriate descriptive statistics.

9.4.3.2 Analysis of Primary Pharmacokinetic Endpoint

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. Covariates may be included in the models, to be specified in the SAP.

9.4.3.3 Analysis of Secondary Pharmacokinetic Endpoints

The $AUC_{0\text{-last}}$ as a secondary parameter may also be tested for PK similarity as described above.

All PK parameters will be summarized by treatment using N, n, mean, standard deviation (SD), %CV, minimum, median, maximum, geometric mean, and geometric %CV defined as

$$100 \cdot \sqrt{\left(\exp\left(s^2\right)-1\right)}$$

where s is the SD of the data on a log scale, except that t_{max} will be reported with n, minimum, median, and maximum only.

Graphs may be added at the discretion of the PK scientist, as appropriate, and will be described in detail in the SAP.

9.4.4 Safety Analyses

All safety analyses will be based on the SA population. No statistical tests will be performed for the safety data.

Safety data including laboratory assessments, vital signs, and ECG parameters will be summarized by treatment and/or time point using descriptive statistics for observed values and change from baseline values (as appropriate).

Adverse events will be tabulated and summarized according to the current version of MedDRA.

For the laboratory data, vital signs and ECGs, out of range values will be flagged in the data listings and a list of clinically significantly abnormal values will be presented as appropriate.

Physical examination will be presented in listing only.

Concomitant medications will be presented in listings.

9.4.5 Immunogenicity

The proportion of subjects with ADA, with NAb and the corresponding titers will be summarized using descriptive statistics for the Safety Analysis Population by visit for each parameter and presented in listings.

9.4.6 Missing Data

Data from subjects who withdraw from the study, including AEs and any follow-up, will be included in the analyses of primary and secondary outcomes. Missing safety data will not be imputed. PK concentrations may be imputed for the derivation of PK parameters, to be defined in the SAP.

9.5 Interim Analyses

After approximately 20 subjects per treatment arm have been observed for a minimum of 20 days, an interim safety report will be generated and approved by the Sponsor. The interim safety report will be generated using data that is source verified by the Clinical Research Assistant, including blinded safety laboratory, AE, and ECG data accumulated to that point (Day 20 of the Study). The review of the interim report will be performed by the SRC. Details regarding the review process will be available in the relevant SRC charter. This evaluation will allow a preliminary assessment of safety findings with a time to onset longer than 24 hours.

The SAP will describe the planned interim analyses in greater detail.

9.5.1 Blinded Sample Size Re-evaluation

Due to the uncertainty in the actual variability and trying to limit the study size to those strictly needed, a BSSR will be performed after approximately 120 evaluable subjects (40 subjects per arm) have completed the study. This number of subjects is expected to provide a sufficiently precise calculation of the variability in the actual study population (8). The BSSR will aim to provide at least 90% power for each of the pairwise comparisons and approximately 80% overall power, as specified in the sample size determination.

The BSSR will estimate the geometric CV in the primary endpoint, ignoring any potential differences due to treatment. If the geometric CV is greater than 25%, the number of randomized subject 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.

At the time of the BSSR, the study recruitment will be stopped until the BSSR results become available.

If additional subjects are enrolled the Principal Investigator will decide on the timing and group size for enrollment according to the capability of the study center.

9.6 Safety Review Committee

After the safety and tolerability data from the first 3 groups are available, a 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.

Further details will be available in the SRC charter.

10.0 REFERENCES

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11.0 APPENDICES

Appendix 1 Abbreviations

Abbreviation	Definition
AE	Adverse event
ADA	Antidrug antibodies
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-inf}}$	Area under the plasma concentration-time curve from time zero extrapolated to infinity, calculated by linear up/log down trapezoidal summation
$AUC_{0\text{-last}}$	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration, calculated by linear up/log down trapezoidal summation
BSSR	Blinded sample size re-evaluation
CI	Confidence interval
CL	Systemic clearance
C_{max}	Maximum observed plasma concentration
CRF	Case report form
CV	Coefficient of variation
ECG	Electrocardiogram
EU	European Union
EU GMP	European Union Good Manufacturing Practice
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous(ly)
λ_z	Lambda z; terminal rate constant
NAb	Neutralizing antibody
NSAID	Non-steroidal anti-inflammatory drug
PD	Pharmacodynamic(s)

Abbreviation	Definition
PK	Pharmacokinetic(s)
PKC Population	Pharmacokinetic Concentration Population
PKNN Population	Pharmacokinetic Non-Neutralizing Population
PKP Population	Pharmacokinetic Parameter Population
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SoA	Schedule of Assessments
SRC	Safety Review Committee
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Terminal half-life
t_{max}	Time to C_{max}
ULN	Upper limit of normal
US	United States (of America)
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
V_{ss}	Volume of distribution at steady state
WOCBP	Woman of childbearing potential

Appendix 2 Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable ICH GCP Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and regulatory authority approval, when applicable, before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to subjects.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the study center and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative (Appendix 6). The study will not start at any study center at which the Investigator has not signed the protocol.

Adequate Resources

The Investigator is responsible for supervising any individual or party to whom the Investigator delegates study-related duties and functions conducted at the study center.

If the Investigator/institution retains the services of any individual or party to perform study-related duties and functions, the Investigator/institution should ensure this individual or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.

Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the subjects in this study. The terms of the insurance will be kept in the study files.

Insurance

The Sponsor has obtained liability insurance, which covers this study as required by local law and/or national regulations and/or ICH guidelines, whichever is applicable. The terms of the insurance will be kept in the study files.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

Data Protection

- Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.
- The Sponsor or its representative will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician, or any other third party, unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, the Sponsor or representative physician or an Investigator might know a subject's identity and also have access to his or her genetic data. Also, regulatory authorities may require access to the relevant files.

Administrative Structure

The safety committee will include, at a minimum, the Sponsor's responsible physician and the Principal Investigator. The Principal Investigator and the Sponsor, when appropriate, will invite other specialist individuals to participate in the review, eg, PK scientists, statisticians, clinical specialists etc.

Table 9 Study Administrative Structure

Function	Responsible Organization
Principle Investigator and Primary Investigational Site	Dr. Christian Schwabe Auckland Clinical Studies Ltd Ground Floor, MEDACS House, 3 Ferncroft Street, Grafton, Auckland, New Zealand Tel: +64 373 3474 Fax: +64 373 3479
Investigators and Other Investigational Sites	Dr. Chris Wynne Christchurch Clinical Studies Trust, Ltd, 31 Tuam Street, Post Office Box 2856, Christchurch 8011 New Zealand Tel: +64 3372 9477 Fax: +64 3372 9478
Study Operations Management Medical Monitoring	Sponsor/CRO
Study Master File	CRO
Randomization Code	Sponsor/CRO/3rd party

Function	Responsible Organization
Data Management	Sponsor/CRO
Clinical Supply Management	Sponsor/CRO
Quality Assurance Auditing	Sponsor/CRO
Biostatistics Medical Writing	Sponsor/CRO
Laboratory Assessments	Local Laboratory used by Auckland Clinical Studies Ltd: **LabPLUS** Building 31, Auckland City Hospital, Gate 4 off Grafton Road, Auckland, New Zealand Tel: +64 9 307 8995 Fax: +64 9 307 4970 E-mail: Lablink@adhb.govt.nz
Electrocardiogram Collection, Review, and Analysis	Sponsor/CRO/3rd party
Bioanalytical Analysis (Immunogenicity and Pharmacokinetic Analysis)	CPR Pharma Services Pty Ltd 28 Dalgleish St Thebarton SA 5031 AUSTRALIA Tel: Fax: E-mail:
Pharmacokinetic Analysis	IQVIA Overland Park, Kansas, Unites States of America (US) Tel: +913 708 6000
Safety Monitoring Committee (see Section 9.6)	Sponsor/CRO/3rd party
IQVIA Medical Advisor	Charu Gautam
Sponsor Representative	Lisa Soyeon Park
Safety Monitoring Committee (see Section 9.6)	Sponsor/CRO/3rd party

Medical Monitor

Charu Gautam

Charu.Gautam@iqvia.com

Dissemination of Clinical Study Data

The results of the study should be reported within 1 year from the end of the clinical study. Irrespective of the outcome, the Sponsor will submit to the EU database a summary of the results of the clinical study within 1 year from the end of the clinical study. It shall be accompanied by a summary written in a manner that is understandable to laypersons.

Data Quality Assurance

- Monitoring will be carried out as determined by the risk assessment process conducted on the study.
- All subject data relating to the study will be recorded on printed or eCRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized study center personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Source Documents

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study center’s subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail).

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's study center.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Study Center Closure

The Sponsor designee reserves the right to close the study center or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study centers will be closed upon study completion. A study center is considered closed when all required documents and study supplies have been collected and a study center closure visit has been performed.

The Investigator may initiate study center closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study center by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the Investigator.
- Discontinuation of further study treatment development.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual study center data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix 3 Clinical Laboratory Tests

- The tests detailed in Table 10 will be performed by the local laboratory.
- If the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5.0 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 10 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Platelet Count	White Blood Cell Count with Differential:
	Red Blood Cell Count	*Neutrophils
	Hemoglobin	*Lymphocytes
	Hematocrit	*Monocytes
	Red Blood Cell Indices:	*Eosinophils
	Mean corpuscular volume (MCV)	*Basophils
	Mean corpuscular hemoglobin (MCH)	
	Mean cell hemoglobin concentration (MCHC)	
	*Reticulocytes	* Cells to be reported as absolute values.
Clinical Chemistry		Aspartate Aminotransferase (AST)/
	Creatinine	Alanine Aminotransferase (ALT)/
	Glucose (fasting)	Alkaline phosphatase (ALP)
	Gamma- glutamyl transferase (GGT)	Creatine kinase
	Urea	TROP-I or TROP-T will be performed if clinically indicated
	Magnesium	Chloride
	Cholesterol	Amylase
	Potassium	Total bilirubin
	Sodium	Conjugated bilirubin will be performed if clinically indicated
	Calcium	Total protein
	Lactate dehydrogenase	Phosphate
	Albumin	
	Uric acid	Carbon dioxide (bicarbonate)
	C-reactive protein	Triglycerides

Laboratory Assessments	**Parameters**	
Coagulation	International normalized ratio (INR)	Activated partial thromboplastin time (aPTT)
	Prothrombin time (PT)	
		Fibrinogen
Urinalysis	Leucocytes	Red blood cells
	Protein	pH
	Bilirubin	Nitrite
	Urobilinogen	Specific gravity
	Ketones	Glucose
	Microscopy (if clinically indicated)	
Viral serology	HIV I and II	Hepatitis C virus
	HBsAg	
Drugs of abuse and alcohol	Amphetamine/	Opiates
	Cannabinoids	Benzodiazepines
	Cocaine metabolites	Methadone metabolites
	Urine creatinine	Barbiturates
	Cotinine	Ecstasy (3,4-Methylenedioxymethamphetamine)
	Tricyclic anti-depressants (TCA)	Phencyclidine

NOTES:
[a] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to study centers or other blinded personnel until the study has been unblinded.

Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or subject, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgement of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a) Results in death
b) Is life-threatening The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c) Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d) Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e) Is a congenital anomaly/birth defect
f) Other situations: • Medical or scientific judgement should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF. Each event must be recorded separately.
- It is **not** acceptable for the Investigator to send photocopies of the subject's medical records in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. The AE must be characterized as unrelated, unlikely to be related, possibly related, probably related, or unknown (unable to judge).
  - "Probably related" conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
  - "Possibly related" suggests that the association of the AE with the study treatment is unknown; however, the AE is not reasonably supported by other conditions.
  - "Unlikely to be related" suggests that only a remote connection exists between the study treatment and the AE. Other conditions, including chronic illness, progression or expression of the disease state or reaction to concomitant therapy, appear to explain the reported AE.
  - "Unrelated" is used if there is not a reasonable possibility that the study treatment caused the AE.
  - All efforts should be made to classify the AE according to the above categories. The category "unknown" (unable to judge) may be used only if the causality is not assessable, eg, because of insufficient evidence, conflicting evidence, conflicting data, or poor documentation.
- The Investigator will use clinical judgement to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the Investigator will provide a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the study center will use the paper SAE data collection tool (see next section).
- The study center will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given study center, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a study center receives a report of a new SAE from a subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the study center can report this information on a paper SAE form (see next section) or to the Medical Monitor/SAE coordinator] by telephone.

SAE Reporting via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Medical Monitor or the SAE coordinator.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

Appendix 5 Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   a) Documented hysterectomy.
   b) Documented bilateral salpingectomy.
   c) Documented bilateral oophorectomy.
   Note: Documentation can come from the study center personnel's: review of the subject's medical records, medical examination, or medical history interview.
3. Postmenopausal female:
   a) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   b) Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male subjects

- Male subjects with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 5.1:
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent for duration of study and for 6 months after study completion or from last dose.

– Agree to use a male condom and have their partner use of a contraceptive method with a failure rate of <1% per year when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

- In addition, male subjects must refrain from donating sperm for the duration of the study and for 6 months after study completion or the last dose of study treatment.
- Male subjects with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame.

Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral. • Intravaginal. • Transdermal.
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral. • Injectable.
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD). • Intrauterine hormone-releasing system (IUS). Bilateral tubal occlusion.
Vasectomized Partner *A vasectomized partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual Abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for at after the last dose of study treatment.

Collection of Pregnancy Information

Male subjects with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Appendix 6 Signature of Investigator

PROTOCOL TITLE: 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

PROTOCOL NO: SAMSON-1

VERSION: Original Protocol

This protocol is a confidential communication of [Sponsor]. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCPs and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to Sponsor or CRO.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

Protocol Name:	SAMSON-1
Protocol Title:	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
EudraCT no.:	2017-005174-19
Sponsor:	Prestige BioPharma Pte Ltd
Document Type:	Summary of Amendment (1 page)
Effective Date:	22 Jan 2019
Effective Sites:	**All sites** (previously V2.0 dated 23 August 2018)

Affected Page(s)	**Section**	**Changes** (updates highlighted in red)
1	Title/all pages	Update version no to Version 3.0
10, 12-14,16, 24, 31,		Change of last PK timepoint from 95 days to 71 days.

TITLE PAGE

Protocol Title:

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

Protocol Number: SAMSON-1

Amendment Number: Original protocol

Product: HD204

Short Title:

Phase I, Double-blind, Randomized, Parallel Group Study to Demonstrate the Equivalent Pharmacokinetic Properties of a Single Intravenous Dose of HD204 and Avastin in Healthy Male Subjects

Study Phase: Phase I

Local Sponsor Name: IQVIA RDS Pty. Ltd

Legal Registered Address:

Unit A, 2 Rothwell Avenue
Rosedale
Auckland 0632
New Zealand

Sponsor Name: Prestige Biopharma Pte. Ltd

Legal Registered Address:

2 Science Park Drive #04-13/14 Ascent Tower B
Singapore Science Park
Singapore 118222

Regulatory Agency Identifying Number(s):

EudraCT no. 2017-005174-19

Date of Protocol: 23 August 2018, Version 2.0

Sponsor Signatory:

I have read this protocol in its entirety and agree to conduct the study accordingly:



24 Aug 2018

Lisa Soyeon Park
Prestige Biopharma Chief Executive Officer

Date

Medical Monitor name and contact information can be found in Appendix 2.

TABLE OF CONTENTS

TABLE OF TABLES 6

TABLE OF FIGURES 7

1.0 PROTOCOL SUMMARY 8
1.1 Synopsis 8
1.2 Schema 11
1.3 Schedule of Assessments 12

2.0 INTRODUCTION 17
2.1 Study Rationale 17
2.2 Background 17
2.3 Benefit/Risk Assessment 20

3.0 OBJECTIVES AND ENDPOINTS 21

4.0 STUDY DESIGN 22
4.1 Overall Design 22
4.2 Scientific Rationale for Study Design 25
4.3 Justification for Dose 25
4.4 End of Study Definition 25
4.5 Dose Escalation Criteria 25
4.6 Study Stopping Criteria 25
4.6.1 Stopping Criteria for Individual Subjects 25
4.6.2 Criteria for Stopping the Study 26

5.0 STUDY POPULATION 27
5.1 Inclusion Criteria 27
5.2 Exclusion Criteria 28
5.3 Lifestyle Considerations 30
5.3.1 Meals and Dietary Restrictions 30
5.3.2 Caffeine, Alcohol, and Tobacco 31
5.3.3 Activity 31
5.3.4 Avoidance of Pregnancy 31
5.4 Screen Failures 31
5.4.1 Repetition of Screening Assessment(s) 32
5.4.2 Rescreening of Subject(s) 32

6.0 STUDY TREATMENT 33
6.1 Study Treatment(s) Administered 33
6.2 Preparation/Handling/Storage/Accountability 34
6.3 Measures to Minimize Bias: Randomization and Blinding 34

6.3.1 Method of Assigning Subjects to Treatment Groups 34
6.3.2 Randomization Procedures 34
6.3.3 Maintenance of Randomization Codes 34
6.3.4 Unblinding 35
6.4 Study Treatment Compliance 35
6.4.1 Treatment Measures to Ensure Subject Safety 35
6.4.2 Warnings and Precautions 35
6.5 Concomitant Therapy 36
6.6 Dose Modification 36
6.7 Treatment After the End of the Study 36

7.0 DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL 37
7.1 Discontinuation of Study Treatment 37
7.2 Subject Discontinuation/Withdrawal from the Study 37
7.3 Lost to Follow-up 38

8.0 STUDY ASSESSMENTS AND PROCEDURES 39
8.1 Efficacy Assessments 39
8.2 Safety Assessments 39
8.2.1 Physical Examinations 39
8.2.2 Local Infusion Site Reactions 39
8.2.3 Immunogenicity 41
8.2.4 Vital Signs 41
8.2.5 Electrocardiograms 41
8.2.6 Clinical Safety Laboratory Assessments 42
8.3 Adverse Events 42
8.3.1 Time Period and Frequency for Collecting AE and SAE Information 42
8.3.2 Method of Detecting AEs and SAEs 43
8.3.3 Follow-up of AEs and SAEs 43
8.3.4 Regulatory Reporting Requirements for SAEs 43
8.3.5 Pregnancy 44
8.3.6 Adverse Events of Special Interest 44
8.4 Treatment of Overdose 44
8.5 Pharmacokinetics 44
8.5.1 Collection of Samples 44
8.5.2 Determination of Drug Concentration 45
8.5.3 Derivation of Pharmacokinetic Parameters 45
8.6 Pharmacodynamics 46
8.7 Genetics 46
8.8 Biomarkers 46

9.0 STATISTICAL CONSIDERATIONS 47
9.1 Statistical Hypotheses 47
9.2 Sample Size Determination 47

9.3 Populations for Analyses **47**
9.4 Statistical Analyses **48**
9.4.1 Primary Endpoint 48
9.4.2 Secondary Endpoints 48
9.4.3 Pharmacokinetic/Pharmacodynamic Analyses 48
9.4.4 Safety Analyses 49
9.4.5 Immunogenicity 49
9.4.6 Missing Data 49
9.5 Interim Analyses **50**
9.5.1 Blinded Sample Size Re-evaluation 50
9.6 Safety Review Committee **50**

10.0 REFERENCES **51**

11.0 APPENDICES **52**
Appendix 1 Abbreviations **53**
Appendix 2 Regulatory, Ethical, and Study Oversight Considerations **55**
Regulatory and Ethical Considerations 55
Adequate Resources 55
Financial Disclosure 56
Insurance 56
Informed Consent Process 56
Data Protection 56
Administrative Structure 57
Medical Monitor 58
Dissemination of Clinical Study Data 59
Data Quality Assurance 59
Source Documents 59
Study and Study Center Closure 60
Publication Policy 60
Appendix 3 Clinical Laboratory Tests **61**
Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting **63**
Appendix 5 Contraceptive Guidance and Collection of Pregnancy Information **68**
Appendix 6 Signature of Investigator **71**

TABLE OF TABLES

Table 1	Schedule of Assessments	12
Table 2	Schedule of Assessments for Day 1	15
Table 3	Schedule of Pharmacokinetic Assessments	16
Table 4	Study Objectives and Endpoints	21
Table 5	Study Treatment Details	33
Table 6	Infusion Site Reaction Grading Scheme	40
Table 7	Serum Pharmacokinetic Parameters	46
Table 8	Analysis Sets	47
Table 9	Study Administrative Structure	57
Table 10	Protocol-required Safety Laboratory Assessments	61

TABLE OF FIGURES

Figure 1 Study Schema.....11
Figure 2 Study Design.....23

1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

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

Short Title:

Phase I, Double-blind, Randomized, Parallel Group Study to Demonstrate the Equivalent Pharmacokinetic Properties of a Single Intravenous Dose of HD204 and Avastin in Healthy Male Subjects

Rationale:

Prestige Biopharma Pte. Ltd is developing HD204, a biosimilar of the European Union (EU)-approved and US-licensed bevacizumab (Avastin®). Bevacizumab is a recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody that binds to vascular endothelial growth factor (VEGF) extracellularly to prevent interaction with VEGF receptors (VEGFRs). Avastin is licensed for clinical use in the US (US-Avastin) and the EU (EU-Avastin) for a variety of tumor types.

