PROTOCOL TROIKA-1

A DOUBLE-BLIND, RANDOMISED, PARALLEL GROUP STUDY TO DEMONSTRATE THE EQUIVALENT PHARMACOKINETIC PROPERTIES OF A SINGLE INTRAVENOUS DOSE OF HD201 VERSUS EU-HERCEPTIN® AND US-HERCEPTIN® IN HEALTHY MALE SUBJECTS

Sponsor: Prestige BioPharma Pte Ltd.
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Contract Research Organization:

Protocol Version: Final

Date of Protocol: 17-JAN-2019

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Protocol Historical File

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Signature Page

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Principal Investigator:

I have carefully read this study protocol and agree that it contains all necessary information required to conduct this study. I agree to conduct the study according to this protocol (including any amendments) and in accordance with the clinical facility Standard Operating Procedures (SOPs), ICH Good Clinical Practices (GCP), Directive 2001/83/EC Annex I, as amended by Directive 2003/63/EC and Directive 2001/20/EC, and all other applicable regulations, including the recommendations laid down in the most recent version of the Declaration of Helsinki.



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Principal Investigator:

I have carefully read this study protocol and agree that it contains all necessary information required to conduct this study. I agree to conduct the study according to this protocol (including any amendments) and in accordance with the clinical facility Standard Operating Procedures (SOPs), ICH Good Clinical Practices (GCP), Directive 2001/83/EC Annex I, as amended by Directive 2003/63/EC and Directive 2001/20/EC, and all other applicable regulations, including the recommendations laid down in the most recent version of the Declaration of Helsinki.

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1. Facilities and Responsible Staff

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If another biomedical laboratory is used, this will be documented and annexed to the protocol.

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2. Synopsis of Protocol

Project No.:	TROIKA-1
Study Title:	A DOUBLE-BLIND, RANDOMISED, PARALLEL GROUP STUDY TO DEMONSTRATE THE EQUIVALENT PHARMACOKINETIC PROPERTIES OF A SINGLE INTRAVENOUS DOSE OF HD201 VERSUS EU-HERCEPTIN® AND US-HERCEPTIN® IN HEALTHY MALE SUBJECTS
Study Phase and Type:	Phase 1 - Pharmacokinetic (PK) Study
Objectives:	Primary objective: • To demonstrate the pharmacokinetic (PK) similarity of HD201 to the European (EU) and American (US) reference products Herceptin, following a single i.v. infusion of 6 mg/kg in healthy volunteers. Secondary objectives: • To evaluate the safety, tolerability and immunogenicity of HD201 and the EU and US reference products Herceptin, following a single i.v. infusion of 6 mg/kg in healthy volunteers. • To evaluate the PK similarity between the EU and US reference products Herceptin, following a single i.v. infusion of 6 mg/kg.
Study Design:	A two-center, Phase 1, double-blind, randomised, single-dose, 3-arm, parallel study.
Subjects:	A total of 105 healthy adult male volunteers, ≥ 18 and ≤ 55 years of age, non-smoker, will be dosed; 35 subjects per treatment group, randomly assigned to one of the 3 treatment arms.
Screening Procedures:	Demographic data, medical and medication histories, physical examination, body measurements, electrocardiogram (ECG), echocardiogram, vital signs (blood pressure [BP], heart rate [HR], respiratory rate [RR] and oral temperature [OT]), hematology, biochemistry, human immunodeficiency virus (HIV), hepatitis B and C tests, urinalysis, and urine drug screen.
Confinement and Visits	Subjects will be confined from at least 10 hours before dosing until after the 48-hour post-dose blood draw. Subjects will come back for all subsequent blood draws. The duration of the study for each subject will be approximately 14 weeks: 4 weeks for screening, and approximately 8 weeks for single dose pharmacokinetic and safety assessments.
Drug Administration:	Subjects will be randomized to receive a single dose of 6 mg/kg of one of the following treatments by i.v. infusion over 90 minutes: Treatment A (Test): Trastuzumab 150 mg powder for concentrate for solution for I.V. infusion (Prestige BioPharma Pte Ltd) Treatment B (Reference 1): Herceptin (EU-licensed trastuzumab, Roche Pharma AG, Germany) 150 mg powder for concentrate for solution for i.v. infusion. Treatment C (Reference 2): Herceptin (US-licensed trastuzumab, Genentech, USA) 150 mg powder for concentrate for solution for i.v. infusion. Dosing time (Hour 0) is considered as the start of infusion.