The purpose of this study is to compare the pharmacokinetics (PK) of HD204, US-Avastin, and EU-Avastin in healthy male subjects after intravenous (IV) administration of a single dose. As a First-in-Human study, the study will also evaluate the safety, tolerability, and immunogenicity of HD204, US-Avastin, and EU-Avastin in healthy subjects.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• The primary objective of the study is to establish pairwise PK equivalence between HD204 (Prestige Biopharma Pte. Ltd bevacizumab), EU-Avastin, and US-Avastin after a single IV infusion of 1 mg/kg in healthy male subjects	• Area under the concentration-time curve (AUC) of the analyte in plasma over the time interval from time 0 (baseline) extrapolated to infinity ($AUC_{0\text{-}inf}$)

Secondary	
• The secondary objectives are to evaluate the safety and 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	• AUC from time 0 to the last quantifiable data point ($AUC_{0\text{-last}}$), maximum observed plasma concentration (C_{max}), time to maximum observed concentration (t_{max}), terminal half-life ($t_{1/2}$), terminal rate constant (λ_z), systemic clearance (CL), and volume of distribution at steady state (V_{ss}) • Pharmacokinetic equivalence of the EU and the US-Avastin will be evaluated • Immunogenicity will be assessed by the incidence of anti-bevacizumab antibodies (ADA), including neutralizing antibodies (NAb) (if ADA positive) from Day 1 through last subject last visit • Safety and tolerability will be assessed by clinical laboratory tests, vital signs, 12-lead electrocardiograms (ECGs), physical examinations, assessment of adverse events (AE), injection site reactions, and concomitant medications

Overall Design:

This is a 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 (bevacizumab) after a single IV infusion of 1 mg/kg in healthy adult male subjects. The PK of bevacizumab is independent of dose between 1 and 10 mg/kg, so the lowest possible dose is chosen for administration to healthy volunteers in this study. Healthy male subjects will be enrolled to minimize the variability in the PK data by minimizing the variability due to physiological factors. Initially, subjects will be administered the study treatment in staggered groups; the first sentinel group will comprise 3 subjects, the second group 6 subjects and the third group 9 subjects. 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. Subjects will be randomized to ensure equal numbers of subjects receive each of the 3 treatments. Safety assessments will include: adverse events (AE), vital signs, electrocardiograms (ECG) parameters, clinical safety laboratory tests (hematology, clinical biochemistry, coagulation, urinalysis [including proteinuria], and urine microscopy where clinically indicated), physical examination, injection site assessments, and concomitant medications. Blood samples will be collected for PK evaluations and measurement of antidrug antibodies (ADA) and neutralizing antibodies (NAb) will be conducted.

Number of Investigators and Study Centers:

Approximately 2 Investigators and study centers are expected to participate in this study.

Number of 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 (40 subjects per treatment arm).

Treatment Groups and Duration:

This study will have a screening period of up to 28 days. Subjects will be admitted to the study center on Day -1, receive a single IV infusion of 1 mg/kg of HD204 (Prestige Biopharma Pte. Ltd bevacizumab),

EU-sourced Avastin (bevacizumab) or US sourced Avastin (bevacizumab) on Day 1. Subjects will be resident until the Day 3 discharge procedures have been completed and then return to the study center for 11 ambulatory visits (Days 4, 8, 15, 22, 29, 36, 43, 50, 64, 78, and 95 [end of study]).

Statistical Methods:

Pharmacokinetic Parameters:

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% confidence intervals (CIs) 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.

Similar analysis will be carried out for the secondary PK parameter $AUC_{0\text{-}last}$.

Safety Parameters:

All study subjects who have received the study treatment (partial or complete) will be included in the safety analysis.

Safety and tolerability will be assessed using reporting of AEs, concomitant medication, injection site reactions, physical examinations, vital signs, 12-lead ECGs, and laboratory parameters. Listings and descriptive statistics summary tables will be provided as appropriate.

Other Parameters:

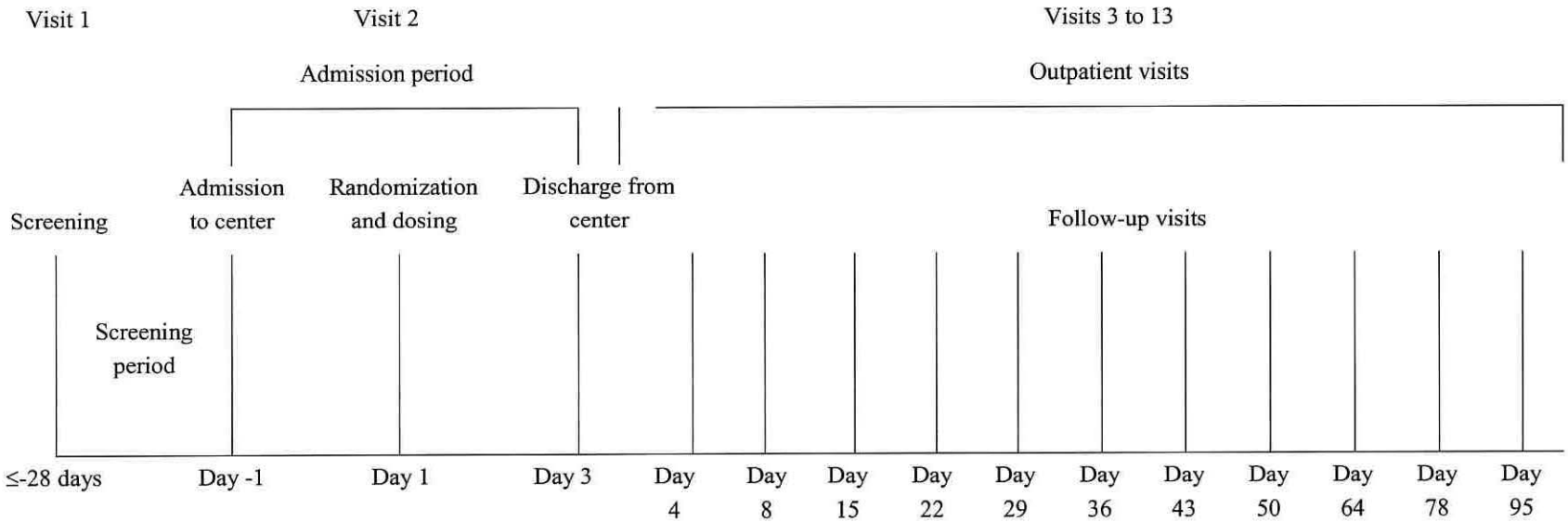
Proportion of subjects with ADA and with NAb will be summarized using descriptive statistics by visit for each parameter and presented in listings.

Safety Review Committee: Yes

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 next group will be dosed provided there are no serious or unexpected drug-related safety issues. The SRC will consist of the Principal Investigator, Investigator(s), Sponsor representative and IQVIA Medical Monitor.

1.2 Schema

Figure 1 Study Schema



The Day 95 visit will serve as the final follow-up visit for the study. However, subjects who are confirmed positive for anti-bevacizumab antibodies at the this visit or at and early termination visit (subjects who discontinue from the study following drug administration), will be followed up for up to 12 months or until 2 consecutive samples have been confirmed negative for anti-bevacizumab antibodies, whichever occurs earlier. These subjects will attend the clinical center at 6, 9, and 12 months after study completion post-dose for blood sampling to confirm their immunoglobulin status.

1.3 Schedule of Assessments

Table 1 Schedule of Assessments

Visit	1	2			3 to 12										13	
	Screen	Treatment and in-patient stay			Outpatient visits										Final Follow-up/ Early termination	ADA FU (if required)
Day (time windows are days unless specified otherwise)	-28 to -2	-1	1	2	3	4	8	15 ±1	22 ±1	29 ±1	36 ±1	43 ±2	50 ±2	64 ±3	78 ±3	95 ±4	
Informed consent	X																
Inclusion/exclusion criteria	X	X															
Demographics	X																
Medical history	X	X															
Height and weight[c]	X	X															
Physical examination[a]	X	X	X[b]		X			X		X[c]		X[c]	X[c]	X[c]		X	
Viral serology[d]	X																
Drug, alcohol, and cotinine screen[e]	X	X															
Vital signs	X	X	X[f]	X[g]	X[g]	X	X	X	X[h]	X[h]	X[h]	X	X[h]	X[h]	X[h]	X	
12-lead ECG	X	X	X[i]	X		X		X				X				X	
Clinical laboratory tests[j]	X	X			X	X		X				X		X		X	
Randomization			X														
Drug infusion			X														
Pharmacokinetic blood sampling[k]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ADA/NAb test[l]			X[m]					X	X	X	X	X	X	X	X	X	X
Adverse events and infusion site assessment	X	X														X	X

Visit	1	2				3 to 12										13	
	Screen	Treatment and in-patient stay				Outpatient visits										Final Follow-up/ Early terminatio n	ADA FU (if required)
Day (time windows are days unless specified otherwise)	-28 to -2	-1	1	2	3	4	8	15 ±1	22 ±1	29 ±1	36 ±1	43 ±2	50 ±2	64 ±3	78 ±3	95 ±4	
Concomitant medications	X	X														X	X

ADA = antidrug antibodies; ECG = electrocardiogram; FU = follow-up; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; NAb = neutralizing antibodies; PK = pharmacokinetic

Where time points of clinical assessments and collection of biological samples coincide the order of priority will be:

- ECG
- Vital signs
- Pharmacokinetic samples
- Immunogenicity samples (ADA and NAb)
- Clinical laboratory samples

ECG will be conducted in time intervals of 15 minutes on either side of scheduled time point (ie ± 15 minutes) and vital signs will be collected in time interval of 10 minutes on either side of scheduled time point (ie ± 10 minutes). ECG and vital signs measurements performed outside of this window period will be considered protocol deviations. For PK sample collection, window period as specified in protocol will be followed.

If clinical assessments are required for the immediate safety monitoring of the subject they will take priority over all other sample collection or clinical assessments.

Footnotes:

a Full physical examination will be performed at screening, admission to the study center (Day -1), discharge (Day 3), Day 15, and follow-up (Day 95).

b Infusion site check only.

c Physical examination will be performed if clinically indicated. Height will be measured at screening only.
Body weight will be measured at admission (during the physical examination) as this measurement will be used to calculate the dose to be administered to the subject. Body weight at admission is required for the calculation of the dose to be administered to the subjects. Height will be only assessed at screening.

d Viral serology will include HIV 1 and 2, HBsAg and hepatitis C antibody screening.

e Urine screen for drugs of abuse, alcohol, and cotinine. The screen for alcohol may be performed by a breath test according to local procedures.

f Vital signs on Day 1 will be measured at the following times: pre-dose (within 1 hour prior to the start of the infusion) and 0.5 and 1 hour post start of infusion; 0.25, 0.5, 1, 2, 3, 5, 6, 8, and 12 hours post end of infusion.

g Vital signs are to be measured at 24 and 36 hours post-dose on Day 2 and at 48 hours post-dose on Day 3.

h Blood pressure and pulse rate measurements only.

i 12-lead ECG on Day 1 will be measured at the following times: pre-dose (within 1 hour prior to the start of the infusion) and 0.75 and 1.0 hours post start of infusion; 3 and 12 hours post end of infusion and according to the PK sample schedule below for any other visits. ECG assessments will be obtained after the subject has been in the semi-supine position for at least 5 minutes.

j Clinical laboratory tests include hematology, clinical chemistry, coagulation and urinalysis (urine microscopy will be performed if clinically indicated) (see Appendix 3). Subjects with a 1+ or greater dipstick reading should undergo further assessment as per the clinical judgement of the Investigator or delegate.

k PK blood samples will be collected as indicated in the Schedule of Pharmacokinetics Assessments (Table 3).

l Subjects who are confirmed positive for anti-bevacizumab antibodies at the follow-up visit (Day 95) or at and early termination visit (subjects who discontinue from the study following drug administration), will be followed up for up to 12 months or until 2 consecutive samples have been confirmed negative for anti-bevacizumab antibodies, whichever occurs earlier. These subjects will attend the clinical center at 6, 9, and 12 months after study completion post-dose for blood sampling to confirm their immunoglobulin status.

m Within 1 hour prior to the start of the infusion.

Table 2 Schedule of Assessments for Day 1

Hours post start of infusion	**Pre[a]**	**0**	**0.5**	**0.75**	**1.0**	**1.5[c]**									
Hours post end of infusion							**0.25**	**0.5**	**1.0**	**2.0**	**3.0**	**5.0**	**6.0**	**8.0**	**12.0**
Randomization	X														
Drug infusion		X----------X													
Vital signs	X		X		X		X	X	X	X	X	X	X	X	X
12-lead ECG	X			X	X						X				X
Pharmacokinetic blood sampling[b]	X			X		X					X		X		X
ADA/NAb test	X														
Adverse events	X----------X														
Concomitant medications	X----------X														

ADA = antidrug antibodies; NAb = neutralizing antibodies

a Within 1 hour prior to the start of the infusion.

b PK blood samples will be collected at pre-infusion (or 0 hour, collected within 1 hour prior to the start of the infusion), 0.75 hours from the start of infusion (± 2 min), the end of infusion (0 hour post end of infusion +≤ 2 min [which is approximately 1.5 hours from the start of infusion]), at 3 hours (± 5 min), 6 hours (± 15 min), and 12 hours (± 15 min) from the end of infusion on Day 1.

c On completion of the infusion.

Table 3 Schedule of Pharmacokinetic Assessments

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

2.0 INTRODUCTION

2.1 Study Rationale

Prestige Biopharma Pte. Ltd is developing HD204, a biosimilar of the European Union (EU)-approved and United States of America (US) US-licensed bevacizumab (Avastin®). Bevacizumab is a recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody that binds to vascular endothelial growth factor (VEGF) extracellularly to prevent interaction with VEGF receptors (VEGFRs). Avastin is licensed for clinical use in the US (US-Avastin®) and the EU (EU-Avastin®) for a variety of tumor types.

The purpose of this study is to compare the pharmacokinetics (PK) of HD204, US-Avastin, and EU-Avastin in healthy male subjects after intravenous (IV) administration of a single dose. As a First-in-Human study, the study will also evaluate the safety, tolerability, and immunogenicity of HD204, US-Avastin, and EU-Avastin in healthy subjects.

2.2 Background

Since initial approval of bevacizumab (Avastin) in the US (2004) and in the EU (2005), for advanced colorectal cancer, bevacizumab has made anti-angiogenic therapy a fundamental pillar of cancer treatment. Avastin is approved in many countries for the treatment of advanced stages of colorectal cancer, metastatic non-squamous non-small cell lung cancer (NSCLC), metastatic renal cell cancer, breast cancer, epithelial ovarian cancer, and glioblastoma (1, 2).

However, the cost of biologic therapies has become increasingly prohibitive which can limit the therapeutic use of the drugs in patients. Moreover, globally, colorectal cancer is the third most common cancer in men and the second most common cancer in women (3). In the US, the National Cancer Institute estimates that 140 250 new cases will be reported in 2018, leading to the estimated deaths of 50 630 patients, or 8.3% of all cancer deaths (4). Overall, solid tumors constitute more than 94.4% and 96.8% of cancer-caused mortalities in males and females, respectively (2).

Angiogenesis is a physiological process in which new blood vessels are formed from pre-existing vessels. It occurs during normal growth and development, as well as during wound healing. Under physiological conditions, angiogenesis is tightly regulated. To date, many pro-angiogenic factors and their cognate receptors have been identified, including VEGF. Tumor angiogenesis is a hallmark of cancer and plays a crucial role in providing oxygen and nutrients to tumor cells during cancer progression and metastasis. Under pathological conditions, many pro-angiogenic factors and their receptors are upregulated; among these factors, VEGF is generally regarded as a key regulator of tumor angiogenesis (1).

Bevacizumab binds to VEGF and thereby inhibits the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. Neutralizing the

biological activity of VEGF regresses the vascularization of tumors, normalizes remaining tumor vasculature, and inhibits the formation of new tumor vasculature, thereby inhibiting tumor growth (5, 6).

HD204 is a biosimilar to Avastin being developed by Prestige Biopharma Pte. Ltd.

Bevacizumab is a monoclonal antibody recombinant humanized immunoglobulin of the human immunoglobulin G subclass 1, kappa light chain (IgG1κ). HD204 is produced in a mammalian cell (Chinese hamster ovary [CHO]) expression system and is subsequently purified and formulated.

Analytical assays have been conducted to compare the purity of multiple lots of HD204 and Avastin. The data indicate that HD204 is at least as pure as Avastin and that the molecular weight and binding affinity are consistent between HD204 and Avastin.

HD204 and Avastin have similar post translational modification in terms of glycan variant distribution, overall galactosylation, fucosylation, and distribution of glycan variants. Charge variant distribution, as measured by ion exchange chromatography, and capillary iso-electric focusing were also similar.

Biological functional assays showed very similar results. Overall, the data have demonstrated that HD204 is highly similar to the reference product, Avastin, in structure and function.

Nonclinical Studies Using HD204

In vitro assessments of antibody functionality (including Fab, Fc, and complement functions) of HD204 have been performed in comparison with Avastin. In addition, in vitro and in vivo pharmacodynamic (PD) studies have been performed in a variety of test systems. Toxicokinetic investigations in the non-human primate were performed in a single dose study and as part of the 4-week and 13-week repeated dose toxicity studies. In addition, the immunogenicity of the antibody was evaluated in the repeated dose toxicity studies. In all of these investigations, HD204 was compared against Avastin sourced in the EU (7).

The in vitro comparative analysis of HD204 and Avastin demonstrated:

- The binding affinities of 3 VEGF isomers ($VEGF_{121}$, $VEGF_{165}$, $VEGF_{189}$), which can bind to bevacizumab, were compared by enzyme-linked immunosorbent assay (ELISA). Relative binding affinity was measured using the in-house reference standard. The antigen binding affinity for HD204 excluding $VEGF_{189}$ was found to be similar to that of the reference drug value.

- The binding affinity of 4 Fc receptors capable of binding to the Fc portion of the antibody was measured by the surface plasmon resonance method. Affinity for FcγRI, FcγRIIa, and FcγRIIIa receptors, which directly affect effector functions such as antibody-dependent cell-mediated cytotoxicity (ADCC), and FcRn receptors which are closely related to blood half-life was measured. A commercially available recombinant protein was used as a receptor for the assay. The analysis showed that the min/max values of the binding affinity measurements of all 4 HD204 samples in all Fc receptors were within the measurement range of the reference drug.
- The binding affinity to C1q, which binds to the hinge region of the antibody and is involved in complement-dependent cytotoxicity (CDC) activity, was measured by ELISA. HD204 and Avastin demonstrated similar binding activity.
- The degree of inhibition of cell activity was measured to confirm antigen binding affinity indirectly. Human umbilical vein endothelial cells (HUVEC) were used and the relative anti-proliferative effect of each sample was measured after $VEGF_{165}$ treatment using the in-house reference standard. The anti-proliferative effect of 2 HD204 clinical samples (BEA-14001, BEA-14002) was within the range of the reference drug. The third sample (HD204 BEA-14003) exceeded the upper limit of the reference drug's range.
- In the A549 lung cancer model, the efficacy of HD204 and the control agent on the size of the tumor when intraperitoneally administered twice weekly was comparable.
- No treatment-related adverse effects were observed in the animals treated with HD204 and Avastin.

Nonclinical Pharmacokinetics and Product Metabolism

The PK profile of HD204 was compared to that of Avastin in Cynomolgus monkeys (male and female), in a single subcutaneous dose study. HD204 and Avastin were administered by subcutaneous injection at a dose of 2 mg/kg. The result indicated comparable systemic clearance (CL) and concentration-time curve from time zero extrapolated to infinity ($AUC_{0\text{-}inf}$) between HD204 and Avastin.

Summary of Clinical Findings of HD204

At the time of preparation of this protocol, HD204 has not been administered to human subjects.

Additional information can be found in the Investigator's Brochure (IB).

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of HD204 may be found in the IB.

The subjects enrolled are not expected to gain any clinical benefit from participation in this clinical study. However, since a healthy subject population is most sensitive to product differences, such a population is expected to show a better response than patients to detect differences in PK profiles.

The safety procedures to be followed during the study have been selected to minimize the risk of harm to the subjects and to ensure the scientific integrity of the data collected during the study. All study treatment administrations will occur under medical supervision in the study center and subjects will remain at the study center for 48 hours following study treatment administration. The lowest dose of 1 mg/kg has been selected for the study to minimize exposure to healthy subjects and it is expected to be well tolerated in healthy subjects.

This study will be performed in compliance with the protocol, the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), European Union Good Manufacturing Practice (EU GMP) and applicable regulatory requirements.

The Sponsor will immediately notify the Principal Investigator if any additional safety or toxicology information becomes available during the study.

3.0 OBJECTIVES AND ENDPOINTS

Table 4 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• The primary objective of the study is to establish pairwise pharmacokinetic (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	• Area under the concentration-time curve (AUC) of the analyte in plasma over the time interval from time 0 (baseline) extrapolated to infinity ($AUC_{0\text{-}inf}$)
Secondary	
• 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	• AUC from time 0 to the last quantifiable data point ($AUC_{0\text{-}last}$), maximum observed plasma concentration (C_{max}), time to maximum observed concentration (t_{max}), terminal half-life ($t_{1/2}$), terminal rate constant (λ_z), systemic clearance (CL), and volume of distribution at steady state (V_{ss}) • Pharmacokinetic equivalence of the EU and the US-Avastin will be evaluated • Immunogenicity will be assessed by the incidence of anti-bevacizumab antibodies (ADA), including neutralizing antibodies (NAb) (if ADA positive) from Day 1 through last subject last visit • Safety and tolerability will be assessed by clinical laboratory tests, vital signs, 12-lead electrocardiograms (ECGs), physical examinations, assessment of adverse events (AE), injection site reactions and concomitant medications

4.0 STUDY DESIGN

4.1 Overall Design

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.

Initially, subjects will be administered the study treatment 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.

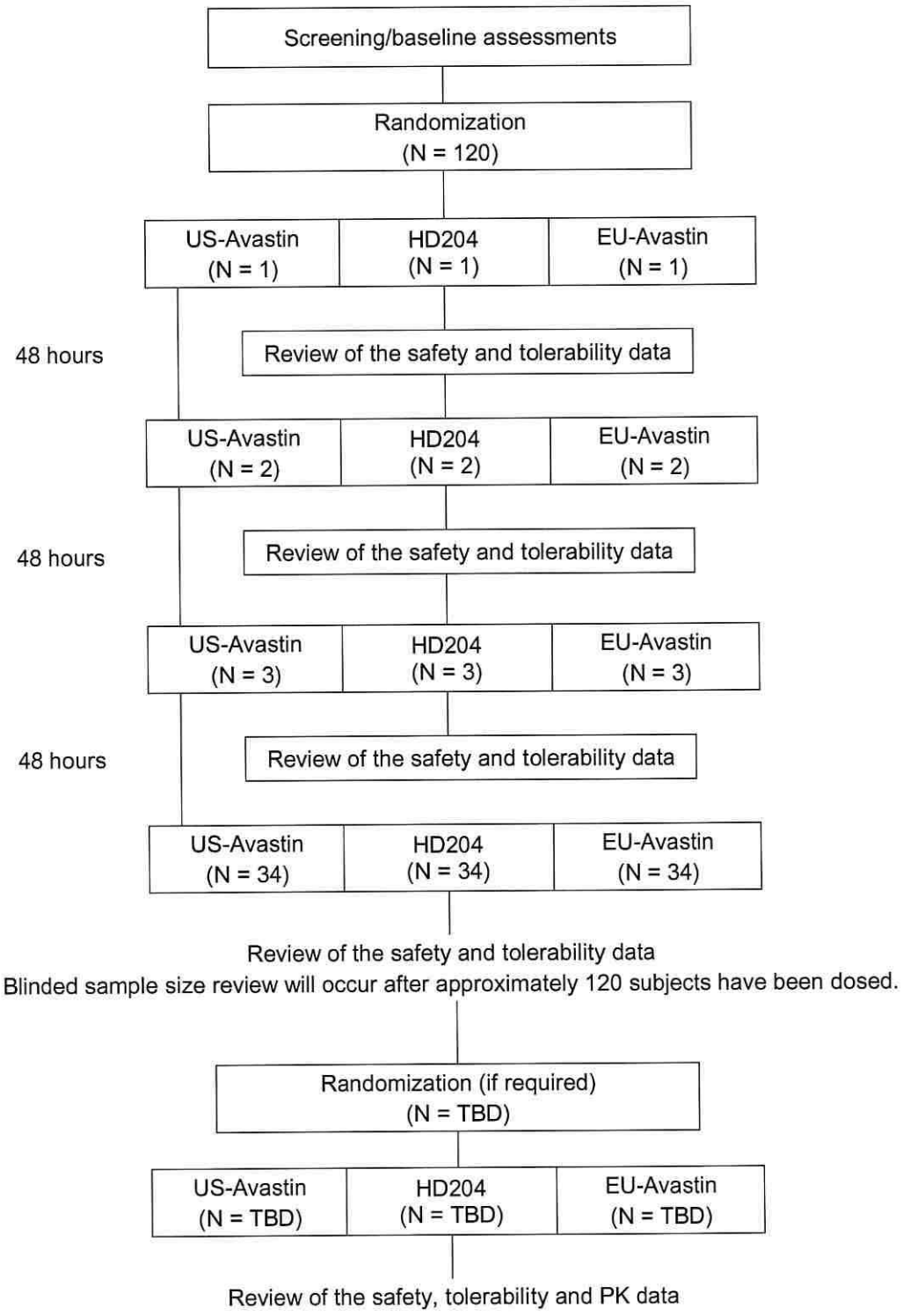
There will be at least 48 hours between administrations of study treatment to each staggered group. Prior to administration of study treatment to the next group, the blinded safety and tolerability findings of the preceding group will be reviewed by the Principal Investigator. The Principal Investigator will consult with the Investigator(s) when subjects have been enrolled over all sites. The next group will be administered study treatment 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 treatment for safety evaluation.

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.

The Study Schema is presented in Figure 1 and a summary of the study design is presented in Figure 2.

The Schedule of Assessments (SoA) for the whole study is described in Table 1, and those for Day 1 in Table 2. The Schedule of Pharmacokinetic Assessments can be found in Table 3.

Figure 2 Study Design



TBD = To be determined

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 (ie, 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 Table 1.

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 treatment (Visit 2) and a 95-day follow-up period (Visits 3 to 13).

Subjects who are confirmed positive for anti-bevacizumab antibodies, including subjects who discontinue from the study following drug administration, will be followed up for up to 12 months. These subjects will attend the study center at 6, 9, and 12 months post-dose for blood sampling to confirm their immunoglobulin status or until 2 consecutive samples have been 'confirmed negative' for anti-bevacizumab antibodies, whichever occurs earlier.

A summary of study visits is presented in the study flow diagram in Figure 1. The start of the study is considered the date of the first subject providing informed consent and the end of the study will be the last subject's last scheduled visit. Additional follow-up visits for subjects who are positive for anti-bevacizumab antibodies or have ongoing/resolving AEs will be conducted and reported separately.

Enrollment of Additional Subjects Following a Blinded 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.

If additional subjects are enrolled the Principal Investigator will decide on the timing and group size for enrollment according to the capability of the study center. The subjects will be 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 and will follow the study timeline and assessments described above.

4.2 Scientific Rationale for Study Design

A parallel group design is the preferred design for this study due to the long half-life (approximately 20 days) of bevacizumab and the potential development of immunogenicity.

The study design is expected to provide sufficient PK, immunogenicity and safety data to meet the study objectives. A healthy subject population was chosen as the recommended approach by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), to allow characterization of PK in the most homogenous population with the lowest variability.

The safety of the subjects will be ensured by means of regular medical supervision and assessment throughout their residential stay at the study center, and periodic health assessments thereafter throughout the study.

Additionally, as a safety measure, subjects will be administered the study treatment in separate staggered groups starting with a sentinel group of 3 subjects (1 subject per treatment). The second group will comprise 6 subjects and the third group 9 subjects. After the first 3 groups have been evaluated, the SRC will decide whether to proceed with continuous enrollment according to the study center's capability.

4.3 Justification for Dose

The PK of bevacizumab is independent of dose between 1 and 10 mg/kg, so the lowest possible dose is chosen for administration to healthy subjects in this study.

4.4 End of Study Definition

A subject is considered to have completed the study if he/she has completed all phases of the study including the last visit.

The end of the study is defined as the date of the last visit of the last subject in the study.

4.5 Dose Escalation Criteria

Not applicable.

4.6 Study Stopping Criteria

4.6.1 Stopping Criteria for Individual Subjects

The infusion will be stopped at any time if the subject experiences a severe infusion reaction (Table 6) or a serious adverse event (SAE) during the infusion period. The subject will be followed up until resolution of the SAE and then withdrawn from the study.

4.6.2 Criteria for Stopping the Study

The study may be stopped if any of the following occur:

- ≥ 1 subject experiences SAEs considered to have a reasonable possibility of relationship to the study treatment.
- ≥ 1 subject experiences a drop in absolute neutrophil count to below 1.0×10^9/L on repeat measurement and for which there is no other likely cause.
- ≥ 1 subject experiences a drop in platelet count to below 100×10^9/L.
- ≥ 2 subjects experience non-tolerable AEs that are considered to have a reasonable possibility of relationship to the study treatment.
- ≥ 2 subjects who receive study treatment have a QTc prolongation defined as QTcF > 500 ms, or an increase of QTcF > 60 ms above baseline on the 12-lead ECG, confirmed (persistent for > 5 minutes) on repeated 12-lead ECGs.
- ≥ 1 subject who receives study treatment fulfils Hy's law, defined as an increase in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 × the upper limit of normal (ULN) and total bilirubin ≥ 2 × ULN, where no other reason can be found to explain the combination of increases.
- ≥ 2 subjects have > 3 × ULN of either ALT, AST, bilirubin, or alkaline phosphatase (ALP)
- The occurrence of significant safety events (as judged by the Investigator) other than those described above that in the opinion of the Principal Investigator requires evaluation before any further subjects are dosed.

5.0 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

1. Adult healthy male subjects aged 18 to 50 years (inclusive) and body mass index 18.0 to 30.0 kg/m^2 (inclusive) and body weight ≥ 60 kg to ≤ 100 kg.
2. Subjects who are healthy as determined by pre-study medical history, physical examination, vital signs, and 12-lead ECG at screening and admission on Day -1.
3. Subjects whose clinical laboratory test results are normal, or where outside the reference range is judged as not clinically relevant by the Investigator.
4. Have systolic blood pressure ≥ 90 and ≤ 140 mmHg, diastolic blood pressure ≥ 50 and ≤ 90 mmHg and heart rate ≥ 40 and ≤ 90 bpm at screening and admission on Day -1. For single measurements in the 141 to 160 mmHg range (systolic) or in the 91 to 100 mmHg range (diastolic), a single repetition on the same day is allowed and, in this case, the mean of both measurements will guide eligibility. The mean of both the measurements should be ≤ 140 mmHg (systolic) and ≤ 90 mmHg (diastolic).
5. Have physical examination results without clinically relevant findings at screening and admission on Day -1.
6. Have 12-lead ECG results without clinically relevant findings at screening and admission on Day -1.
7. Subjects who are non-smokers and have not regularly used tobacco or nicotine containing products for at least 3 months prior to screening and have a < 10 pack year smoking history.
8. Males must be willing to use a medically acceptable method of contraception from the time of the administration of study treatment, throughout the study and for a period of 6 months after the administration of the study treatment (see Appendix 5). This requirement may be waived if the Principal Investigator or delegate is satisfied that the subject or subject's female partner is sterile ie, if female has undergone a hysterectomy or tubal ligation at least 3 months prior to screening or is postmenopausal (defined as no menses for 12 months without an alternative medical cause) or if the subject has undergone a vasectomy at least 6 months prior to screening.
9. Must agree not to donate sperm for at least 6 months after the administration of study treatment.
10. Must be willing and able to comply with scheduled visits, laboratory tests, and other study procedures.

11. Must be able to provide informed consent which must be obtained prior to any study-related procedures.
12. Subjects who are willing to comply with the study restrictions, and comply with the scheduled visits from screening and throughout the study.

5.2 Exclusion Criteria

1. Have a history of hypersensitivity or allergic reactions (either spontaneous or following drug administration) to bevacizumab or VEGF targeted treatment or to any other excipients.
2. Have a history of or presence of current clinically significant gastrointestinal (including diverticulitis, stomach ulcers, inflammatory intestinal disease, gastrointestinal perforations/fistulae/intra-abdominal abscess), any other internal, non-gastrointestinal fistulae that is at an increased risk of bleeding, renal, hepatic, cardiovascular, hematological (including pancytopenia, aplastic anemia or blood dyscrasia), pulmonary, neurologic, metabolic (including known diabetes mellitus), psychiatric or allergic disease excluding mild asymptomatic seasonal allergies.
3. Have a history of and/or current cardiac disease defined as one of the following:
   - History of congestive heart failure;
   - Angina pectoris requiring antianginal medication;
   - Evidence of transmural infarction on ECG;
   - History of sustained hypertension (systolic > 180 mmHg and/or diastolic > 100 mmHg) or hypertensive crisis or hypertensive encephalopathy;
   - Clinically significant valvular heart disease; or
   - Severe arterial thromboembolic events.
4. Have a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus, or human immunodeficiency virus (HIV) I and II at screening.
5. Have any history of malignancy including lymphoma, leukemia, and skin cancer (even resected basal cell carcinoma or squamous cell carcinoma).
6. Have an illness within 30 days prior to screening, or prior to Day -1, that is considered as clinically significant by the Investigator.
7. Prior exposure to any investigational monoclonal antibody within 12 months of Day -1. Prior investigational exposure to Avastin > 12 month is acceptable.
8. Any clinically significant infection, in the opinion of the Investigator, ongoing at screening or admission on Day -1.

9. Have had major surgery within 3 months prior to screening, or will have an operation between screening and the end of study visit, or still has an unhealed wound, including wound dehiscence and wound healing complications requiring medical intervention. Major Surgery would include any surgery which is invasive, and allows access to body cavities beyond the skin, superficial tissues or mucous membranes, requires beyond local anesthesia, or requires in house hospitalization.
10. Have received live vaccine(s) within 3 months prior to screening or will require a live vaccine(s) between screening and the end of study visit.
11. Have an intake of alcoholic beverages of more than 14 units per week (1 unit = 250 mL of beer, 25 mL of spirits or 1 glass [125 mL] of wine).
12. Have reasonable evidence (in the opinion of the Investigator) of drug abuse as indicated by a positive urinary drug test at screening or admission on Day -1.
13. Have taken medication with a half-life of > 24 hours within 30 days or less than 10 half-lives of the medication prior to Day -1 as determined by the Investigator.
14. Have donated blood and blood products within 3 months prior to Day -1. Blood donation and blood products are not permitted throughout study.
15. Have participated in another clinical study of an investigational drug within 90 days or 5 half-lives of the investigational drug (whichever is longer) prior to Day -1, or are currently participating in another clinical study of an investigational drug, or intending to participate in another clinical study of an investigational drug before completion of all scheduled evaluations in this clinical study.
16. Subjects who, in the opinion of the Investigator, are not likely to complete the study for whatever reason.
17. The Investigator or any sub-investigator, research assistant, pharmacist, study coordinator, other staff directly involved in the conduct of the clinical study or any of their immediate family members (parents, siblings or spouses).
18. Abnormal or irregular bowel movements eg, less than 1 bowel movement every 3 days.
19. Any history of non-traumatic hemorrhage (ie, any hemorrhage requiring medical intervention) or any condition which may increase bleeding risk including clotting disorders, thrombocytopenia (platelet count < 150, 000 per μL) or an international normalized ratio higher than 1.5 at screening.

20. Impaired liver function as determined by:
    - Serum ALT and/or AST > 1.5 × ULN at screening or admission. Subjects with values between ULN and 1.5 × ULN may be included in the study if considered not clinically significant by the Investigator.
21. Any intake of a non-steroidal anti-inflammatory drug (NSAID) including any dose of aspirin in the 30 days before Day -1 (NSAIDs are not allowed for the duration of the study).
22. Intake of herbal drugs or dietary supplements excluding routine vitamins but including megadose (intake of 20 to 600 times the recommended daily dose) vitamin therapy within 30 days prior to Day -1, unless agreed as not clinically relevant by the Investigator and Sponsor.
23. Strenuous exercise or activity within 96 hours prior to admission on Day -1 and has a creatinine kinase value > 2.5 × ULN.
24. Subjects with unsuitable veins for infusion or venipuncture.
25. Subjects with a non-healing wound or hematoma of a clinically relevant size as assessed by the Investigator, or a clinically significant current fracture.
26. Presence of proteinuria (other than trace amounts ie, +, ++/+++) at screening or admission on Day -1.
27. Known personal or family history of venous thromboembolic events or idiopathic venous thromboembolic events in first degree relatives.
28. Inability to refrain from contact or collision sport until Day 30.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

1. Study treatment administration will occur on Day 1 after a fast of at least 8 hours. Water will be permitted as required. The study treatment will be administered intravenously to the subjects in bed in the semi-supine position. Subjects will remain fasting until 1 hour following completion of the study treatment infusion after which a meal will be served on completion of the scheduled assessments.
2. Subjects will receive a standard diet while resident in the study center and will only consume food and beverages provided by the study center.
3. Subjects will refrain from consumption of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, and Seville orange juice or other products containing grapefruit or Seville oranges from 30 days prior to admission on Day -1 and for the duration of the residential period.

4. Subjects should refrain from consumption of any foods containing poppy seeds within 48 hours prior to screening and admission to the study center on Day -1.

5.3.2 Caffeine, Alcohol, and Tobacco

1. Subjects should refrain from smoking for the duration of the study (through Day 95).
2. Subjects should refrain from alcoholic beverages from 48 hours prior to Day 1 until discharge on Day 3 and for 24 hours prior to each outpatient visit; at other times alcohol intake should be limited to ≤ 2 units per day (1 unit = 250 mL of beer, 25 mL of spirits or 1 glass [125 mL] of wine).
3. Subjects should refrain from taking drugs of abuse during the study (up to the final follow-up visit).

5.3.3 Activity

1. Subjects should refrain from strenuous exercise or activity from admission on Day -1 until Day 10 of the study. Subjects should not participate in contact/collision sports until Day 30.
2. Subjects should adhere to study requirements for contraceptives.
3. Subjects should adhere to the concomitant medication restrictions.
4. Subjects should refrain from blood or blood product donation for the duration of the study (through Day 95).

5.3.4 Avoidance of Pregnancy

1. Female subjects will not be enrolled on this clinical study.
2. The use of contraception will not be required if the female partner of the subject has undergone a hysterectomy or tubal ligation at least 3 months prior to screening or is postmenopausal (defined as no menses for 12 months without an alternative medical cause).
3. As a precaution, all male subjects should avoid fathering a child by either true abstinence or, in conjunction with their partner (if the partner is of childbearing potential), the use of 2 acceptable means of contraception from the time of the administration of the study treatment, throughout the study and for a period of 6 months after the administration of the study treatment (see details in Appendix 5).

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomly assigned to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

5.4.1 Repetition of Screening Assessment(s)

Repetition of a screening assessment would be allowed if there is evidence of a laboratory error or if there is reason to believe that the result is not an accurate reflection of the subject's clinical status. One repeat test will be permitted to re-assess a subject's eligibility. The Investigator is encouraged to discuss or seek advice with the Medical Monitor if needed.

5.4.2 Rescreening of Subject(s)

Subjects may only be rescreened with the approval of the Medical Monitor in case a permanent change has occurred in eligibility criteria (medical status or laboratory findings) that previously led to screen failure. If a subject is rescreened, all screening assessments will be repeated.

6.0 STUDY TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a subject according to the study protocol.

6.1 Study Treatment(s) Administered

Table 5 Study Treatment Details

Study Treatment Name	HD204 (bevacizumab)	EU-Avastin (bevacizumab)	US-Avastin (bevacizumab)
Dosage Formulation	Sterile solution	Sterile solution	Sterile solution
Unit Dose Strength(s)/Dosage Level(s)	100 mg/4 mL, a single dose of 1 mg/kg will be administered	100 mg/4 mL, a single dose of 1 mg/kg will be administered	100 mg/4 mL, a single dose of 1 mg/kg will be administered
Route of Administration	IV infusion	IV infusion	IV infusion
Dosing Instructions	Individual subject treatments will be dispensed by the unblinded pharmacist in IV infusion bags, diluted with 0.9% sodium chloride. Subjects will receive a single administration 90-minute IV infusion. All dose administrations will be performed in the study center under the supervision of appropriately trained staff.	Individual subject treatments will be dispensed by the unblinded pharmacist in IV infusion bags, diluted with 0.9% sodium chloride. Subjects will receive a single administration 90-minute IV infusion. All dose administrations will be performed in the study center under the supervision of appropriately trained staff.	Individual subject treatments will be dispensed by the unblinded pharmacist in IV infusion bags, diluted with 0.9% sodium chloride. Subjects will receive a single administration 90-minute IV infusion. All dose administrations will be performed in the study center under the supervision of appropriately trained staff.
Packaging and Labeling	Study treatment will be provided in glass vials. Each vial will be labeled as required per country requirement.	Study treatment will be provided in glass vials. Each vial will be labeled as required per country requirement.	Study treatment will be provided in glass vials. Each vial will be labeled as required per country requirement.
Manufacturer	Prestige Biopharma Pte. Ltd	Roche	Genetech
First-in-Human	For the purpose of the first human dose study, drug product will be prepared at the study center, diluted to the required volume using 0.9% sodium chloride solution.	For the purpose of the first human dose study, drug product will be prepared at the study center, diluted to the required volume using 0.9% sodium chloride solution.	For the purpose of the first human dose study, drug product will be prepared at the study center, diluted to the required volume using 0.9% sodium chloride solution.

EU: European Union; IV: intravenously; US: Unites States

6.2 Preparation/Handling/Storage/Accountability

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only subjects enrolled in the study may receive study treatment and only authorized study center staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study center staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual.

The Investigator, a member of the study center staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study medication using the Drug Accountability Form. These forms must be available for inspection at any time.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Method of Assigning Subjects to Treatment Groups

At screening, potential study subjects will be assigned a screening number. Following confirmation of eligibility, prior to study treatment administration, subjects will be assigned a subject number in the order in which they are enrolled in the study.

6.3.2 Randomization Procedures

The randomization list will be generated using a validated system by an unblinded statistician who will not be involved in the analysis of the study data before unblinding. The unblinded statistician will provide the independent pharmacist of the study center with the subject randomization.

Subjects will be randomly assigned to one of the study treatments in a 1:1:1 ratio. The subject number will determine the allocation of treatment, per the randomization schedule with the subject numbers starting with X001, where 'X' would be the study center number.

6.3.3 Maintenance of Randomization Codes

Randomization codes will be provided to the independent pharmacist, and an unblinded Medical Monitor as a list. Individual treatment disclosure envelopes (code break) will be kept by the independent pharmacist at the study center and the Investigator will be able to access these during the study if required for safety reasons. The independent pharmacist will use the

randomization code list for preparing subject doses throughout the study. The individual disclosure envelopes will be used if it is necessary to break the blind for an individual subject.

The unblinded/independent study center pharmacist (or an appropriately qualified designee) will be responsible for preparation of the blinded study treatment infusion bags for each subject according to the instructions in the Pharmacy Manual.

6.3.4 Unblinding

Unblinding can only take place for the purpose of managing an SAE if deemed necessary by the Investigator. If the code for a subject is broken, the Investigator must withdraw the subject from the study, document the details of the event and the reason for unblinding in the subject's case report form (CRF) and promptly inform the Sponsor's study physician/Medical Monitor and the Ethics Committee. Additionally, the Sponsor and/or designee may be required to unblind the subject if the AE meets criteria of a suspected unexpected serious adverse reaction (SUSAR) in order to fulfil expedited regulatory reporting requirements.