	For standardisation purposes, the study drug will be administered in all subjects approximately 0.5 to 2 hours after a light breakfast.
Study Restrictions:	Subjects will be asked to refrain from using products that may potentially affect their safety and/or the PK profile of the study drug. Main study restrictions include: - prescription medication from 14 days prior to the first dosing until after the last PK blood sample collection of the study; - over-the-counter products from 7 days prior to the first dosing until after the last PK blood sample collection of the study; - natural health products from 7 days pre-dose until after the last PK blood sample collection; - food containing poppy seeds within 24 hours prior to admission; - food or beverages containing xanthine derivatives or xanthine-related compounds or energy drinks from 48 hours pre-dose until after the 168-hour post-dose sample collection; - alcohol-based products from 24 hours prior to admission until after the 168-hour post-dose sample collection. For safety reasons, subjects will be required to remain seated or semi-reclined during the infusion and for at least 4 hours after the start of infusion.
Sample Collection for PK Analysis:	A total of 13 blood samples will be collected for assessment of serum concentrations of trastuzumab: pre-dose (0 hour), 1.5 (within 5 minutes before the end of infusion), 3 (1.5 hours post-end of infusion), 8, 24, 48 (Day 3), 96 (Day 5), 168 (Day 8), 336 (Day 15), 504 (Day 22), 672 (Day 29), 1008 (Day 43), and 1272 hours (Day 54) post-dose.
Sample Collection for Immunogenicity Evaluation:	A total of 5 blood samples will be collected for anti-drug antibodies (ADA) detection and neutralizing antibodies (NAb): pre-dose (0 hour), 336 (Day 15), 672 (Day 29), 1008 (Day 43), and 1272 hours (Day 54) post-dose.
On-Study Safety Procedures:	Physical examination: Brief physical examination: at check-in (Day -1). Body weight: at check-in Vital signs: BP and HR: at check-in, before dosing, and approximately 1, 6, 12, 24 hours and 48 hours (Day 3) post-dose, and at each visit. OT will be measured at check-in, prior to dosing, and approximately 4, 8, 12, 24, 36, and 48hours post-dose (Day 3), and at each visit. ECG: before dosing and approximately 1, 6, 12, and 24 hours post-dose. Echocardiogram: Evaluation of left ventricular ejection fraction (LVEF) will be measured by an echocardiogram on study only if a subject experiences a cardiac AE that would require echocardiographic evaluation. Laboratory tests: Hematology, urinalysis, and biochemistry: at Day -1, at Day 3, at Day 8, and at Day 29. Alcohol test (breath or urine) and urine drug screen: at check-in. Infusion site evaluation: Infusion site evaluation: before dosing and approximately 1, 1.5 (at the end of infusion), 2, 4, and 24 hours post-dose.

	Medical surveillance and AE monitoring: Subjects will be monitored throughout the study for adverse events. A physician will be on site for drug administration and until 4 hours after administration of the study medication (end of infusion) to the last subject, and available on call for the remainder of the study.
Study Exit / Early Termination Procedures:	Study exit procedures are scheduled to be performed at the last study visit on Day 54 after the infusion or within 14 days after the last participation of the subject in the study in case of early termination. The study exit procedures include: hematology, biochemistry, urinalysis, vital signs, ECG, echocardiogram, and adverse events monitoring.
Analytical Method:	CPR Pharma Services will analyse trastuzumab in serum samples using an enzyme linked immunosorbent assay (ELISA). ADA samples will be analyzed using an immunoassay with tiered approaches (screening, confirmatory and titrations) by CPR Pharma Services. Samples confirmed to be positive for ADA will be further tested for NAb using a non-cell based antibody neutralization assay. All methods used for bioanalysis will be validated assays.
Pharmacokinetic Parameters:	Primary parameter: $AUC_{0\text{-}inf}$ Secondary parameters: $AUC_{0\text{-}t}$, C_{max}, Residual area, T_{max}, $T_{½\ el}$, K_{el}, Cl, and V_d.
Safety, Tolerability, and Immunogenicity Endpoints:	AEs will be summarized by treatment and categorized in subsets of all treatment-emergent AEs (TEAEs), and of all treatment-related AEs. Clinical laboratory parameters and vital signs will be summarized by treatment and changes from baseline. Immunogenicity assessments will be summarized by treatment.
Statistical Analyses:	Pharmacokinetics: Summary statistics will be used to describe the PK profile of trastuzumab. Individual and mean serum concentration versus time curves will be presented for both linear and semi-log scales. Descriptive statistics (arithmetic and geometric mean, standard deviation [SD], coefficient of variation [CV%], minimum [min.], maximum [max.], and median) of the serum concentrations versus time will be presented as well as for the PK parameters. The analysis for each comparison (A vs. B, A vs. C, and B vs. C) will be conducted excluding the data from the treatment that is not relevant for the comparison in question. **EMA (A vs. B):** Using GLM procedure in SAS, analysis of variance (ANOVA) will be performed on untransformed K_{el} and $T_{½\ el}$ and on ln-transformed $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} at the alpha level of 0.05. The ratio of geometric means (A/B) and 90% confidence interval for the ratio of geometric means, based on least-squares means from the ANOVA of the ln-transformed data, will be calculated for $AUC_{0\text{-}t,}$ $AUC_{0\text{-}inf}$ and C_{max}. Wilcoxon's test will be performed on T_{max}. **References Comparison for EMA bridging (B vs. C):** Using GLM procedure in SAS, ANOVA will be performed on untransformed

	K_{el} and $T_{½\ el}$ and on ln-transformed AUC_{0-t}, $AUC_{0\ inf}$, and C_{max} at the alpha level of 0.05. The ratio of geometric means (B/C) and 90% confidence interval for the ratio of geometric means, based on least-squares means from the ANOVA of the ln-transformed data, will be calculated for $AUC_{0-t,}$ AUC_{0-inf} and C_{max}. Wilcoxon's test will be performed on T_{max}. **FDA (A vs. C):** Using GLM procedure in SAS, ANOVA will be performed on untransformed T_{max}, K_{el} and $T_{½\ el}$ and on ln-transformed AUC_{0-t}, $AUC_{0\ inf}$, and C_{max} at the alpha level of 0.05. The ratio of geometric means (A/C) and 90% confidence interval for the ratio of geometric means, based on least-squares means from the ANOVA of the ln-transformed data, will be calculated for $AUC_{0-t,}$ AUC_{0-inf} and C_{max}. <u>Safety, Tolerability and Immunogenicity:</u> Safety, tolerability, and immunogenicity data will be reported using descriptive statistics (arithmetic mean , SD, CV%, min., max., and median). A complete description of the statistical analyses to be performed with the safety, tolerability and immunogenicity data, as well as PK parameters will be presented in a Statistical Analysis Plan.
Standards for Pharmacokinetic Similarity Acceptance:	**EMA (A vs. B; B vs. C):** The 90% confidence intervals for the ratio of geometric means (A/B) based on least-squares means from the ANOVA of the ln-transformed AUC_{0-inf} must be within 80.00% to 125.00%. The 90% confidence intervals for the ratio of geometric means (B/C) based on least-squares means from the ANOVA of the ln-transformed $AUC_{0\ inf}$ must be within 80.00% to 125.00%. **FDA (A vs. C):** The 90% confidence intervals for the ratio of geometric means (A/C) based on least-squares means from the ANOVA of the ln-transformed AUC_{0-inf} must be within 80.00% to 125.00%.

3. Schedule of Events

PROCEDURE	Screening Up to -28 days	D-1	D1	D2	D3	D5	D8	D15	D22	D29	D43	Study Exit (D54 or early termination)
Informed Consent	X											
Demographic Data	X											
Medical and Medication Histories	X											
Review and Monitoring of AEs and Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X
Physical Exam. & Body Measurements	X	X[1]										
Vital Signs	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X
Oral Temperature	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[3]
ECG	X		X[3]	X[3]								X
Echocardiogram	X											X
Biochemistry	X	X			X		X			X		X
Hematology	X	X			X		X			X		X
HIV and Hepatitis	X											
Urinalysis	X	X			X		X			X		X
Urine Drug Screen	X	X										
Alcohol Test		X										
Confinement		X	X	X	X							
Return Visit[4]						X	X	X	X	X	X	X
Drug Infusion			X									
Injection Site Evaluation			X[5]	X[5]								
PK Sample[6]			X	X	X	X	X	X	X	X	X	X
Immunogenicity Sample[8]			X					X		X	X	X