After completion of the study, all code break envelopes will be returned to the Sponsor or a delegate.

6.4 Study Treatment Compliance

The prescribed dose, timing, and mode of administration may not be changed. Any departures from the intended regimen must be recorded in the CRF.

All dose administrations will be performed in the study center under the supervision of appropriately trained staff.

6.4.1 Treatment Measures to Ensure Subject Safety

The clinical staff is responsible for the ongoing safety and wellbeing of the subjects in this First-in-Human study while they are in the study center. There is a paging system to alert the clinical staff to any area in the center where a subject may need medical attention. In the case of an emergency, cardiac resuscitation trolleys are found in the main ward areas of the study center. These trolleys contain drugs, equipment for airway insertion, circulation lines, defibrillation etc, together with oxygen cylinders and portable suction machines. There is a physician on site 24 hours a day. In addition, if necessary the clinical staff can contact further on-call physicians or public emergencies services in the event of a serious medical event. Equipment and emergency drugs are available to treat common medical emergencies that might occur in a Phase 1 study.

6.4.2 Warnings and Precautions

As this is the first administration of HD204 to man, all effects cannot be reliably predicted. The preclinical data suggest an acceptable safety margin. Facilities and staff for resuscitation and the treatment of other medical emergencies will be provided.

6.5 Concomitant Therapy

Subjects are not allowed to take the following medications except for management of AEs as advised by the Principal Investigator:

- Any prescription or over-the-counter medication with a half-life of > 24 hours within 30 days or less than 10 half-lives of the medication prior to Day 1 and for the duration of the study (except paracetamol as detailed below)
- Any herbal remedies or dietary supplements within 30 days prior to Day 1 and for the duration of the study, unless agreed as not clinically relevant by the Investigator and Sponsor
- Any NSAIDs (including aspirin) within 30 days prior to Day 1 and for the duration of the study
- Any live virus vaccination within 30 days before screening and during study participation until the final follow-up visit

In the interests of subject safety and acceptable standards of medical care the Investigator will be permitted to prescribe treatment(s) at his/her discretion. All treatments must be recorded in the subjects' CRF (medication, dose, treatment duration and indication).

Paracetamol, up to 2 g per day, will be allowed.

6.6 Dose Modification

Dose modifications are not planned or allowed in this study.

6.7 Treatment After the End of the Study

The Sponsor will not provide any additional care to subjects after they leave the study.

7.0 DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

The infusion will be stopped at any time if the subject experiences a severe infusion reaction (Table 6) or a SAE during the infusion period. The subject will be followed up until resolution of the SAE and then withdrawn from the study.

If a subject who does not meet enrollment criteria is inadvertently enrolled, that subject must be discontinued from study treatment and the Sponsor or Sponsor designee must be contacted. An exception may be granted in rare circumstances for which there is a compelling safety reason to allow the subject to continue. In these rare cases, the Investigator must obtain documented approval from the Sponsor or Sponsor designee to allow the subject to continue in the study.

Subjects who discontinue study treatment will not be replaced.

7.2 Subject Discontinuation/Withdrawal from the Study

- A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the study center study records.
- See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. Should a subject request or decide to withdraw from the study, all efforts must be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. Subjects withdrawing due to an AE should be followed up according to the follow-up visit.
- Subjects who voluntarily withdraw are termed dropouts. Dropouts and subjects withdrawn due to protocol violations may be replaced following discussion with the Principal Investigator and Sponsor.
- Subjects withdrawn due to an AE will not be replaced.

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study center.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The study center must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

8.0 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (see Section 1.3).

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor and SRC upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

The number of samples collected and the volume required for each analysis may be changed during the study (eg, if additional samples are collected for repeat or additional safety assessments at the request of the Investigator).

The total volume of blood to be collected per subject during the study will not exceed 400 mL.

8.1 Efficacy Assessments

Not applicable.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (see Section 1.3).

8.2.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Any clinically significant changes from admission will be recorded as treatment-emergent AEs (TEAEs).

8.2.2 Local Infusion Site Reactions

Infusion site evaluations will be made by clinical staff during the administration of the infusion and during Day 1 as described below; if an infusion site reaction is observed, a physician will characterize and document the reaction as an AE. Review of the infusion site will continue until the AE is resolved.

If infusion site reactions are observed after Day 1 the same grading system may be used and the site reaction recorded as an AE and review of the infusion site will continue until the AE is resolved.

The infusion sites will be monitored for pain, tenderness, erythema and swelling. Each infusion site reaction will be categorized using the intensity grading scheme presented in Table 6; the intensity of each resulting AE will be categorized (eg, a moderate intensity infusion site reaction may be recorded as a mild AE if considered appropriate according to the Investigator's judgement).

Table 6 Infusion Site Reaction Grading Scheme

	Intensity Grading				
Reaction	**Absent (0)**	**Mild [a] (1)**	**Moderate [a] (2)**	**Severe [a] (3)**	**Potentially Life-threatening (4)**
Pain	Absent	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Hospital visit (A and E) or hospitalization
Tenderness	Absent	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Hospital visit (A and E) or hospitalization
Erythema/ redness	Absent	2.5 to 5.0 cm	5.1 to 10.0 cm	> 10.0 cm	Necrosis or exfoliative dermatitis
Induration/ swelling	Absent	2.5 to 5.0 cm and does not interfere with activity	5.1 to 10.0 cm or interferes with activity	> 10.0 cm or prevents daily activity	Necrosis
Other [b]	Absent		Present		

A and E = accident and emergency department; AE = adverse event.

[a] Measurements refer to the reaction at the greatest single diameter.

[b] Any other reactions such as bruising, itching or ulceration will be recorded as absent or present and will be recorded as AEs; AEs will be categorized according to the Investigator's judgement.

Reference:

http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm074775.htm

8.2.3 Immunogenicity

Blood samples for analysis of the incidence and titer of antibodies to bevacizumab and the incidence of any NAbs in serum will be collected as indicated in the SoA (see Section 1.3).

Subjects who are confirmed positive for anti-bevacizumab antibodies at the follow-up visit (Day 95) or at an early termination visit (subjects who discontinue from the study following drug administration), will be followed up for up to 12 months or until 2 consecutive samples have been confirmed negative for anti-bevacizumab antibodies, whichever occurs earlier. These subjects will attend the study center at 6, 9, and 12 months after study completion post-dose for blood sampling to confirm their immunoglobulin status.

Blood sample processing and handling details will be presented in a separate Laboratory Manual.

8.2.4 Vital Signs

Aural temperature, pulse rate, blood pressure, and respiratory rate will be assessed.

Blood pressure and pulse measurements will be assessed in the semi-supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (eg, television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 1 blood pressure measurements (one repeat measurement may be taken if out of range).

8.2.5 Electrocardiograms

A single 12-lead ECG will be obtained at time points indicated in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

ECG assessments will be obtained after the subject has been in the semi-supineposition for at least 5 minutes.

The ECGs will be reviewed by the Investigator, or a designee, to assess for any abnormalities. Refer to Section 4.6.2 for QTcF-related stopping criteria and any additional QTcF readings that may be necessary.

8.2.6 Clinical Safety Laboratory Assessments

See Appendix 3 for the list of clinical laboratory tests to be performed and to the SoA (see Section 1.3) for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the subject's health status, unless judged by the Investigator to be more severe than expected for the subject's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 3, must be conducted in accordance with the Laboratory Manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.3 Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the subject to discontinue the study (see Section 7.0).

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 1.3).

All AEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

8.3.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences. All study assessments results (eg, laboratory tests, vital signs, ECGs, etc) will be reviewed by the Investigator for determination of AE occurrence.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 4.

8.3.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of all pregnancies in female partners of male subjects will be collected after the start of study treatment and until 6 months after the last dose.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Adverse Events of Special Interest

Not applicable.

8.4 Treatment of Overdose

For this study, any dose of study treatment greater than 1 mg/kg within a 24-hour time period will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the subject for any AE/SAE and laboratory abnormalities until study treatment can no longer be detected systemically.
3. Obtain a plasma sample for PK analysis within 1 day from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

8.5 Pharmacokinetics

8.5.1 Collection of Samples

Venous blood samples of approximately 2.5 mL will be collected for measurement of serum concentrations of bevacizumab at times as specified in the SoA. Instructions for the collection and handling of biological samples will be provided by the Sponsor. Blood samples will be taken either by direct venipuncture or an indwelling cannula inserted in a forearm vein. Blood samples for PK will not be collected from the arm used for the IV infusion for at least 24 hours after administration. The actual date and time (24-hour clock time) of each sample will be recorded in the CRF. The time and date of study treatment administration including infusion start and stop

times and any infusion interruptions will also be recorded in the CRF. Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

Pre-dose samples may be collected within 1 hour of dose administration. The post-dose sample windows are specified in the SoA (see Section 1.3).

8.5.2 Determination of Drug Concentration

Samples for the determination of bevacizumab in serum will be analyzed on behalf of CPR Pharma using appropriate validated bioanalytical methods. Full details of the bioanalytical methods will be described in a separate Bioanalytical Report.

All samples still within the known stability of the analyte of interest at the time of receipt by the bioanalytical laboratory will be analyzed.

Remaining serum samples may be subjected to further analysis by the Sponsor or designee for the purpose of the development of additional bioanalytical assays and/or to investigate the presence of analytes of interest. Samples collected for analyses of bevacizumab serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained. At visits during which serum samples for the determination of biosimilarity of HD204 will be taken, 1 sample of sufficient volume can be used.

8.5.3 Derivation of Pharmacokinetic Parameters

Pharmacokinetic parameters will be derived using noncompartmental methods with Phoenix® WinNonlin® Version 6.4 or higher (Certara, L.P. Princeton, New Jersey, US) and/or SAS® Version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina, US). Actual elapsed time from dosing will be used for the final serum PK parameter calculations. In cases where the actual sampling time is missing, calculations will be performed using the scheduled time. Otherwise, there will be no further imputation of missing data. Interim PK analyses will be performed by using scheduled time post-dose for all calculations.

Serum Pharmacokinetic Parameters

The PK parameters in Table 7 will be determined for bevacizumab when possible. A minimum of 3 quantifiable post-dose concentrations will be required for all calculations.

Table 7 Serum Pharmacokinetic Parameters

Primary Pharmacokinetic Parameter	**Definition**
$AUC_{0\text{-}inf}$	Area under the concentration-time curve from time 0 extrapolated to infinity
Secondary Pharmacokinetic Parameters	**Definition**
$AUC_{0\text{-}last}$	Area under the concentration-time curve from time 0 to the last quantifiable data point
C_{max}	Maximum observed concentration
t_{max}	Time to maximum observed concentration
$t_{½}$	Terminal half-life
λ_z	Terminal rate constant
V_{ss}	Volume of distribution at steady state
CL	Systemic clearance

The calculation of AUCs will be performed using the mixed log-linear trapezoidal method (linear up/log down). The pre-dose samples will be considered as if they had been taken immediately before the administration. Concentrations below the lower limit of quantification (BLQ) will be taken as zero for calculating the AUC of single dose profiles. The PK parameters will be evaluated and listed for all subjects who provide sufficient concentration-time data.

Other parameters may be added as appropriate. Final PK parameters reported will be detailed in the Statistical Analysis Plan (SAP).

8.6 Pharmacodynamics

Pharmacodynamics are not evaluated in this study.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary statistical null hypothesis is that $AUC_{0\text{-inf}}$ is not equivalent between HD204 and the reference products within 80% to 125% limits, against the alternative that HD204 is equivalent to the reference products.

9.2 Sample Size Determination

Based on historical data, an inter-subject variability of 25% and a proportion of 20% of non-PK evaluable subjects have been assumed for sample size determination. Assuming an inter-subject geometric coefficient of variation (CV) of 25% and a geometric mean ratio of 1.05, 40 evaluable subjects per arm are required for the 2-sided 90% confidence interval (CI) of the geometric mean ratio being completely contained within 80% to 125% with 80% overall power and at least 90% power for each pairwise comparison (HD204 versus EU-Avastin, HD204 versus US-Avastin, and EU-Avastin versus US-Avastin). To allow for a proportion of 20% non-PK evaluable subjects, 150 subjects (50 subjects per arm) are planned to be enrolled.

9.3 Populations for Analyses

For purposes of analysis, the analysis sets are defined in Table 8.

Table 8 Analysis Sets

Analysis Set	Description
Pharmacokinetic Concentration (PKC) Population	The PKC population includes subjects with at least 1 valid post-dose concentration and includes all subjects who have received 1 dose of study treatment and completed the study assessments without major protocol violations which may significantly affect the pharmacokinetic (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 will be summarized based on the PKC population. Serum bevacizumab concentrations will be listed and summarized using descriptive statistics in tables and graphs, as appropriate.
Pharmacokinetic Parameter (PKP) Population	The PKP population is a subpopulation of the PKC population, which includes all subjects in 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 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.
PK Non-Neutralizing (PKNN) Population	The PKNN population will include those members of the PKP population without sustained neutralizing antidrug antibodies (ADAs). Sustained neutralizing antibodies occur when a patient has 2 consecutive visits with neutralizing antibodies. Pharmacokinetic analyses will be repeated on the PKNN population to assess robustness of results.

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

9.4 Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the subject analysis sets to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1 Primary Endpoint

The primary PK parameter for assessment of PK equivalence is $AUC_{0\text{-inf}}$.

9.4.2 Secondary Endpoints

The secondary PK parameters are: $AUC_{0\text{-last}}$, C_{max}, t_{max}, $t_{½}$, λ_z, V_{ss} and CL. In addition, the PK similarity of the EU and the US-Avastin will be evaluated to provide the bridging data justifying the use of a single reference product in further comparative clinical studies in patient populations.

Immunogenicity will be assessed by the incidence of anti-bevacizumab antibodies, including NAbs from Day 1 through last subject last visit. NAbs will only be assessed in those subjects in whom positive ADA antibodies are detected.

The safety and tolerability will be assessed by clinical laboratory tests, vital signs, 12-lead ECGs, physical examinations, assessment of AEs, injection site reactions, and concomitant medications.

9.4.3 Pharmacokinetic/Pharmacodynamic Analyses

9.4.3.1 Serum Bevacizumab Concentration Data

All analyses of PK endpoints will be performed using the PKP population. A subject listing of all concentration-time data for each treatment will be presented.

Concentration data of bevacizumab will be summarized by treatment and nominal time point using appropriate descriptive statistics.

9.4.3.2 Analysis of Primary Pharmacokinetic Endpoint

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. Covariates may be included in the models, to be specified in the SAP.

9.4.3.3 Analysis of Secondary Pharmacokinetic Endpoints

The $AUC_{0\text{-last}}$ as a secondary parameter may also be tested for PK similarity as described above.

All PK parameters will be summarized by treatment using N, n, mean, standard deviation (SD), %CV, minimum, median, maximum, geometric mean, and geometric %CV defined as

$$100 \cdot \sqrt{(\exp(s^2)-1)}$$

where s is the SD of the data on a log scale, except that t_{max} will be reported with n, minimum, median, and maximum only.

Graphs may be added at the discretion of the PK scientist, as appropriate, and will be described in detail in the SAP.

9.4.4 Safety Analyses

All safety analyses will be based on the SA population. No statistical tests will be performed for the safety data.

Safety data including laboratory assessments, vital signs, and ECG parameters will be summarized by treatment and/or time point using descriptive statistics for observed values and change from baseline values (as appropriate).

Adverse events will be tabulated and summarized according to the current version of MedDRA.

For the laboratory data, vital signs and ECGs, out of range values will be flagged in the data listings and a list of clinically significantly abnormal values will be presented as appropriate.

Physical examination will be presented in listing only.

Concomitant medications will be presented in listings.

9.4.5 Immunogenicity

The proportion of subjects with ADA, with NAb and the corresponding titers will be summarized using descriptive statistics for the Safety Analysis Population by visit for each parameter and presented in listings.

9.4.6 Missing Data

Data from subjects who withdraw from the study, including AEs and any follow-up, will be included in the analyses of primary and secondary outcomes. Missing safety data will not be imputed. PK concentrations may be imputed for the derivation of PK parameters, to be defined in the SAP.

9.5 Interim Analyses

After approximately 20 subjects per treatment arm have been observed for a minimum of 20 days, an interim safety report will be generated and approved by the Sponsor. The interim safety report will be generated using data that is source verified by the Clinical Research Assistant, including blinded safety laboratory, AE, and ECG data accumulated to that point (Day 20 of the Study). The review of the interim report will be performed by the SRC. Details regarding the review process will be available in the relevant SRC charter. This evaluation will allow a preliminary assessment of safety findings with a time to onset longer than 24 hours.

The SAP will describe the planned interim analyses in greater detail.

9.5.1 Blinded Sample Size Re-evaluation

Due to the uncertainty in the actual variability and trying to limit the study size to those strictly needed, a BSSR will be performed after approximately 120 evaluable subjects (40 subjects per arm) have completed the study. This number of subjects is expected to provide a sufficiently precise calculation of the variability in the actual study population (8). The BSSR will aim to provide at least 90% power for each of the pairwise comparisons and approximately 80% overall power, as specified in the sample size determination.

The BSSR will estimate the geometric CV in the primary endpoint, ignoring any potential differences due to treatment. If the geometric CV is greater than 25%, the number of randomized subject 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.

At the time of the BSSR, the study recruitment will be stopped until the BSSR results become available.

If additional subjects are enrolled the Principal Investigator will decide on the timing and group size for enrollment according to the capability of the study center.

9.6 Safety Review Committee

After the safety and tolerability data from the first 3 groups are available, a 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.

Further details will be available in the SRC charter.

10.0 REFERENCES

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11.0 APPENDICES

Appendix 1 Abbreviations

Abbreviation	Definition
AE	Adverse event
ADA	Antidrug antibodies
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-inf}}$	Area under the plasma concentration-time curve from time zero extrapolated to infinity, calculated by linear up/log down trapezoidal summation
$AUC_{0\text{-last}}$	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration, calculated by linear up/log down trapezoidal summation
BSSR	Blinded sample size re-evaluation
CI	Confidence interval
CL	Systemic clearance
C_{max}	Maximum observed plasma concentration
CRF	Case report form
CV	Coefficient of variation
ECG	Electrocardiogram
EU	European Union
EU GMP	European Union Good Manufacturing Practice
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous(ly)
λ_z	Lambda z; terminal rate constant
NAb	Neutralizing antibody
NSAID	Non-steroidal anti-inflammatory drug
PD	Pharmacodynamic(s)

Abbreviation	Definition
PK	Pharmacokinetic(s)
PKC Population	Pharmacokinetic Concentration Population
PKNN Population	Pharmacokinetic Non-Neutralizing Population
PKP Population	Pharmacokinetic Parameter Population
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SoA	Schedule of Assessments
SRC	Safety Review Committee
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Terminal half-life
t_{max}	Time to C_{max}
ULN	Upper limit of normal
US	United States (of America)
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
V_{ss}	Volume of distribution at steady state
WOCBP	Woman of childbearing potential

Appendix 2 Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable ICH GCP Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and regulatory authority approval, when applicable, before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to subjects.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the study center and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative (Appendix 6). The study will not start at any study center at which the Investigator has not signed the protocol.

Adequate Resources

The Investigator is responsible for supervising any individual or party to whom the Investigator delegates study-related duties and functions conducted at the study center.

If the Investigator/institution retains the services of any individual or party to perform study-related duties and functions, the Investigator/institution should ensure this individual or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.

Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the subjects in this study. The terms of the insurance will be kept in the study files.

Insurance

The Sponsor has obtained liability insurance, which covers this study as required by local law and/or national regulations and/or ICH guidelines, whichever is applicable. The terms of the insurance will be kept in the study files.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

Data Protection

- Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.
- The Sponsor or its representative will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician, or any other third party, unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, the Sponsor or representative physician or an Investigator might know a subject's identity and also have access to his or her genetic data. Also, regulatory authorities may require access to the relevant files.

Administrative Structure

The safety committee will include, at a minimum, the Sponsor's responsible physician and the Principal Investigator. The Principal Investigator and the Sponsor, when appropriate, will invite other specialist individuals to participate in the review, eg, PK scientists, statisticians, clinical specialists etc.

Table 9 Study Administrative Structure

Function	Responsible Organization
Principle Investigator and Primary Investigational Site	Dr. Christian Schwabe Auckland Clinical Studies Ltd Ground Floor, MEDACS House, 3 Ferncroft Street, Grafton, Auckland, New Zealand Tel: +64 373 3474 Fax: +64 373 3479
Investigators and Other Investigational Sites	Dr. Chris Wynne Christchurch Clinical Studies Trust, Ltd, 31 Tuam Street, Post Office Box 2856, Christchurch 8011 New Zealand Tel: +64 3372 9477 Fax: +64 3372 9478
Study Operations Management Medical Monitoring	Sponsor/CRO
Study Master File	CRO
Randomization Code	Sponsor/CRO/3rd party

Function	Responsible Organization
Data Management	Sponsor/CRO
Clinical Supply Management	Sponsor/CRO
Quality Assurance Auditing	Sponsor/CRO
Biostatistics Medical Writing	Sponsor/CRO
Laboratory Assessments	Local Laboratory used by Auckland Clinical Studies Ltd: **LabPLUS** Building 31, Auckland City Hospital, Gate 4 off Grafton Road, Auckland, New Zealand Tel: +64 9 307 8995 Fax: +64 9 307 4970 E-mail: Lablink@adhb.govt.nz
Electrocardiogram Collection, Review, and Analysis	Sponsor/CRO/3rd party
Bioanalytical Analysis (Immunogenicity and Pharmacokinetic Analysis)	CPR Pharma Services Pty Ltd 28 Dalgleish St Thebarton SA 5031 AUSTRALIA Tel: Fax: E-mail:
Pharmacokinetic Analysis	IQVIA Overland Park, Kansas, Unites States of America (US) Tel: +913 708 6000
Safety Monitoring Committee (see Section 9.6)	Sponsor/CRO/3rd party
IQVIA Medical Advisor	Charu Gautam
Sponsor Representative	Lisa Soyeon Park
Safety Monitoring Committee (see Section 9.6)	Sponsor/CRO/3rd party

Medical Monitor

Charu Gautam

Charu.Gautam@iqvia.com

Dissemination of Clinical Study Data

The results of the study should be reported within 1 year from the end of the clinical study. Irrespective of the outcome, the Sponsor will submit to the EU database a summary of the results of the clinical study within 1 year from the end of the clinical study. It shall be accompanied by a summary written in a manner that is understandable to laypersons.