1. Brief examination including body weight
2. BP and HR only: at check-in, at pre-dose, approximately 1, 6, 12, 24, and 48 hours (Day 3) post-dose, and at each visit. Oral temperature will be measured at check-in, prior to dosing, and approximately 4, 8, 12, 24, 36, and 48 hours (Day 3) post-dose, and at each visit.
3. ECG: at pre-dose and approximately 1, 6, 12, and 24 hours post-dose.
4. For the 96–hour and 168–hour post-dose visits, a window of 60 minutes will be allowed for these visits. Return visits beyond that time point are allowed to be performed with a maximum deviation of 24 hours from the scheduled time.
5. Injection site evaluation: before dosing, at the end of infusion (1.5) and approximately 1, 2, 4, and 24 hours after the start of infusion.
6. PK Samples: pre-dose and 1.5 (within 5 minutes before the end of infusion), 3 (1.5 hours post-end of infusion), 8, 24, 48 (Day 3), 96 (Day 5), 168 (Day 8), 336 (Day 15), 504 (Day 22), 672 (Day 29), 1008 (Day 43), and 1272 hours (Day 54) post-dose.
7. Immunogenicity Samples: pre-dose and at 336 (Day 15), 672 (Day 29), 1008 (Day 43), and 1272 hours (Day 54) post-dose.

4. List of Abbreviations

ADA	Anti-Drug Antibodies
ADCC	Antibody-Dependent Cell-mediated Cytotoxicity
AE	Adverse Event
AGC	Advanced Gastric Cancer
ANOVA	Analysis of Variance
AUC	Area Under the Concentration-Time Curve
BMI	Body Mass Index
BP	Blood Pressure
bpm	Beat per Minute
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CL	Total Body Clearance
C_{max}	Maximum Observed Concentration
CRF	Case Report Form
CV	Coefficient of Variation
EBC	Early Breast Cancer
ECG	Electrocardiogram
ECHO	Echocardiogram
ECL	Electrochemiluminescent
EEA	European Economic Area
ELISA	Enzyme Linked Immunosorbent Assay
EMA	European Medicines Agency
EOS	End-Of-Study
EU	Europe
FDA	United States Food and Drug Administration
g	Gram
GCP	Good Clinical Practice
GLM	Generalized Linear Model
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HBsAg	Surface Antigen of the Hepatitis B Virus
HCV	Human Hepatitis C Virus
HDL	High-Density Lipoprotein
HEENT	Head, Eyes, Ears, Nose and Throat
HER2	Human Epidermal Growth Factor Receptor 2

HIV	Human Immunodeficiency Virus
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
i.v.	Intravenous
k_{el}	Elimination Rate Constant
kg	Kilogram
L	Liter
LDL	Low-Density Lipoprotein
LVEF	Left Ventricular Ejection Fraction
m	Meter
max	Maximum
MBC	Metastatic Breast Cancer
MDMA	3,4-methylenedioxy-N-methylamphetamine
mg	Milligram
MGC	Metastatic Gastric Cancer
min	Minimum
mL	Milliliter
mm	Millimeter
mmHg	Millimeter of Mercury
NAb	Neutralizing Antibodies
NCI	National Cancer Institute
PCP	Phencyclidine
PK	Pharmacokinetic
RR	Respiratory Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event
T_{max}	Time to Reach Peak Serum Concentration
$T_{½\ el}$	Half-Life
US	United States
USA	United States of America

V_d	Apparent Volume of Distribution

5. Introduction

5.1 Background Information

Trastuzumab is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human epidermal growth factor receptor 2 (HER2). Trastuzumab is indicated for the treatment of the following conditions: HER2 overexpressing metastatic breast cancer (MBC), HER2 overexpressing early breast cancer (EBC), HER2 overexpressing metastatic adenocarcinoma of the stomach or gastroesophageal junction, in combination with capecitabine or 5-fluorouracil and cisplatin. Posology varies with the indication and ranges between 2 mg/kg and 8 mg/kg. Adverse events associated with trastuzumab are listed in the product monograph. [1, 2]