Data Quality Assurance

- Monitoring will be carried out as determined by the risk assessment process conducted on the study.
- All subject data relating to the study will be recorded on printed or eCRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized study center personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Source Documents

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study center's subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail).

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's study center.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Study Center Closure

The Sponsor designee reserves the right to close the study center or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study centers will be closed upon study completion. A study center is considered closed when all required documents and study supplies have been collected and a study center closure visit has been performed.

The Investigator may initiate study center closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study center by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the Investigator.
- Discontinuation of further study treatment development.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual study center data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix 3 Clinical Laboratory Tests

- The tests detailed in Table 10 will be performed by the local laboratory.
- If the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5.0 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 10 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Platelet Count	White Blood Cell Count with Differential:
	Red Blood Cell Count	*Neutrophils
	Hemoglobin	*Lymphocytes
	Hematocrit	*Monocytes
	Red Blood Cell Indices:	*Eosinophils
	Mean corpuscular volume (MCV)	*Basophils
	Mean corpuscular hemoglobin (MCH)	
	Mean cell hemoglobin concentration (MCHC)	
	*Reticulocytes	* Cells to be reported as absolute values.
Clinical Chemistry		Aspartate Aminotransferase (AST)/
	Creatinine	Alanine Aminotransferase (ALT)/
	Glucose (fasting)	Alkaline phosphatase (ALP)
	Gamma- glutamyl transferase (GGT)	Creatine kinase
	Urea	TROP-I or TROP-T will be performed if clinically indicated
	Magnesium	Chloride
	Cholesterol	Amylase
	Potassium	Total bilirubin
	Sodium	Conjugated bilirubin will be performed if clinically indicated
	Calcium	Total protein
	Lactate dehydrogenase	Phosphate
	Albumin	
	Uric acid	Carbon dioxide (bicarbonate)
	C-reactive protein	Triglycerides

Laboratory Assessments	Parameters	
Coagulation	International normalized ratio (INR)	Activated partial thromboplastin time (aPTT)
	Prothrombin time (PT)	
		Fibrinogen
Urinalysis	Leucocytes	Red blood cells
	Protein	pH
	Bilirubin	Nitrite
	Urobilinogen	Specific gravity
	Ketones	Glucose
	Microscopy (if clinically indicated)	
Viral serology	HIV I and II	Hepatitis C virus
	HBsAg	
Drugs of abuse and alcohol	Amphetamine/	Opiates
	Cannabinoids	Benzodiazepines
	Cocaine metabolites	Methadone metabolites
	Urine creatinine	Barbiturates
	Cotinine	Ecstasy (3,4-Methylenedioxymethamphetamine)
	Tricyclic anti-depressants (TCA)	Phencyclidine
NOTES: [a] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.		

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to study centers or other blinded personnel until the study has been unblinded.

Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or subject, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgement of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a) Results in death
b) Is life-threatening The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c) Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d) Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e) Is a congenital anomaly/birth defect
f) Other situations: • Medical or scientific judgement should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF. Each event must be recorded separately.
- It is **not** acceptable for the Investigator to send photocopies of the subject's medical records in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. The AE must be characterized as unrelated, unlikely to be related, possibly related, probably related, or unknown (unable to judge).
  - "Probably related" conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
  - "Possibly related" suggests that the association of the AE with the study treatment is unknown; however, the AE is not reasonably supported by other conditions.
  - "Unlikely to be related" suggests that only a remote connection exists between the study treatment and the AE. Other conditions, including chronic illness, progression or expression of the disease state or reaction to concomitant therapy, appear to explain the reported AE.
  - "Unrelated" is used if there is not a reasonable possibility that the study treatment caused the AE.
  - All efforts should be made to classify the AE according to the above categories. The category "unknown" (unable to judge) may be used only if the causality is not assessable, eg, because of insufficient evidence, conflicting evidence, conflicting data, or poor documentation.
- The Investigator will use clinical judgement to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the Investigator will provide a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the study center will use the paper SAE data collection tool (see next section).
- The study center will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given study center, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a study center receives a report of a new SAE from a subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the study center can report this information on a paper SAE form (see next section) or to the Medical Monitor/SAE coordinator] by telephone.

SAE Reporting via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Medical Monitor or the SAE coordinator.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

Appendix 5 Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   a) Documented hysterectomy.
   b) Documented bilateral salpingectomy.
   c) Documented bilateral oophorectomy.
   Note: Documentation can come from the study center personnel's: review of the subject's medical records, medical examination, or medical history interview.
3. Postmenopausal female:
   a) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   b) Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male subjects

- Male subjects with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 5.1:
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent for duration of study and for 6 months after study completion or from last dose.

- Agree to use a male condom and have their partner use of a contraceptive method with a failure rate of <1% per year when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

- In addition, male subjects must refrain from donating sperm for the duration of the study and for 6 months after study completion or the last dose of study treatment.
- Male subjects with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame.

Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral. • Intravaginal. • Transdermal.
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral. • Injectable.
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD). • Intrauterine hormone-releasing system (IUS). Bilateral tubal occlusion.
Vasectomized Partner *A vasectomized partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual Abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for at after the last dose of study treatment.

Collection of Pregnancy Information

Male subjects with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Appendix 6 Signature of Investigator

PROTOCOL TITLE: 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

PROTOCOL NO: SAMSON-1

VERSION: Original Protocol

This protocol is a confidential communication of [Sponsor]. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCPs and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to Sponsor or CRO.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

Protocol Clarification Letter

Date: 26th July 2018

Study Title: 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

Protocol Number: SAMSON-1

Clinical Trial Protocol Version: 13th July 2018 / Version 1.0

There are several items in the current SAMSON-1 protocol dated 13th July 2018 that the clinical study sites have requested further clarification on by the Sponsor. These have been listed below and will be updated in the current protocol when there is a protocol amendment.

Sequence of Assessments and Sample Collection
There is an inconsistency on page 13 and 41 regarding assessments and collection of samples when time points coincide:

Page 13:
Where time points of clinical assessments and collection of biological samples coincide the order of priority will be:
- Pharmacokinetic samples
- Clinical laboratory samples
- Immunogenicity samples (ADA and NAb)
- Vital signs
- ECG

Page 41:
Vital signs (to be taken before blood collection for laboratory tests)

This letter is to clarify that the order of assessments would be ECG, Vitals, PK, PD, ADA, Nab and clinical labs. The window allowed for ECG and Vitals would be used and then the bloods would be taken on the time point, also within the allowed windows.

Definition of Major Surgery
The current protocol, section 5.2 Exclusion Criteria, point number 9, excludes volunteers who have had major surgery within **3 months** prior to screening, or will have an operation between screening and the end of study visit, or still has an unhealed wound, including wound dehiscence and wound healing complications requiring medical intervention.

This note is to clarify that Major Surgery would include any surgery which is invasive, and allows access to body cavities beyond the skin, superficial tissues or mucous membranes, requires beyond local anesthesia, or requires in house hospitalization.

Blood Pressure Measurement
The current protocol section 8.2.4. Vital Signs states ‘Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3

consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the CRF.'

The site standard is to measure BP once and repeat if abnormal. The protocol will be amended at a later date to change the text above to "Vital signs will consist of 1 pulse and 1 blood pressure measurement."

Signed:



CEO, Prestige Biopharma

TITLE PAGE

Protocol Title:

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

Protocol Number: SAMSON-1

Amendment Number: Original protocol

Product: HD204

Short Title:

Phase I, Double-blind, Randomized, Parallel Group Study to Demonstrate the Equivalent Pharmacokinetic Properties of a Single Intravenous Dose of HD204 and Avastin in Healthy Male Subjects

Study Phase: Phase I

Local Sponsor Name: IQVIA RDS Pty. Ltd

Legal Registered Address:

Unit A, 2 Rothwell Avenue
Rosedale
Auckland 0632
New Zealand

Sponsor Name: Prestige Biopharma Pte. Ltd

Legal Registered Address:

2 Science Park Drive #04-13/14 Ascent Tower B
Singapore Science Park
Singapore 118222

Regulatory Agency Identifying Number(s):

EudraCT no. 2017-005174-19

Date of Protocol: 13 July 2018, Version 1.0

Sponsor Signatory:

I have read this protocol in its entirety and agree to conduct the study accordingly:



17 July 2018

Lisa Soyeon Park
Prestige Biopharma Chief Executive Officer

Date

Medical Monitor name and contact information can be found in Appendix 2.

TABLE OF CONTENTS

TABLE OF TABLES 6

TABLE OF FIGURES 7

1.0 PROTOCOL SUMMARY 8
1.1 Synopsis 8
1.2 Schema 11
1.3 Schedule of Assessments 12

2.0 INTRODUCTION 17
2.1 Study Rationale 17
2.2 Background 17
2.3 Benefit/Risk Assessment 20

3.0 OBJECTIVES AND ENDPOINTS 21

4.0 STUDY DESIGN 22
4.1 Overall Design 22
4.2 Scientific Rationale for Study Design 25
4.3 Justification for Dose 25
4.4 End of Study Definition 25
4.5 Dose Escalation Criteria 25
4.6 Study Stopping Criteria 25
4.6.1 Stopping Criteria for Individual Subjects 25
4.6.2 Criteria for Stopping the Study 26

5.0 STUDY POPULATION 27
5.1 Inclusion Criteria 27
5.2 Exclusion Criteria 28
5.3 Lifestyle Considerations 30
5.3.1 Meals and Dietary Restrictions 30
5.3.2 Caffeine, Alcohol, and Tobacco 31
5.3.3 Activity 31
5.3.4 Avoidance of Pregnancy 31
5.4 Screen Failures 31
5.4.1 Repetition of Screening Assessment(s) 32
5.4.2 Rescreening of Subject(s) 32

6.0 STUDY TREATMENT 33
6.1 Study Treatment(s) Administered 33
6.2 Preparation/Handling/Storage/Accountability 34
6.3 Measures to Minimize Bias: Randomization and Blinding 34

6.3.1 Method of Assigning Subjects to Treatment Groups 34
6.3.2 Randomization Procedures 34
6.3.3 Maintenance of Randomization Codes 34
6.3.4 Unblinding 35
6.4 Study Treatment Compliance 35
6.4.1 Treatment Measures to Ensure Subject Safety 35
6.4.2 Warnings and Precautions 35
6.5 Concomitant Therapy 36
6.6 Dose Modification 36
6.7 Treatment After the End of the Study 36

7.0 DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL 37
7.1 Discontinuation of Study Treatment 37
7.2 Subject Discontinuation/Withdrawal from the Study 37
7.3 Lost to Follow-up 38

8.0 STUDY ASSESSMENTS AND PROCEDURES 39
8.1 Efficacy Assessments 39
8.2 Safety Assessments 39
8.2.1 Physical Examinations 39
8.2.2 Local Infusion Site Reactions 39
8.2.3 Immunogenicity 41
8.2.4 Vital Signs 41
8.2.5 Electrocardiograms 41
8.2.6 Clinical Safety Laboratory Assessments 42
8.3 Adverse Events 42
8.3.1 Time Period and Frequency for Collecting AE and SAE Information 42
8.3.2 Method of Detecting AEs and SAEs 43
8.3.3 Follow-up of AEs and SAEs 43
8.3.4 Regulatory Reporting Requirements for SAEs 43
8.3.5 Pregnancy 44
8.3.6 Adverse Events of Special Interest 44
8.4 Treatment of Overdose 44
8.5 Pharmacokinetics 44
8.5.1 Collection of Samples 44
8.5.2 Determination of Drug Concentration 45
8.5.3 Derivation of Pharmacokinetic Parameters 45
8.6 Pharmacodynamics 46
8.7 Genetics 46
8.8 Biomarkers 46

9.0 STATISTICAL CONSIDERATIONS 47
9.1 Statistical Hypotheses 47
9.2 Sample Size Determination 47

9.3 Populations for Analyses 47
9.4 Statistical Analyses 48
9.4.1 Primary Endpoint 48
9.4.2 Secondary Endpoints 48
9.4.3 Pharmacokinetic/Pharmacodynamic Analyses 48
9.4.4 Safety Analyses 49
9.4.5 Immunogenicity 49
9.4.6 Missing Data 49
9.5 Interim Analyses 50
9.5.1 Blinded Sample Size Re-evaluation 50
9.6 Safety Review Committee 50

10.0 REFERENCES 51

11.0 APPENDICES 52
Appendix 1 Abbreviations 53
Appendix 2 Regulatory, Ethical, and Study Oversight Considerations 55
Regulatory and Ethical Considerations 55
Adequate Resources 55
Financial Disclosure 56
Insurance 56
Informed Consent Process 56
Data Protection 56
Administrative Structure 57
Medical Monitor 58
Dissemination of Clinical Study Data 59
Data Quality Assurance 59
Source Documents 59
Study and Study Center Closure 60
Publication Policy 60
Appendix 3 Clinical Laboratory Tests 61
Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 63
Appendix 5 Contraceptive Guidance and Collection of Pregnancy Information 68
Appendix 6 Signature of Investigator 71

TABLE OF TABLES

Table 1	Schedule of Assessments	12
Table 2	Schedule of Assessments for Day 1	15
Table 3	Schedule of Pharmacokinetic Assessments	16
Table 4	Study Objectives and Endpoints	21
Table 5	Study Treatment Details	33
Table 6	Infusion Site Reaction Grading Scheme	40
Table 7	Serum Pharmacokinetic Parameters	46
Table 8	Analysis Sets	47
Table 9	Study Administrative Structure	57
Table 10	Protocol-required Safety Laboratory Assessments	61

TABLE OF FIGURES

Figure 1 Study Schema.....11
Figure 2 Study Design.....23

1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

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

Short Title:

Phase I, Double-blind, Randomized, Parallel Group Study to Demonstrate the Equivalent Pharmacokinetic Properties of a Single Intravenous Dose of HD204 and Avastin in Healthy Male Subjects

Rationale:

Prestige Biopharma Pte. Ltd is developing HD204, a biosimilar of the European Union (EU)-approved and US-licensed bevacizumab (Avastin®). Bevacizumab is a recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody that binds to vascular endothelial growth factor (VEGF) extracellularly to prevent interaction with VEGF receptors (VEGFRs). Avastin is licensed for clinical use in the US (US-Avastin) and the EU (EU-Avastin) for a variety of tumor types.

The purpose of this study is to compare the pharmacokinetics (PK) of HD204, US-Avastin, and EU-Avastin in healthy male subjects after intravenous (IV) administration of a single dose. As a First-in-Human study, the study will also evaluate the safety, tolerability, and immunogenicity of HD204, US-Avastin, and EU-Avastin in healthy subjects.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• The primary objective of the study is to establish pairwise PK equivalence between HD204 (Prestige Biopharma Pte. Ltd bevacizumab), EU-Avastin, and US-Avastin after a single IV infusion of 1 mg/kg in healthy male subjects	• Area under the concentration-time curve (AUC) of the analyte in plasma over the time interval from time 0 (baseline) extrapolated to infinity ($AUC_{0\text{-}inf}$)

Secondary	
• The secondary objectives are to evaluate the safety and 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	• AUC from time 0 to the last quantifiable data point ($AUC_{0\text{-last}}$), maximum observed plasma concentration (C_{max}), time to maximum observed concentration (t_{max}), terminal half-life ($t_{1/2}$), terminal rate constant (λ_z), systemic clearance (CL), and volume of distribution at steady state (V_{ss}) • Pharmacokinetic equivalence of the EU and the US-Avastin will be evaluated • Immunogenicity will be assessed by the incidence of anti-bevacizumab antibodies (ADA), including neutralizing antibodies (NAb) (if ADA positive) from Day 1 through last subject last visit • Safety and tolerability will be assessed by clinical laboratory tests, vital signs, 12-lead electrocardiograms (ECGs), physical examinations, assessment of adverse events (AE), injection site reactions, and concomitant medications

Overall Design:

This is a 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 (bevacizumab) after a single IV infusion of 1 mg/kg in healthy adult male subjects. The PK of bevacizumab is independent of dose between 1 and 10 mg/kg, so the lowest possible dose is chosen for administration to healthy volunteers in this study. Healthy male subjects will be enrolled to minimize the variability in the PK data by minimizing the variability due to physiological factors. Initially, subjects will be administered the study treatment in staggered groups; the first sentinel group will comprise 3 subjects, the second group 6 subjects and the third group 9 subjects. 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. Subjects will be randomized to ensure equal numbers of subjects receive each of the 3 treatments. Safety assessments will include: adverse events (AE), vital signs, electrocardiograms (ECG) parameters, clinical safety laboratory tests (hematology, clinical biochemistry, coagulation, urinalysis [including proteinuria], and urine microscopy where clinically indicated), physical examination, injection site assessments, and concomitant medications. Blood samples will be collected for PK evaluations and measurement of antidrug antibodies (ADA) and neutralizing antibodies (NAb) will be conducted.

Number of Investigators and Study Centers:

Approximately 2 Investigators and study centers are expected to participate in this study.

Number of 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 (40 subjects per treatment arm).

Treatment Groups and Duration:

This study will have a screening period of up to 28 days. Subjects will be admitted to the study center on Day -1, receive a single IV infusion of 1 mg/kg of HD204 (Prestige Biopharma Pte. Ltd bevacizumab),

EU-sourced Avastin (bevacizumab) or US sourced Avastin (bevacizumab) on Day 1. Subjects will be resident until the Day 3 discharge procedures have been completed and then return to the study center for 11 ambulatory visits (Days 4, 8, 15, 22, 29, 36, 43, 50, 64, 78, and 95 [end of study]).

Statistical Methods:

Pharmacokinetic Parameters:

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% confidence intervals (CIs) 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.

Similar analysis will be carried out for the secondary PK parameter $AUC_{0\text{-}last}$.

Safety Parameters:

All study subjects who have received the study treatment (partial or complete) will be included in the safety analysis.

Safety and tolerability will be assessed using reporting of AEs, concomitant medication, injection site reactions, physical examinations, vital signs, 12-lead ECGs, and laboratory parameters. Listings and descriptive statistics summary tables will be provided as appropriate.

Other Parameters:

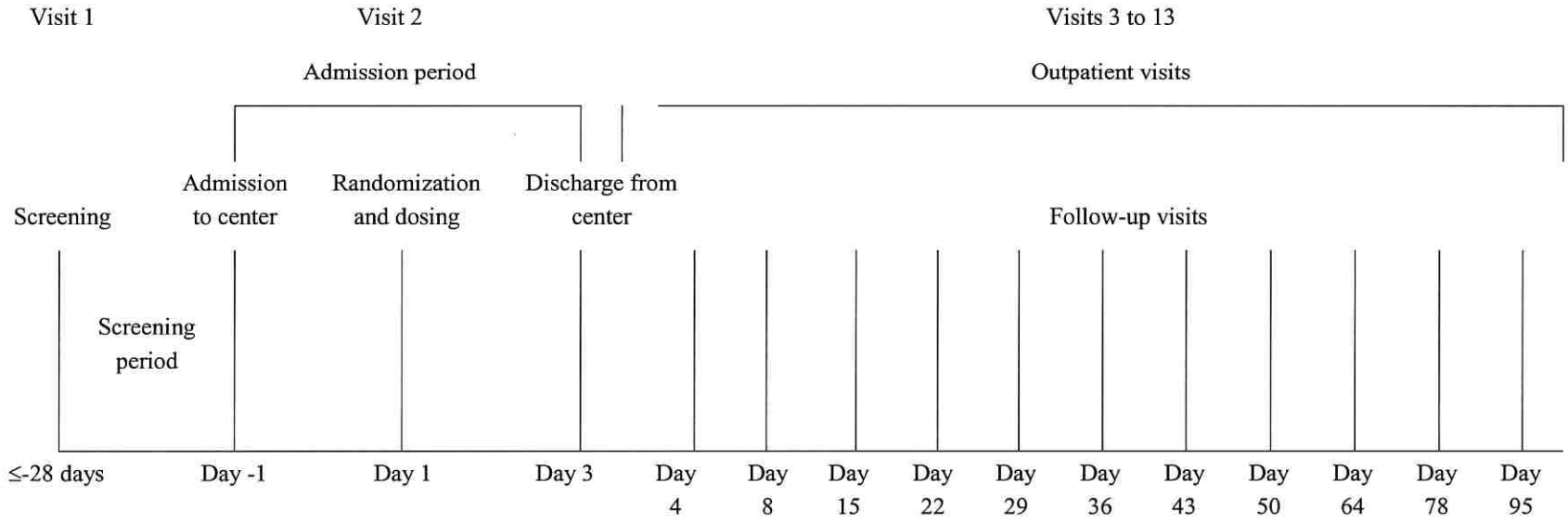
Proportion of subjects with ADA and with NAb will be summarized using descriptive statistics by visit for each parameter and presented in listings.

Safety Review Committee: Yes

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 next group will be dosed provided there are no serious or unexpected drug-related safety issues. The SRC will consist of the Principal Investigator, Investigator(s), Sponsor representative and IQVIA Medical Monitor.

1.2 Schema

Figure 1 Study Schema



The Day 95 visit will serve as the final follow-up visit for the study. However, subjects who are confirmed positive for anti-bevacizumab antibodies at the this visit or at and early termination visit (subjects who discontinue from the study following drug administration), will be followed up for up to 12 months or until 2 consecutive samples have been confirmed negative for anti-bevacizumab antibodies, whichever occurs earlier. These subjects will attend the clinical center at 6, 9, and 12 months after study completion post-dose for blood sampling to confirm their immunoglobulin status.

1.3 Schedule of Assessments

Table 1 Schedule of Assessments

Visit	1	2			3 to 12										13	
	Screen	Treatment and in-patient stay			Outpatient visits										Final Follow-up/ Early termination	ADA FU (if required)
Day (time windows are days unless specified otherwise)	-28 to -2	-1	1	2	3	4	8	15 ±1	22 ±1	29 ±1	36 ±1	43 ±2	50 ±2	64 ±3	78 ±3	95 ±4	
Informed consent	X																
Inclusion/exclusion criteria	X	X															
Demographics	X																
Medical history	X	X															
Height and weight[c]	X	X															
Physical examination[a]	X	X	X[b]		X			X		X[c]		X[c]	X[c]	X[c]		X	
Viral serology[d]	X																
Drug, alcohol, and cotinine screen[e]	X	X															
Vital signs	X	X	X[f]	X[g]	X[g]	X	X	X	X[h]	X[h]	X[h]	X	X[h]	X[h]	X[h]	X	
12-lead ECG	X	X	X[i]	X		X		X				X				X	
Clinical laboratory tests[j]	X	X			X	X		X				X		X		X	
Randomization			X														
Drug infusion			X														
Pharmacokinetic blood sampling[k]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ADA/NAb test[l]			X[m]					X	X	X	X	X	X	X	X	X	X
Adverse events and infusion site assessment	X	X														X	X

Visit	1	2				3 to 12										13	
	Screen	Treatment and in-patient stay				Outpatient visits										Final Follow-up/ Early terminatio n	ADA FU (if required)
Day (time windows are days unless specified otherwise)	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**8**	**15 ±1**	**22 ±1**	**29 ±1**	**36 ±1**	**43 ±2**	**50 ±2**	**64 ±3**	**78 ±3**	**95 ±4**	
Concomitant medications	X	X														X	X

ADA = antidrug antibodies; ECG = electrocardiogram; FU = follow-up; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; NAb = neutralizing antibodies; PK = pharmacokinetic

Where time points of clinical assessments and collection of biological samples coincide the order of priority will be:

- Pharmacokinetic samples
- Clinical laboratory samples
- Immunogenicity samples (ADA and NAb)
- Vital signs
- ECG

ECG will be conducted in time intervals of 15 minutes on either side of scheduled time point (ie ± 15 minutes) and vital signs will be collected in time interval of 10 minutes on either side of scheduled time point (ie ± 10 minutes). ECG and vital signs measurements performed outside of this window period will be considered protocol deviations. For PK sample collection, window period as specified in protocol will be followed.

If clinical assessments are required for the immediate safety monitoring of the subject they will take priority over all other sample collection or clinical assessments.

Footnotes:

a Full physical examination will be performed at screening, admission to the study center (Day -1), discharge (Day 3), Day 15, and follow-up (Day 95).

b Infusion site check only.

c Physical examination will be performed if clinically indicated. Height will be measured at screening only.
Body weight will be measured at admission (during the physical examination) as this measurement will be used to calculate the dose to be administered to the subject. Body weight at admission is required for the calculation of the dose to be administered to the subjects. Height will be only assessed at screening.

d Viral serology will include HIV 1 and 2, HBsAg and hepatitis C antibody screening.

e Urine screen for drugs of abuse, alcohol, and cotinine. The screen for alcohol may be performed by a breath test according to local procedures.

f Vital signs on Day 1 will be measured at the following times: pre-dose (within 1 hour prior to the start of the infusion) and 0.5 and 1 hour post start of infusion; 0.25, 0.5, 1, 2, 3, 5, 6, 8, and 12 hours post end of infusion.

g Vital signs are to be measured at 24 and 36 hours post-dose on Day 2 and at 48 hours post-dose on Day 3.

h Blood pressure and pulse rate measurements only.

i 12-lead ECG on Day 1 will be measured at the following times: pre-dose (within 1 hour prior to the start of the infusion) and 0.75 and 1.0 hours post start of infusion; 3 and 12 hours post end of infusion and according to the PK sample schedule below for any other visits. ECG assessments will be obtained after the subject has been in the supine or sitting position for at least 5 minutes.

j Clinical laboratory tests include hematology, clinical chemistry, coagulation and urinalysis (urine microscopy will be performed if clinically indicated) (see Appendix 3). Subjects with a 1+ or greater dipstick reading should undergo further assessment as per the clinical judgement of the Investigator or delegate.

k PK blood samples will be collected as indicated in the Schedule of Pharmacokinetics Assessments (Table 3).

l Subjects who are confirmed positive for anti-bevacizumab antibodies at the follow-up visit (Day 95) or at and early termination visit (subjects who discontinue from the study following drug administration), will be followed up for up to 12 months or until 2 consecutive samples have been confirmed negative for anti-bevacizumab antibodies, whichever occurs earlier. These subjects will attend the clinical center at 6, 9, and 12 months after study completion post-dose for blood sampling to confirm their immunoglobulin status.

m Within 1 hour prior to the start of the infusion.

Table 2 Schedule of Assessments for Day 1

Hours post start of infusion	**Pre[a]**	**0**	**0.5**	**0.75**	**1.0**	**1.5[c]**									
Hours post end of infusion							**0.25**	**0.5**	**1.0**	**2.0**	**3.0**	**5.0**	**6.0**	**8.0**	**12.0**
Randomization	X														
Drug infusion		X----------X													
Vital signs	X		X		X		X	X	X	X	X	X	X	X	X
12-lead ECG	X			X	X						X				X
Pharmacokinetic blood sampling[b]	X			X		X					X		X		X
ADA/NAb test	X														
Adverse events	X----------X														
Concomitant medications	X----------X														

ADA = antidrug antibodies; NAb = neutralizing antibodies

a Within 1 hour prior to the start of the infusion.

b PK blood samples will be collected at pre-infusion (or 0 hour, collected within 1 hour prior to the start of the infusion), 0.75 hours from the start of infusion (± 2 min), the end of infusion (0 hour post end of infusion +≤ 2 min [which is approximately 1.5 hours from the start of infusion]), at 3 hours (± 5 min), 6 hours (± 15 min), and 12 hours (± 15 min) from the end of infusion on Day 1.

c On completion of the infusion.

Table 3 Schedule of Pharmacokinetic Assessments

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

2.0 INTRODUCTION

2.1 Study Rationale

Prestige Biopharma Pte. Ltd is developing HD204, a biosimilar of the European Union (EU)-approved and United States of America (US) US-licensed bevacizumab (Avastin®). Bevacizumab is a recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody that binds to vascular endothelial growth factor (VEGF) extracellularly to prevent interaction with VEGF receptors (VEGFRs). Avastin is licensed for clinical use in the US (US-Avastin®) and the EU (EU-Avastin®) for a variety of tumor types.

The purpose of this study is to compare the pharmacokinetics (PK) of HD204, US-Avastin, and EU-Avastin in healthy male subjects after intravenous (IV) administration of a single dose. As a First-in-Human study, the study will also evaluate the safety, tolerability, and immunogenicity of HD204, US-Avastin, and EU-Avastin in healthy subjects.

2.2 Background

Since initial approval of bevacizumab (Avastin) in the US (2004) and in the EU (2005), for advanced colorectal cancer, bevacizumab has made anti-angiogenic therapy a fundamental pillar of cancer treatment. Avastin is approved in many countries for the treatment of advanced stages of colorectal cancer, metastatic non-squamous non-small cell lung cancer (NSCLC), metastatic renal cell cancer, breast cancer, epithelial ovarian cancer, and glioblastoma (1, 2).

However, the cost of biologic therapies has become increasingly prohibitive which can limit the therapeutic use of the drugs in patients. Moreover, globally, colorectal cancer is the third most common cancer in men and the second most common cancer in women (3). In the US, the National Cancer Institute estimates that 140 250 new cases will be reported in 2018, leading to the estimated deaths of 50 630 patients, or 8.3% of all cancer deaths (4). Overall, solid tumors constitute more than 94.4% and 96.8% of cancer-caused mortalities in males and females, respectively (2).

Angiogenesis is a physiological process in which new blood vessels are formed from pre-existing vessels. It occurs during normal growth and development, as well as during wound healing. Under physiological conditions, angiogenesis is tightly regulated. To date, many pro-angiogenic factors and their cognate receptors have been identified, including VEGF. Tumor angiogenesis is a hallmark of cancer and plays a crucial role in providing oxygen and nutrients to tumor cells during cancer progression and metastasis. Under pathological conditions, many pro-angiogenic factors and their receptors are upregulated; among these factors, VEGF is generally regarded as a key regulator of tumor angiogenesis (1).

Bevacizumab binds to VEGF and thereby inhibits the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. Neutralizing the

biological activity of VEGF regresses the vascularization of tumors, normalizes remaining tumor vasculature, and inhibits the formation of new tumor vasculature, thereby inhibiting tumor growth (5, 6).

HD204 is a biosimilar to Avastin being developed by Prestige Biopharma Pte. Ltd.

Bevacizumab is a monoclonal antibody recombinant humanized immunoglobulin of the human immunoglobulin G subclass 1, kappa light chain (IgG1κ). HD204 is produced in a mammalian cell (Chinese hamster ovary [CHO]) expression system and is subsequently purified and formulated.

Analytical assays have been conducted to compare the purity of multiple lots of HD204 and Avastin. The data indicate that HD204 is at least as pure as Avastin and that the molecular weight and binding affinity are consistent between HD204 and Avastin.

HD204 and Avastin have similar post translational modification in terms of glycan variant distribution, overall galactosylation, fucosylation, and distribution of glycan variants. Charge variant distribution, as measured by ion exchange chromatography, and capillary iso-electric focusing were also similar.

Biological functional assays showed very similar results. Overall, the data have demonstrated that HD204 is highly similar to the reference product, Avastin, in structure and function.

Nonclinical Studies Using HD204

In vitro assessments of antibody functionality (including Fab, Fc, and complement functions) of HD204 have been performed in comparison with Avastin. In addition, in vitro and in vivo pharmacodynamic (PD) studies have been performed in a variety of test systems. Toxicokinetic investigations in the non-human primate were performed in a single dose study and as part of the 4-week and 13-week repeated dose toxicity studies. In addition, the immunogenicity of the antibody was evaluated in the repeated dose toxicity studies. In all of these investigations, HD204 was compared against Avastin sourced in the EU (7).

The in vitro comparative analysis of HD204 and Avastin demonstrated:

- The binding affinities of 3 VEGF isomers ($VEGF_{121}$, $VEGF_{165}$, $VEGF_{189}$), which can bind to bevacizumab, were compared by enzyme-linked immunosorbent assay (ELISA). Relative binding affinity was measured using the in-house reference standard. The antigen binding affinity for HD204 excluding $VEGF_{189}$ was found to be similar to that of the reference drug value.

- The binding affinity of 4 Fc receptors capable of binding to the Fc portion of the antibody was measured by the surface plasmon resonance method. Affinity for FcγRI, FcγRIIa, and FcγRIIIa receptors, which directly affect effector functions such as antibody-dependent cell-mediated cytotoxicity (ADCC), and FcRn receptors which are closely related to blood half-life was measured. A commercially available recombinant protein was used as a receptor for the assay. The analysis showed that the min/max values of the binding affinity measurements of all 4 HD204 samples in all Fc receptors were within the measurement range of the reference drug.
- The binding affinity to C1q, which binds to the hinge region of the antibody and is involved in complement-dependent cytotoxicity (CDC) activity, was measured by ELISA. HD204 and Avastin demonstrated similar binding activity.
- The degree of inhibition of cell activity was measured to confirm antigen binding affinity indirectly. Human umbilical vein endothelial cells (HUVEC) were used and the relative anti-proliferative effect of each sample was measured after $VEGF_{165}$ treatment using the in-house reference standard. The anti-proliferative effect of 2 HD204 clinical samples (BEA-14001, BEA-14002) was within the range of the reference drug. The third sample (HD204 BEA-14003) exceeded the upper limit of the reference drug's range.
- In the A549 lung cancer model, the efficacy of HD204 and the control agent on the size of the tumor when intraperitoneally administered twice weekly was comparable.
- No treatment-related adverse effects were observed in the animals treated with HD204 and Avastin.

Nonclinical Pharmacokinetics and Product Metabolism

The PK profile of HD204 was compared to that of Avastin in Cynomolgus monkeys (male and female), in a single subcutaneous dose study. HD204 and Avastin were administered by subcutaneous injection at a dose of 2 mg/kg. The result indicated comparable systemic clearance (CL) and concentration-time curve from time zero extrapolated to infinity ($AUC_{0\text{-}inf}$) between HD204 and Avastin.

Summary of Clinical Findings of HD204

At the time of preparation of this protocol, HD204 has not been administered to human subjects.

Additional information can be found in the Investigator's Brochure (IB).

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of HD204 may be found in the IB.

The subjects enrolled are not expected to gain any clinical benefit from participation in this clinical study. However, since a healthy subject population is most sensitive to product differences, such a population is expected to show a better response than patients to detect differences in PK profiles.

The safety procedures to be followed during the study have been selected to minimize the risk of harm to the subjects and to ensure the scientific integrity of the data collected during the study. All study treatment administrations will occur under medical supervision in the study center and subjects will remain at the study center for 48 hours following study treatment administration. The lowest dose of 1 mg/kg has been selected for the study to minimize exposure to healthy subjects and it is expected to be well tolerated in healthy subjects.

This study will be performed in compliance with the protocol, the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), European Union Good Manufacturing Practice (EU GMP) and applicable regulatory requirements.

The Sponsor will immediately notify the Principal Investigator if any additional safety or toxicology information becomes available during the study.

3.0 OBJECTIVES AND ENDPOINTS

Table 4 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• The primary objective of the study is to establish pairwise pharmacokinetic (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	• Area under the concentration-time curve (AUC) of the analyte in plasma over the time interval from time 0 (baseline) extrapolated to infinity ($AUC_{0\text{-}inf}$)
Secondary	
• 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	• AUC from time 0 to the last quantifiable data point ($AUC_{0\text{-}last}$), maximum observed plasma concentration (C_{max}), time to maximum observed concentration (t_{max}), terminal half-life ($t_{1/2}$), terminal rate constant (λ_z), systemic clearance (CL), and volume of distribution at steady state (V_{ss}) • Pharmacokinetic equivalence of the EU and the US-Avastin will be evaluated • Immunogenicity will be assessed by the incidence of anti-bevacizumab antibodies (ADA), including neutralizing antibodies (NAb) (if ADA positive) from Day 1 through last subject last visit • Safety and tolerability will be assessed by clinical laboratory tests, vital signs, 12-lead electrocardiograms (ECGs), physical examinations, assessment of adverse events (AE), injection site reactions and concomitant medications

4.0 STUDY DESIGN

4.1 Overall Design

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.

Initially, subjects will be administered the study treatment 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.

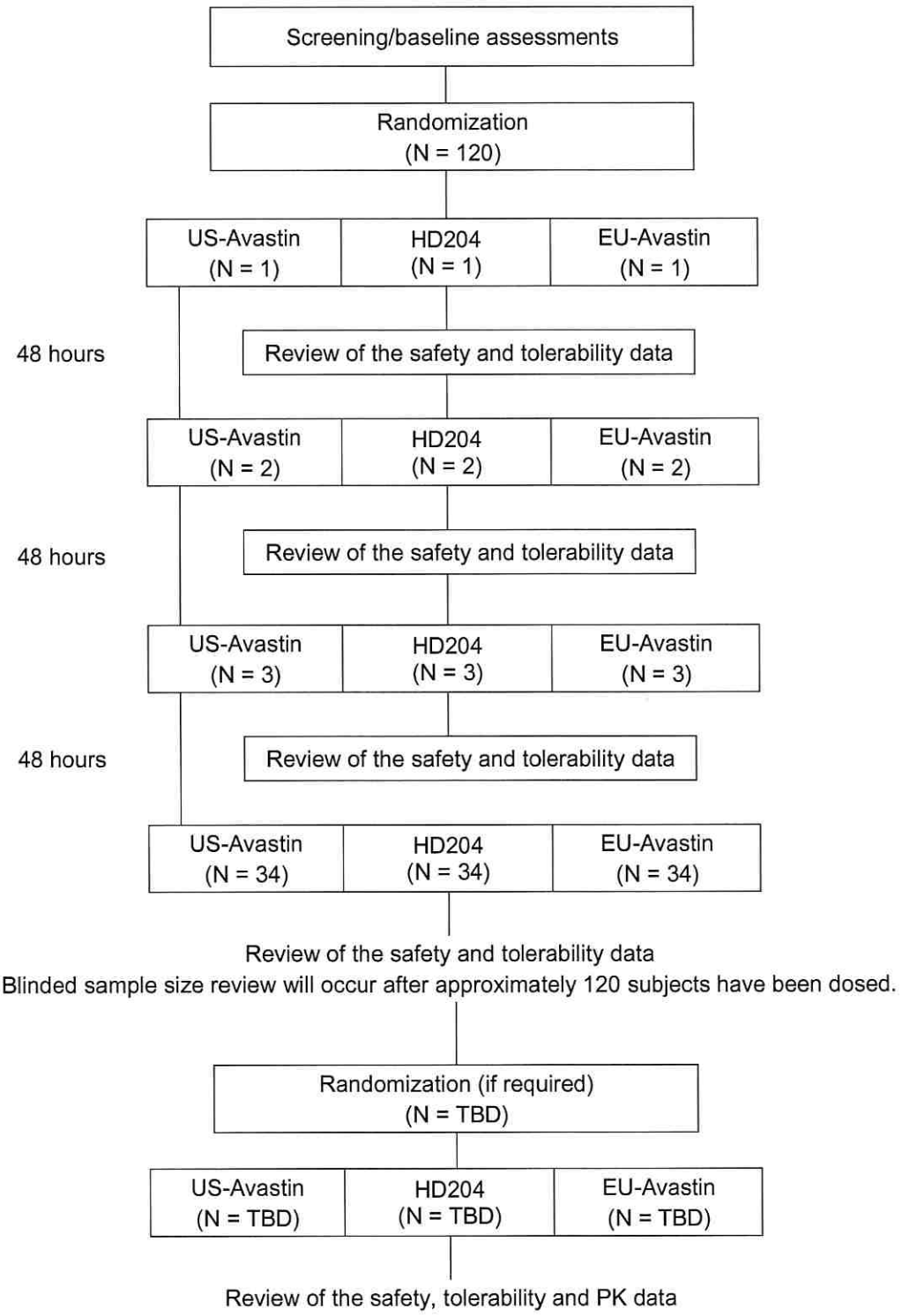
There will be at least 48 hours between administrations of study treatment to each staggered group. Prior to administration of study treatment to the next group, the blinded safety and tolerability findings of the preceding group will be reviewed by the Principal Investigator. The Principal Investigator will consult with the Investigator(s) when subjects have been enrolled over all sites. The next group will be administered study treatment 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 treatment for safety evaluation.

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.

The Study Schema is presented in Figure 1 and a summary of the study design is presented in Figure 2.

The Schedule of Assessments (SoA) for the whole study is described in Table 1, and those for Day 1 in Table 2. The Schedule of Pharmacokinetic Assessments can be found in Table 3.

Figure 2 Study Design



TBD = To be determined

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 (ie, 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 Table 1.

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 treatment (Visit 2) and a 95-day follow-up period (Visits 3 to 13).

Subjects who are confirmed positive for anti-bevacizumab antibodies, including subjects who discontinue from the study following drug administration, will be followed up for up to 12 months. These subjects will attend the study center at 6, 9, and 12 months post-dose for blood sampling to confirm their immunoglobulin status or until 2 consecutive samples have been 'confirmed negative' for anti-bevacizumab antibodies, whichever occurs earlier.

A summary of study visits is presented in the study flow diagram in Figure 1. The start of the study is considered the date of the first subject providing informed consent and the end of the study will be the last subject's last scheduled visit. Additional follow-up visits for subjects who are positive for anti-bevacizumab antibodies or have ongoing/resolving AEs will be conducted and reported separately.

Enrollment of Additional Subjects Following a Blinded 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.

If additional subjects are enrolled the Principal Investigator will decide on the timing and group size for enrollment according to the capability of the study center. The subjects will be 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 and will follow the study timeline and assessments described above.

4.2 Scientific Rationale for Study Design

A parallel group design is the preferred design for this study due to the long half-life (approximately 20 days) of bevacizumab and the potential development of immunogenicity.

The study design is expected to provide sufficient PK, immunogenicity and safety data to meet the study objectives. A healthy subject population was chosen as the recommended approach by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), to allow characterization of PK in the most homogenous population with the lowest variability.

The safety of the subjects will be ensured by means of regular medical supervision and assessment throughout their residential stay at the study center, and periodic health assessments thereafter throughout the study.

Additionally, as a safety measure, subjects will be administered the study treatment in separate staggered groups starting with a sentinel group of 3 subjects (1 subject per treatment). The second group will comprise 6 subjects and the third group 9 subjects. After the first 3 groups have been evaluated, the SRC will decide whether to proceed with continuous enrollment according to the study center's capability.

4.3 Justification for Dose

The PK of bevacizumab is independent of dose between 1 and 10 mg/kg, so the lowest possible dose is chosen for administration to healthy subjects in this study.

4.4 End of Study Definition

A subject is considered to have completed the study if he/she has completed all phases of the study including the last visit.

The end of the study is defined as the date of the last visit of the last subject in the study.

4.5 Dose Escalation Criteria

Not applicable.

4.6 Study Stopping Criteria

4.6.1 Stopping Criteria for Individual Subjects

The infusion will be stopped at any time if the subject experiences a severe infusion reaction (Table 6) or a serious adverse event (SAE) during the infusion period. The subject will be followed up until resolution of the SAE and then withdrawn from the study.

4.6.2 Criteria for Stopping the Study

The study may be stopped if any of the following occur:

- ≥ 1 subject experiences SAEs considered to have a reasonable possibility of relationship to the study treatment.
- ≥ 1 subject experiences a drop in absolute neutrophil count to below 1.0×10^9/L on repeat measurement and for which there is no other likely cause.
- ≥ 1 subject experiences a drop in platelet count to below 100×10^9/L.
- ≥ 2 subjects experience non-tolerable AEs that are considered to have a reasonable possibility of relationship to the study treatment.
- ≥ 2 subjects who receive study treatment have a QTc prolongation defined as QTcF > 500 ms, or an increase of QTcF > 60 ms above baseline on the 12-lead ECG, confirmed (persistent for > 5 minutes) on repeated 12-lead ECGs.
- ≥ 1 subject who receives study treatment fulfils Hy's law, defined as an increase in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 × the upper limit of normal (ULN) and total bilirubin ≥ 2 × ULN, where no other reason can be found to explain the combination of increases.
- ≥ 2 subjects have > 3 × ULN of either ALT, AST, bilirubin, or alkaline phosphatase (ALP)
- The occurrence of significant safety events (as judged by the Investigator) other than those described above that in the opinion of the Principal Investigator requires evaluation before any further subjects are dosed.

5.0 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

1. Adult healthy male subjects aged 18 to 50 years (inclusive) and body mass index 18.0 to 30.0 kg/m^2 (inclusive) and body weight ≥ 60 kg to ≤ 100 kg.
2. Subjects who are healthy as determined by pre-study medical history, physical examination, vital signs, and 12-lead ECG at screening and admission on Day -1.
3. Subjects whose clinical laboratory test results are normal, or where outside the reference range is judged as not clinically relevant by the Investigator.
4. Have systolic blood pressure ≥ 90 and ≤ 140 mmHg, diastolic blood pressure ≥ 50 and ≤ 90 mmHg and heart rate ≥ 40 and ≤ 90 bpm at screening and admission on Day -1. For single measurements in the 141 to 160 mmHg range (systolic) or in the 91 to 100 mmHg range (diastolic), a single repetition on the same day is allowed and, in this case, the mean of both measurements will guide eligibility. The mean of both the measurements should be ≤ 140 mmHg (systolic) and ≤ 90 mmHg (diastolic).
5. Have physical examination results without clinically relevant findings at screening and admission on Day -1.
6. Have 12-lead ECG results without clinically relevant findings at screening and admission on Day -1.
7. Subjects who are non-smokers and have not regularly used tobacco or nicotine containing products for at least 3 months prior to screening and have a < 10 pack year smoking history.
8. Males must be willing to use a medically acceptable method of contraception from the time of the administration of study treatment, throughout the study and for a period of 6 months after the administration of the study treatment (see Appendix 5). This requirement may be waived if the Principal Investigator or delegate is satisfied that the subject or subject's female partner is sterile ie, if female has undergone a hysterectomy or tubal ligation at least 3 months prior to screening or is postmenopausal (defined as no menses for 12 months without an alternative medical cause) or if the subject has undergone a vasectomy at least 6 months prior to screening.
9. Must agree not to donate sperm for at least 6 months after the administration of study treatment.
10. Must be willing and able to comply with scheduled visits, laboratory tests, and other study procedures.

11. Must be able to provide informed consent which must be obtained prior to any study-related procedures.
12. Subjects who are willing to comply with the study restrictions, and comply with the scheduled visits from screening and throughout the study.

5.2 Exclusion Criteria

1. Have a history of hypersensitivity or allergic reactions (either spontaneous or following drug administration) to bevacizumab or VEGF targeted treatment or to any other excipients.
2. Have a history of or presence of current clinically significant gastrointestinal (including diverticulitis, stomach ulcers, inflammatory intestinal disease, gastrointestinal perforations/fistulae/intra-abdominal abscess), any other internal, non-gastrointestinal fistulae that is at an increased risk of bleeding, renal, hepatic, cardiovascular, hematological (including pancytopenia, aplastic anemia or blood dyscrasia), pulmonary, neurologic, metabolic (including known diabetes mellitus), psychiatric or allergic disease excluding mild asymptomatic seasonal allergies.
3. Have a history of and/or current cardiac disease defined as one of the following:
    - History of congestive heart failure;
    - Angina pectoris requiring antianginal medication;
    - Evidence of transmural infarction on ECG;
    - History of sustained hypertension (systolic > 180 mmHg and/or diastolic > 100 mmHg) or hypertensive crisis or hypertensive encephalopathy;
    - Clinically significant valvular heart disease; or
    - Severe arterial thromboembolic events.
4. Have a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus, or human immunodeficiency virus (HIV) I and II at screening.
5. Have any history of malignancy including lymphoma, leukemia, and skin cancer (even resected basal cell carcinoma or squamous cell carcinoma).
6. Have an illness within 30 days prior to screening, or prior to Day -1, that is considered as clinically significant by the Investigator.
7. Prior exposure to any investigational monoclonal antibody within 12 months of Day -1. Prior investigational exposure to Avastin > 12 month is acceptable.
8. Any clinically significant infection, in the opinion of the Investigator, ongoing at screening or admission on Day -1.

9. Have had major surgery within 3 months prior to screening, or will have an operation between screening and the end of study visit, or still has an unhealed wound, including wound dehiscence and wound healing complications requiring medical intervention.
10. Have received live vaccine(s) within 3 months prior to screening or will require a live vaccine(s) between screening and the end of study visit.
11. Have an intake of alcoholic beverages of more than 14 units per week (1 unit = 250 mL of beer, 25 mL of spirits or 1 glass [125 mL] of wine).
12. Have reasonable evidence (in the opinion of the Investigator) of drug abuse as indicated by a positive urinary drug test at screening or admission on Day -1.
13. Have taken medication with a half-life of > 24 hours within 30 days or less than 10 half-lives of the medication prior to Day -1 as determined by the Investigator.
14. Have donated blood and blood products within 3 months prior to Day -1. Blood donation and blood products are not permitted throughout study.
15. Have participated in another clinical study of an investigational drug within 90 days or 5 half-lives of the investigational drug (whichever is longer) prior to Day -1, or are currently participating in another clinical study of an investigational drug, or intending to participate in another clinical study of an investigational drug before completion of all scheduled evaluations in this clinical study.
16. Subjects who, in the opinion of the Investigator, are not likely to complete the study for whatever reason.
17. The Investigator or any sub-investigator, research assistant, pharmacist, study coordinator, other staff directly involved in the conduct of the clinical study or any of their immediate family members (parents, siblings or spouses).
18. Abnormal or irregular bowel movements eg, less than 1 bowel movement every 3 days.
19. Any history of non-traumatic hemorrhage (ie, any hemorrhage requiring medical intervention) or any condition which may increase bleeding risk including clotting disorders, thrombocytopenia (platelet count < 150, 000 per μL) or an international normalized ratio higher than 1.5 at screening.
20. Impaired liver function as determined by:
    - Serum ALT and/or AST > 1.5 × ULN at screening or admission. Subjects with values between ULN and 1.5 × ULN may be included in the study if considered not clinically significant by the Investigator.
21. Any intake of a non-steroidal anti-inflammatory drug (NSAID) including any dose of aspirin in the 30 days before Day -1 (NSAIDs are not allowed for the duration of the study).

22. Intake of herbal drugs or dietary supplements excluding routine vitamins but including megadose (intake of 20 to 600 times the recommended daily dose) vitamin therapy within 30 days prior to Day -1, unless agreed as not clinically relevant by the Investigator and Sponsor.
23. Strenuous exercise or activity within 96 hours prior to admission on Day -1 and has a creatinine kinase value > 2.5 × ULN.
24. Subjects with unsuitable veins for infusion or venipuncture.
25. Subjects with a non-healing wound or hematoma of a clinically relevant size as assessed by the Investigator, or a clinically significant current fracture.
26. Presence of proteinuria (other than trace amounts ie, +, ++/+++) at screening or admission on Day -1.
27. Known personal or family history of venous thromboembolic events or idiopathic venous thromboembolic events in first degree relatives.
28. Inability to refrain from contact or collision sport until Day 30.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

1. Study treatment administration will occur on Day 1 after a fast of at least 8 hours. Water will be permitted as required. The study treatment will be administered intravenously to the subjects in bed in the semi-supine position. Subjects will remain fasting until 1 hour following completion of the study treatment infusion after which a meal will be served on completion of the scheduled assessments.
2. Subjects will receive a standard diet while resident in the study center and will only consume food and beverages provided by the study center.
3. Subjects will refrain from consumption of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, and Seville orange juice or other products containing grapefruit or Seville oranges from 30 days prior to admission on Day -1 and for the duration of the residential period.
4. Subjects should refrain from consumption of any foods containing poppy seeds within 48 hours prior to screening and admission to the study center on Day -1.

5.3.2 Caffeine, Alcohol, and Tobacco

1. Subjects should refrain from smoking for the duration of the study (through Day 95).
2. Subjects should refrain from alcoholic beverages from 48 hours prior to Day 1 until discharge on Day 3 and for 24 hours prior to each outpatient visit; at other times alcohol intake should be limited to ≤ 2 units per day (1 unit = 250 mL of beer, 25 mL of spirits or 1 glass [125 mL] of wine).
3. Subjects should refrain from taking drugs of abuse during the study (up to the final follow-up visit).

5.3.3 Activity

1. Subjects should refrain from strenuous exercise or activity from admission on Day -1 until Day 10 of the study. Subjects should not participate in contact/collision sports until Day 30.
2. Subjects should adhere to study requirements for contraceptives.
3. Subjects should adhere to the concomitant medication restrictions.
4. Subjects should refrain from blood or blood product donation for the duration of the study (through Day 95).

5.3.4 Avoidance of Pregnancy

1. Female subjects will not be enrolled on this clinical study.
2. The use of contraception will not be required if the female partner of the subject has undergone a hysterectomy or tubal ligation at least 3 months prior to screening or is postmenopausal (defined as no menses for 12 months without an alternative medical cause).
3. As a precaution, all male subjects should avoid fathering a child by either true abstinence or, in conjunction with their partner (if the partner is of childbearing potential), the use of 2 acceptable means of contraception from the time of the administration of the study treatment, throughout the study and for a period of 6 months after the administration of the study treatment (see details in Appendix 5).

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomly assigned to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

5.4.1 Repetition of Screening Assessment(s)

Repetition of a screening assessment would be allowed if there is evidence of a laboratory error or if there is reason to believe that the result is not an accurate reflection of the subject's clinical status. One repeat test will be permitted to re-assess a subject's eligibility. The Investigator is encouraged to discuss or seek advice with the Medical Monitor if needed.

5.4.2 Rescreening of Subject(s)

Subjects may only be rescreened with the approval of the Medical Monitor in case a permanent change has occurred in eligibility criteria (medical status or laboratory findings) that previously led to screen failure. If a subject is rescreened, all screening assessments will be repeated.

6.0 STUDY TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a subject according to the study protocol.

6.1 Study Treatment(s) Administered

Table 5 Study Treatment Details

Study Treatment Name	HD204 (bevacizumab)	EU-Avastin (bevacizumab)	US-Avastin (bevacizumab)
Dosage Formulation	Sterile solution	Sterile solution	Sterile solution
Unit Dose Strength(s)/Dosage Level(s)	100 mg/4 mL, a single dose of 1 mg/kg will be administered	100 mg/4 mL, a single dose of 1 mg/kg will be administered	100 mg/4 mL, a single dose of 1 mg/kg will be administered
Route of Administration	IV infusion	IV infusion	IV infusion
Dosing Instructions	Individual subject treatments will be dispensed by the unblinded pharmacist in IV infusion bags, diluted with 0.9% sodium chloride. Subjects will receive a single administration 90-minute IV infusion. All dose administrations will be performed in the study center under the supervision of appropriately trained staff.	Individual subject treatments will be dispensed by the unblinded pharmacist in IV infusion bags, diluted with 0.9% sodium chloride. Subjects will receive a single administration 90-minute IV infusion. All dose administrations will be performed in the study center under the supervision of appropriately trained staff.	Individual subject treatments will be dispensed by the unblinded pharmacist in IV infusion bags, diluted with 0.9% sodium chloride. Subjects will receive a single administration 90-minute IV infusion. All dose administrations will be performed in the study center under the supervision of appropriately trained staff.
Packaging and Labeling	Study treatment will be provided in glass vials. Each vial will be labeled as required per country requirement.	Study treatment will be provided in glass vials. Each vial will be labeled as required per country requirement.	Study treatment will be provided in glass vials. Each vial will be labeled as required per country requirement.
Manufacturer	Prestige Biopharma Pte. Ltd	Roche	Genetech
First-in-Human	For the purpose of the first human dose study, drug product will be prepared at the study center, diluted to the required volume using 0.9% sodium chloride solution.	For the purpose of the first human dose study, drug product will be prepared at the study center, diluted to the required volume using 0.9% sodium chloride solution.	For the purpose of the first human dose study, drug product will be prepared at the study center, diluted to the required volume using 0.9% sodium chloride solution.

EU: European Union; IV: intravenously; US: Unites States

6.2 Preparation/Handling/Storage/Accountability

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only subjects enrolled in the study may receive study treatment and only authorized study center staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study center staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual.

The Investigator, a member of the study center staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study medication using the Drug Accountability Form. These forms must be available for inspection at any time.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Method of Assigning Subjects to Treatment Groups

At screening, potential study subjects will be assigned a screening number. Following confirmation of eligibility, prior to study treatment administration, subjects will be assigned a subject number in the order in which they are enrolled in the study.

6.3.2 Randomization Procedures

The randomization list will be generated using a validated system by an unblinded statistician who will not be involved in the analysis of the study data before unblinding. The unblinded statistician will provide the independent pharmacist of the study center with the subject randomization.

Subjects will be randomly assigned to one of the study treatments in a 1:1:1 ratio. The subject number will determine the allocation of treatment, per the randomization schedule with the subject numbers starting with X001, where 'X' would be the study center number.

6.3.3 Maintenance of Randomization Codes

Randomization codes will be provided to the independent pharmacist, and an unblinded Medical Monitor as a list. Individual treatment disclosure envelopes (code break) will be kept by the independent pharmacist at the study center and the Investigator will be able to access these during the study if required for safety reasons. The independent pharmacist will use the

randomization code list for preparing subject doses throughout the study. The individual disclosure envelopes will be used if it is necessary to break the blind for an individual subject.

The unblinded/independent study center pharmacist (or an appropriately qualified designee) will be responsible for preparation of the blinded study treatment infusion bags for each subject according to the instructions in the Pharmacy Manual.

6.3.4 Unblinding

Unblinding can only take place for the purpose of managing an SAE if deemed necessary by the Investigator. If the code for a subject is broken, the Investigator must withdraw the subject from the study, document the details of the event and the reason for unblinding in the subject's case report form (CRF) and promptly inform the Sponsor's study physician/Medical Monitor and the Ethics Committee. Additionally, the Sponsor and/or designee may be required to unblind the subject if the AE meets criteria of a suspected unexpected serious adverse reaction (SUSAR) in order to fulfil expedited regulatory reporting requirements.

After completion of the study, all code break envelopes will be returned to the Sponsor or a delegate.

6.4 Study Treatment Compliance

The prescribed dose, timing, and mode of administration may not be changed. Any departures from the intended regimen must be recorded in the CRF.

All dose administrations will be performed in the study center under the supervision of appropriately trained staff.

6.4.1 Treatment Measures to Ensure Subject Safety

The clinical staff is responsible for the ongoing safety and wellbeing of the subjects in this First-in-Human study while they are in the study center. There is a paging system to alert the clinical staff to any area in the center where a subject may need medical attention. In the case of an emergency, cardiac resuscitation trolleys are found in the main ward areas of the study center. These trolleys contain drugs, equipment for airway insertion, circulation lines, defibrillation etc, together with oxygen cylinders and portable suction machines. There is a physician on site 24 hours a day. In addition, if necessary the clinical staff can contact further on-call physicians or public emergencies services in the event of a serious medical event. Equipment and emergency drugs are available to treat common medical emergencies that might occur in a Phase 1 study.

6.4.2 Warnings and Precautions

As this is the first administration of HD204 to man, all effects cannot be reliably predicted. The preclinical data suggest an acceptable safety margin. Facilities and staff for resuscitation and the treatment of other medical emergencies will be provided.

6.5 Concomitant Therapy

Subjects are not allowed to take the following medications except for management of AEs as advised by the Principal Investigator:

- Any prescription or over-the-counter medication with a half-life of > 24 hours within 30 days or less than 10 half-lives of the medication prior to Day 1 and for the duration of the study (except paracetamol as detailed below)
- Any herbal remedies or dietary supplements within 30 days prior to Day 1 and for the duration of the study, unless agreed as not clinically relevant by the Investigator and Sponsor
- Any NSAIDs (including aspirin) within 30 days prior to Day 1 and for the duration of the study
- Any live virus vaccination within 30 days before screening and during study participation until the final follow-up visit

In the interests of subject safety and acceptable standards of medical care the Investigator will be permitted to prescribe treatment(s) at his/her discretion. All treatments must be recorded in the subjects' CRF (medication, dose, treatment duration and indication).

Paracetamol, up to 2 g per day, will be allowed.

6.6 Dose Modification

Dose modifications are not planned or allowed in this study.

6.7 Treatment After the End of the Study

The Sponsor will not provide any additional care to subjects after they leave the study.

7.0 DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

The infusion will be stopped at any time if the subject experiences a severe infusion reaction (Table 6) or a SAE during the infusion period. The subject will be followed up until resolution of the SAE and then withdrawn from the study.

If a subject who does not meet enrollment criteria is inadvertently enrolled, that subject must be discontinued from study treatment and the Sponsor or Sponsor designee must be contacted. An exception may be granted in rare circumstances for which there is a compelling safety reason to allow the subject to continue. In these rare cases, the Investigator must obtain documented approval from the Sponsor or Sponsor designee to allow the subject to continue in the study.

Subjects who discontinue study treatment will not be replaced.

7.2 Subject Discontinuation/Withdrawal from the Study

- A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the study center study records.
- See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. Should a subject request or decide to withdraw from the study, all efforts must be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. Subjects withdrawing due to an AE should be followed up according to the follow-up visit.
- Subjects who voluntarily withdraw are termed dropouts. Dropouts and subjects withdrawn due to protocol violations may be replaced following discussion with the Principal Investigator and Sponsor.
- Subjects withdrawn due to an AE will not be replaced.

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study center.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The study center must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

8.0 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (see Section 1.3).

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor and SRC upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

The number of samples collected and the volume required for each analysis may be changed during the study (eg, if additional samples are collected for repeat or additional safety assessments at the request of the Investigator).

The total volume of blood to be collected per subject during the study will not exceed 400 mL.

8.1 Efficacy Assessments

Not applicable.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (see Section 1.3).

8.2.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Any clinically significant changes from admission will be recorded as treatment-emergent AEs (TEAEs).

8.2.2 Local Infusion Site Reactions

Infusion site evaluations will be made by clinical staff during the administration of the infusion and during Day 1 as described below; if an infusion site reaction is observed, a physician will characterize and document the reaction as an AE. Review of the infusion site will continue until the AE is resolved.

If infusion site reactions are observed after Day 1 the same grading system may be used and the site reaction recorded as an AE and review of the infusion site will continue until the AE is resolved.

The infusion sites will be monitored for pain, tenderness, erythema and swelling. Each infusion site reaction will be categorized using the intensity grading scheme presented in Table 6; the intensity of each resulting AE will be categorized (eg, a moderate intensity infusion site reaction may be recorded as a mild AE if considered appropriate according to the Investigator's judgement).

Table 6 Infusion Site Reaction Grading Scheme

	Intensity Grading				
Reaction	**Absent (0)**	**Mild [a] (1)**	**Moderate [a] (2)**	**Severe [a] (3)**	**Potentially Life-threatening (4)**
Pain	Absent	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Hospital visit (A and E) or hospitalization
Tenderness	Absent	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Hospital visit (A and E) or hospitalization
Erythema/ redness	Absent	2.5 to 5.0 cm	5.1 to 10.0 cm	> 10.0 cm	Necrosis or exfoliative dermatitis
Induration/ swelling	Absent	2.5 to 5.0 cm and does not interfere with activity	5.1 to 10.0 cm or interferes with activity	> 10.0 cm or prevents daily activity	Necrosis
Other [b]	Absent		Present		

A and E = accident and emergency department; AE = adverse event.

[a] Measurements refer to the reaction at the greatest single diameter.

[b] Any other reactions such as bruising, itching or ulceration will be recorded as absent or present and will be recorded as AEs; AEs will be categorized according to the Investigator's judgement.

Reference:

http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm074775.htm

8.2.3 Immunogenicity

Blood samples for analysis of the incidence and titer of antibodies to bevacizumab and the incidence of any NAbs in serum will be collected as indicated in the SoA (see Section 1.3).

Subjects who are confirmed positive for anti-bevacizumab antibodies at the follow-up visit (Day 95) or at an early termination visit (subjects who discontinue from the study following drug administration), will be followed up for up to 12 months or until 2 consecutive samples have been confirmed negative for anti-bevacizumab antibodies, whichever occurs earlier. These subjects will attend the study center at 6, 9, and 12 months after study completion post-dose for blood sampling to confirm their immunoglobulin status.

Blood sample processing and handling details will be presented in a separate Laboratory Manual.

8.2.4 Vital Signs

Aural temperature, pulse rate, blood pressure, and respiratory rate will be assessed.

Blood pressure and pulse measurements will be assessed in the semi-supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (eg, television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the CRF.

8.2.5 Electrocardiograms

A single 12-lead ECG will be obtained at time points indicated in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

ECG assessments will be obtained after the subject has been in the supine or sitting position for at least 5 minutes.

The ECGs will be reviewed by the Investigator, or a designee, to assess for any abnormalities. Refer to Section 4.6.2 for QTcF-related stopping criteria and any additional QTcF readings that may be necessary.

8.2.6 Clinical Safety Laboratory Assessments

See Appendix 3 for the list of clinical laboratory tests to be performed and to the SoA (see Section 1.3) for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the subject's health status, unless judged by the Investigator to be more severe than expected for the subject's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 3, must be conducted in accordance with the Laboratory Manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.3 Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the subject to discontinue the study (see Section 7.0).

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 1.3).

All AEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

8.3.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences. All study assessments results (eg, laboratory tests, vital signs, ECGs, etc) will be reviewed by the Investigator for determination of AE occurrence.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 4.

8.3.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of all pregnancies in female partners of male subjects will be collected after the start of study treatment and until 6 months after the last dose.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Adverse Events of Special Interest

Not applicable.

8.4 Treatment of Overdose

For this study, any dose of study treatment greater than 1 mg/kg within a 24-hour time period will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the subject for any AE/SAE and laboratory abnormalities until study treatment can no longer be detected systemically.
3. Obtain a plasma sample for PK analysis within 1 day from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

8.5 Pharmacokinetics

8.5.1 Collection of Samples

Venous blood samples of approximately 2.5 mL will be collected for measurement of serum concentrations of bevacizumab at times as specified in the SoA. Instructions for the collection and handling of biological samples will be provided by the Sponsor. Blood samples will be taken either by direct venipuncture or an indwelling cannula inserted in a forearm vein. Blood samples for PK will not be collected from the arm used for the IV infusion for at least 24 hours after administration. The actual date and time (24-hour clock time) of each sample will be recorded in the CRF. The time and date of study treatment administration including infusion start and stop

times and any infusion interruptions will also be recorded in the CRF. Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

Pre-dose samples may be collected within 1 hour of dose administration. The post-dose sample windows are specified in the SoA (see Section 1.3).

8.5.2 Determination of Drug Concentration

Samples for the determination of bevacizumab in serum will be analyzed on behalf of CPR Pharma using appropriate validated bioanalytical methods. Full details of the bioanalytical methods will be described in a separate Bioanalytical Report.

All samples still within the known stability of the analyte of interest at the time of receipt by the bioanalytical laboratory will be analyzed.

Remaining serum samples may be subjected to further analysis by the Sponsor or designee for the purpose of the development of additional bioanalytical assays and/or to investigate the presence of analytes of interest. Samples collected for analyses of bevacizumab serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained. At visits during which serum samples for the determination of biosimilarity of HD204 will be taken, 1 sample of sufficient volume can be used.

8.5.3 Derivation of Pharmacokinetic Parameters

Pharmacokinetic parameters will be derived using noncompartmental methods with Phoenix® WinNonlin® Version 6.4 or higher (Certara, L.P. Princeton, New Jersey, US) and/or SAS® Version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina, US). Actual elapsed time from dosing will be used for the final serum PK parameter calculations. In cases where the actual sampling time is missing, calculations will be performed using the scheduled time. Otherwise, there will be no further imputation of missing data. Interim PK analyses will be performed by using scheduled time post-dose for all calculations.

Serum Pharmacokinetic Parameters

The PK parameters in Table 7 will be determined for bevacizumab when possible. A minimum of 3 quantifiable post-dose concentrations will be required for all calculations.

Table 7 Serum Pharmacokinetic Parameters

Primary Pharmacokinetic Parameter	**Definition**
$AUC_{0\text{-}inf}$	Area under the concentration-time curve from time 0 extrapolated to infinity
Secondary Pharmacokinetic Parameters	**Definition**
$AUC_{0\text{-}last}$	Area under the concentration-time curve from time 0 to the last quantifiable data point
C_{max}	Maximum observed concentration
t_{max}	Time to maximum observed concentration
$t_{½}$	Terminal half-life
λ_z	Terminal rate constant
V_{ss}	Volume of distribution at steady state
CL	Systemic clearance

The calculation of AUCs will be performed using the mixed log-linear trapezoidal method (linear up/log down). The pre-dose samples will be considered as if they had been taken immediately before the administration. Concentrations below the lower limit of quantification (BLQ) will be taken as zero for calculating the AUC of single dose profiles. The PK parameters will be evaluated and listed for all subjects who provide sufficient concentration-time data.

Other parameters may be added as appropriate. Final PK parameters reported will be detailed in the Statistical Analysis Plan (SAP).

8.6 Pharmacodynamics

Pharmacodynamics are not evaluated in this study.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary statistical null hypothesis is that $AUC_{0\text{-}inf}$ is not equivalent between HD204 and the reference products within 80% to 125% limits, against the alternative that HD204 is equivalent to the reference products.

9.2 Sample Size Determination

Based on historical data, an inter-subject variability of 25% and a proportion of 20% of non-PK evaluable subjects have been assumed for sample size determination. Assuming an inter-subject geometric coefficient of variation (CV) of 25% and a geometric mean ratio of 1.05, 40 evaluable subjects per arm are required for the 2-sided 90% confidence interval (CI) of the geometric mean ratio being completely contained within 80% to 125% with 80% overall power and at least 90% power for each pairwise comparison (HD204 versus EU-Avastin, HD204 versus US-Avastin, and EU-Avastin versus US-Avastin). To allow for a proportion of 20% non-PK evaluable subjects, 150 subjects (50 subjects per arm) are planned to be enrolled.

9.3 Populations for Analyses

For purposes of analysis, the analysis sets are defined in Table 8.

Table 8 Analysis Sets

Analysis Set	Description
Pharmacokinetic Concentration (PKC) Population	The PKC population includes subjects with at least 1 valid post-dose concentration and includes all subjects who have received 1 dose of study treatment and completed the study assessments without major protocol violations which may significantly affect the pharmacokinetic (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 will be summarized based on the PKC population. Serum bevacizumab concentrations will be listed and summarized using descriptive statistics in tables and graphs, as appropriate.
Pharmacokinetic Parameter (PKP) Population	The PKP population is a subpopulation of the PKC population, which includes all subjects in 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 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.
PK Non-Neutralizing (PKNN) Population	The PKNN population will include those members of the PKP population without sustained neutralizing antidrug antibodies (ADAs). Sustained neutralizing antibodies occur when a patient has 2 consecutive visits with neutralizing antibodies. Pharmacokinetic analyses will be repeated on the PKNN population to assess robustness of results.

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

9.4 Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the subject analysis sets to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1 Primary Endpoint

The primary PK parameter for assessment of PK equivalence is $AUC_{0\text{-inf}}$.

9.4.2 Secondary Endpoints

The secondary PK parameters are: $AUC_{0\text{-last}}$, C_{max}, t_{max}, $t_{½}$, λ_z, V_{ss} and CL. In addition, the PK similarity of the EU and the US-Avastin will be evaluated to provide the bridging data justifying the use of a single reference product in further comparative clinical studies in patient populations.

Immunogenicity will be assessed by the incidence of anti-bevacizumab antibodies, including NAbs from Day 1 through last subject last visit. NAbs will only be assessed in those subjects in whom positive ADA antibodies are detected.

The safety and tolerability will be assessed by clinical laboratory tests, vital signs, 12-lead ECGs, physical examinations, assessment of AEs, injection site reactions, and concomitant medications.

9.4.3 Pharmacokinetic/Pharmacodynamic Analyses

9.4.3.1 Serum Bevacizumab Concentration Data

All analyses of PK endpoints will be performed using the PKP population. A subject listing of all concentration-time data for each treatment will be presented.

Concentration data of bevacizumab will be summarized by treatment and nominal time point using appropriate descriptive statistics.

9.4.3.2 Analysis of Primary Pharmacokinetic Endpoint

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. Covariates may be included in the models, to be specified in the SAP.

9.4.3.3 Analysis of Secondary Pharmacokinetic Endpoints

The $AUC_{0\text{-last}}$ as a secondary parameter may also be tested for PK similarity as described above.

All PK parameters will be summarized by treatment using N, n, mean, standard deviation (SD), %CV, minimum, median, maximum, geometric mean, and geometric %CV defined as

$$100 \cdot \sqrt{(\exp(s^2)-1)}$$

where s is the SD of the data on a log scale, except that t_{max} will be reported with n, minimum, median, and maximum only.

Graphs may be added at the discretion of the PK scientist, as appropriate, and will be described in detail in the SAP.

9.4.4 Safety Analyses

All safety analyses will be based on the SA population. No statistical tests will be performed for the safety data.

Safety data including laboratory assessments, vital signs, and ECG parameters will be summarized by treatment and/or time point using descriptive statistics for observed values and change from baseline values (as appropriate).

Adverse events will be tabulated and summarized according to the current version of MedDRA.

For the laboratory data, vital signs and ECGs, out of range values will be flagged in the data listings and a list of clinically significantly abnormal values will be presented as appropriate.

Physical examination will be presented in listing only.

Concomitant medications will be presented in listings.

9.4.5 Immunogenicity

The proportion of subjects with ADA, with NAb and the corresponding titers will be summarized using descriptive statistics for the Safety Analysis Population by visit for each parameter and presented in listings.

9.4.6 Missing Data

Data from subjects who withdraw from the study, including AEs and any follow-up, will be included in the analyses of primary and secondary outcomes. Missing safety data will not be imputed. PK concentrations may be imputed for the derivation of PK parameters, to be defined in the SAP.

9.5 Interim Analyses

After approximately 20 subjects per treatment arm have been observed for a minimum of 20 days, an interim safety report will be generated and approved by the Sponsor. The interim safety report will be generated using data that is source verified by the Clinical Research Assistant, including blinded safety laboratory, AE, and ECG data accumulated to that point (Day 20 of the Study). The review of the interim report will be performed by the SRC. Details regarding the review process will be available in the relevant SRC charter. This evaluation will allow a preliminary assessment of safety findings with a time to onset longer than 24 hours.

The SAP will describe the planned interim analyses in greater detail.

9.5.1 Blinded Sample Size Re-evaluation

Due to the uncertainty in the actual variability and trying to limit the study size to those strictly needed, a BSSR will be performed after approximately 120 evaluable subjects (40 subjects per arm) have completed the study. This number of subjects is expected to provide a sufficiently precise calculation of the variability in the actual study population (8). The BSSR will aim to provide at least 90% power for each of the pairwise comparisons and approximately 80% overall power, as specified in the sample size determination.

The BSSR will estimate the geometric CV in the primary endpoint, ignoring any potential differences due to treatment. If the geometric CV is greater than 25%, the number of randomized subject 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.

At the time of the BSSR, the study recruitment will be stopped until the BSSR results become available.

If additional subjects are enrolled the Principal Investigator will decide on the timing and group size for enrollment according to the capability of the study center.

9.6 Safety Review Committee

After the safety and tolerability data from the first 3 groups are available, a 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.

Further details will be available in the SRC charter.

10.0 REFERENCES

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11.0 APPENDICES

Appendix 1 Abbreviations

Abbreviation	Definition
AE	Adverse event
ADA	Antidrug antibodies
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-inf}}$	Area under the plasma concentration-time curve from time zero extrapolated to infinity, calculated by linear up/log down trapezoidal summation
$AUC_{0\text{-last}}$	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration, calculated by linear up/log down trapezoidal summation
BSSR	Blinded sample size re-evaluation
CI	Confidence interval
CL	Systemic clearance
C_{max}	Maximum observed plasma concentration
CRF	Case report form
CV	Coefficient of variation
ECG	Electrocardiogram
EU	European Union
EU GMP	European Union Good Manufacturing Practice
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous(ly)
λ_z	Lambda z; terminal rate constant
NAb	Neutralizing antibody
NSAID	Non-steroidal anti-inflammatory drug
PD	Pharmacodynamic(s)

Abbreviation	Definition
PK	Pharmacokinetic(s)
PKC Population	Pharmacokinetic Concentration Population
PKNN Population	Pharmacokinetic Non-Neutralizing Population
PKP Population	Pharmacokinetic Parameter Population
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SoA	Schedule of Assessments
SRC	Safety Review Committee
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Terminal half-life
t_{max}	Time to C_{max}
ULN	Upper limit of normal
US	United States (of America)
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
V_{ss}	Volume of distribution at steady state
WOCBP	Woman of childbearing potential

Appendix 2 Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable ICH GCP Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and regulatory authority approval, when applicable, before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to subjects.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the study center and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative (Appendix 6). The study will not start at any study center at which the Investigator has not signed the protocol.

Adequate Resources

The Investigator is responsible for supervising any individual or party to whom the Investigator delegates study-related duties and functions conducted at the study center.

If the Investigator/institution retains the services of any individual or party to perform study-related duties and functions, the Investigator/institution should ensure this individual or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.

Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the subjects in this study. The terms of the insurance will be kept in the study files.

Insurance

The Sponsor has obtained liability insurance, which covers this study as required by local law and/or national regulations and/or ICH guidelines, whichever is applicable. The terms of the insurance will be kept in the study files.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

Data Protection

- Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.
- The Sponsor or its representative will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician, or any other third party, unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, the Sponsor or representative physician or an Investigator might know a subject's identity and also have access to his or her genetic data. Also, regulatory authorities may require access to the relevant files.

Administrative Structure

The safety committee will include, at a minimum, the Sponsor's responsible physician and the Principal Investigator. The Principal Investigator and the Sponsor, when appropriate, will invite other specialist individuals to participate in the review, eg, PK scientists, statisticians, clinical specialists etc.

Table 9 Study Administrative Structure

Function	Responsible Organization
Principle Investigator and Primary Investigational Site	Dr. Christian Schwabe Auckland Clinical Studies Ltd Ground Floor, MEDACS House, 3 Ferncroft Street, Grafton, Auckland, New Zealand Tel: +64 373 3474 Fax: +64 373 3479
Investigators and Other Investigational Sites	Dr. Chris Wynne Christchurch Clinical Studies Trust, Ltd, 31 Tuam Street, Post Office Box 2856, Christchurch 8011 New Zealand Tel: +64 3372 9477 Fax: +64 3372 9478
Study Operations Management Medical Monitoring	Sponsor/CRO
Study Master File	CRO
Randomization Code	Sponsor/CRO/3rd party

Function	Responsible Organization
Data Management	Sponsor/CRO
Clinical Supply Management	Sponsor/CRO
Quality Assurance Auditing	Sponsor/CRO
Biostatistics Medical Writing	Sponsor/CRO
Laboratory Assessments	Local Laboratory used by Auckland Clinical Studies Ltd: **LabPLUS** Building 31, Auckland City Hospital, Gate 4 off Grafton Road, Auckland, New Zealand Tel: +64 9 307 8995 Fax: +64 9 307 4970 E-mail: Lablink@adhb.govt.nz
Electrocardiogram Collection, Review, and Analysis	Sponsor/CRO/3rd party
Bioanalytical Analysis (Immunogenicity and Pharmacokinetic Analysis)	CPR Pharma Services Pty Ltd 28 Dalgleish St Thebarton SA 5031 AUSTRALIA Tel: Fax: E-mail:
Pharmacokinetic Analysis	IQVIA Overland Park, Kansas, Unites States of America (US) Tel: +913 708 6000
Safety Monitoring Committee (see Section 9.6)	Sponsor/CRO/3rd party
IQVIA Medical Advisor	Charu Gautam
Sponsor Representative	Lisa Soyeon Park
Safety Monitoring Committee (see Section 9.6)	Sponsor/CRO/3rd party

Medical Monitor

Charu Gautam

Charu.Gautam@iqvia.com

Dissemination of Clinical Study Data

The results of the study should be reported within 1 year from the end of the clinical study. Irrespective of the outcome, the Sponsor will submit to the EU database a summary of the results of the clinical study within 1 year from the end of the clinical study. It shall be accompanied by a summary written in a manner that is understandable to laypersons.

Data Quality Assurance

- Monitoring will be carried out as determined by the risk assessment process conducted on the study.
- All subject data relating to the study will be recorded on printed or eCRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized study center personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Source Documents

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study center's subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail).

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's study center.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Study Center Closure

The Sponsor designee reserves the right to close the study center or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study centers will be closed upon study completion. A study center is considered closed when all required documents and study supplies have been collected and a study center closure visit has been performed.

The Investigator may initiate study center closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study center by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the Investigator.
- Discontinuation of further study treatment development.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual study center data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix 3 Clinical Laboratory Tests

- The tests detailed in Table 10 will be performed by the local laboratory.
- If the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5.0 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 10 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Platelet Count	White Blood Cell Count with Differential:
	Red Blood Cell Count	Neutrophils
	Hemoglobin	Lymphocytes
	Hematocrit	Monocytes
	Red Blood Cell Indices:	Eosinophils
	Mean corpuscular volume (MCV)	Basophils
	Mean corpuscular hemoglobin (MCH)	
	Mean cell hemoglobin concentration (MCHC)	
	%Reticulocytes	
Clinical Chemistry	Blood urea nitrogen (BUN)	Aspartate Aminotransferase (AST)/
	Creatinine	Alanine Aminotransferase (ALT)/
	Glucose (fasting)	Alkaline phosphatase (ALP)
	Gamma- glutamyl transferase (GGT)	Creatine kinase
	Urea	Creatine kinase MB fraction will be performed if clinically indicated
	Magnesium	Chloride
	Cholesterol	Amylase
	Potassium	Total and direct bilirubin
	Sodium	Conjugated and unconjugated bilirubin will be performed if clinically indicated
	Calcium	Total protein
	Lactate dehydrogenase	Phosphate
	Albumin	Potassium
	Uric acid	Carbon dioxide (bicarbonate)
	C-reactive protein	Triglycerides

Laboratory Assessments	Parameters	
Coagulation	International normalized ratio (INR)	Activated partial thromboplastin time (aPTT)
	Prothrombin time (PT)	Thrombin time
	Partial prothrombin time	Fibrinogen
Urinalysis	Leucocytes	Red blood cells
	Protein	pH
	Bilirubin	Nitrite
	Urobilinogen	Specific gravity
	Ketones	Glucose
	Microscopy (if clinically indicated)	
Viral serology	HIV I and II	Hepatitis C virus
	HBsAg	
Drugs of abuse and alcohol	Amphetamine/	Opiates
	Cannabinoids	Benzodiazepines
	Cocaine metabolites	Methadone metabolites
	Urine creatinine	Barbiturates
	Cotinine	Ecstasy (3,4-Methylenedioxymethamphetamine)
	Tricyclic anti-depressants (TCA)	Phencyclidine
NOTES: [a] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.		

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to study centers or other blinded personnel until the study has been unblinded.

Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or subject, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgement of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a) Results in death
b) Is life-threatening The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c) Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d) Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e) Is a congenital anomaly/birth defect
f) Other situations: • Medical or scientific judgement should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF. Each event must be recorded separately.
- It is **not** acceptable for the Investigator to send photocopies of the subject's medical records in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. The AE must be characterized as unrelated, unlikely to be related, possibly related, probably related, or unknown (unable to judge).
  - "Probably related" conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
  - "Possibly related" suggests that the association of the AE with the study treatment is unknown; however, the AE is not reasonably supported by other conditions.
  - "Unlikely to be related" suggests that only a remote connection exists between the study treatment and the AE. Other conditions, including chronic illness, progression or expression of the disease state or reaction to concomitant therapy, appear to explain the reported AE.
  - "Unrelated" is used if there is not a reasonable possibility that the study treatment caused the AE.
  - All efforts should be made to classify the AE according to the above categories. The category "unknown" (unable to judge) may be used only if the causality is not assessable, eg, because of insufficient evidence, conflicting evidence, conflicting data, or poor documentation.
- The Investigator will use clinical judgement to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the Investigator will provide a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the study center will use the paper SAE data collection tool (see next section).
- The study center will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given study center, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a study center receives a report of a new SAE from a subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the study center can report this information on a paper SAE form (see next section) or to the Medical Monitor/SAE coordinator] by telephone.

SAE Reporting via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Medical Monitor or the SAE coordinator.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

Appendix 5 Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   a) Documented hysterectomy.
   b) Documented bilateral salpingectomy.
   c) Documented bilateral oophorectomy.
   Note: Documentation can come from the study center personnel's: review of the subject's medical records, medical examination, or medical history interview.
3. Postmenopausal female:
   a) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   b) Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male subjects

- Male subjects with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 5.1:
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent for duration of study and for 6 months after study completion or from last dose.

- Agree to use a male condom and have their partner use of a contraceptive method with a failure rate of <1% per year when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

- In addition, male subjects must refrain from donating sperm for the duration of the study and for 6 months after study completion or the last dose of study treatment.
- Male subjects with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame.

Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral. • Intravaginal. • Transdermal.
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral. • Injectable.
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD). • Intrauterine hormone-releasing system (IUS). Bilateral tubal occlusion.
Vasectomized Partner *A vasectomized partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual Abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for at after the last dose of study treatment.

Collection of Pregnancy Information

Male subjects with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Appendix 6 Signature of Investigator

PROTOCOL TITLE: 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

PROTOCOL NO: SAMSON-1

VERSION: Original Protocol

This protocol is a confidential communication of [Sponsor]. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCPs and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to Sponsor or CRO.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

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