Binding of trastuzumab to HER2 inhibits ligand-independent HER2 signalling and prevents the proteolytic cleavage of its extracellular domain, an activation mechanism of HER2. As a result, trastuzumab has been shown, in both *in vitro* assays and in animals, to inhibit the proliferation of human tumour cells that overexpress HER2. Additionally, trastuzumab is a potent mediator of antibody-dependent cell-mediated cytotoxicity (ADCC). *In vitro*, trastuzumab-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.[1]

The PK of trastuzumab was evaluated in a pooled population PK model analysis of 1,582 subjects with primarily breast cancer and metastatic gastric cancer (MGC) receiving intravenous trastuzumab. Total trastuzumab clearance increases with decreasing concentrations due to parallel linear and non-linear elimination pathways. Following intravenous administration, the elimination half-life is of 15.1-23.3 days in the MBC setting and is 17.5-26.6 days in EBC settings and 12.6-20.6 days in MGC settings with one every three week dose of 6 mg/kg. Steady state should be reached by approximately 12 weeks in the MBC setting, 15 weeks in the EBC setting and 9 weeks in the MGC setting with one every three week dose of 6 mg/kg. [1, 2]

In a population PK (two compartment, model-dependent) assessment in MBC, the median predicted AUC at steady state over a three-week period was three times 1710 µg•day/mL with 3 weekly doses of 2 mg/kg and 1736 µg•day/mL with one every three week dose of 6 mg/kg; the estimated median peak concentrations were 107 µg/mL and 179 µg/mL and the trough concentrations were 63.1 µg/mL and 44.2 µg/mL, respectively. [1, 2]

In EBC, the median predicted AUC at steady state over a three-week period was three times 1893 µg•day/mL with 3 weekly doses of 2 µg/kg and 1927 µg day/mL with one every three week dose of 6 mg/kg; the estimated median peak concentrations were 115 µg/mL and 184 µg/mL and the trough concentrations were 72.6 µg/mL and 53.8 mg/L, respectively. [1, 2]

In MGC, the median predicted AUC at steady state over a three-week period was 1338 µg day/mL with one every three week dose of 6 mg/kg; the estimated median peak concentrations were 131 µg/mL and the trough concentrations were 32.9 µg/mL. [1, 2]

Based on data from literature and sponsor data, the inter-subject coefficients of variation of trastuzumab should be approximately 17 and 19% for AUC and C_{max} respectively. [3,4,5]

5.1 Rationale for Study Design

Prestige BioPharma has developed HD201, a powder for concentrate for solution for i.v. infusion of trastuzumab as a proposed biosimilar to EU-licensed trastuzumab Herceptin and US-licensed trastuzumab Herceptin. According to the EMA guidelines and FDA guidance on similar biological medicinal products, clinical evidence regarding bioequivalence needs to be provided on a PK level and data on similar safety and efficacy has to be provided in a dedicated phase 3 trial. [6,7,8,9]

A phase I study with healthy volunteers to compare PK properties of HD201 and EU Herceptin® has already been done. For the primary analysis, the 90% CIs for the ratio of the geometric means of HD20l to EU Herceptin® were contained within the acceptance interval of 0.80 to 1.25 for both AUC_{inf} and C_{max} thus demonstrating equivalent PK properties of HD20l and Herceptin®.[3]

As per EMA/940451/2011 Committee for Human Medicinal Products (CHMP), if certain studies of the development program are performed with only the non- European Economic Area (EEA) authorized comparator, the Applicant should provide adequate data or information to scientifically justify the relevance of these comparative data and establish an acceptable bridge to the EEA-authorized reference product. Therefore, this trial will be a 3-arm parallel study to demonstrate PK similarity of Prestige BioPharma trastuzumab (HD201) to the EU- and to US-licensed products Herceptin, and to evaluate the PK similarity between the EU- and US-licensed products. A phase 3 comparative study with the US-licensed products of Herceptin is planned following this phase 1 single dose PK study.

The study is designed to be in accordance with EMA and FDA guidances for single-dose PK study with i.v. route of administration of similar biological medicinal products. [6,7,8,9]

The parallel design is proposed due to the long estimated half-life of trastuzumab of approximately 12.6-26.6 days[1,2,3] as well as to avoid the potential influence of immunogenicity upon multiple dosing.

The primary endpoint of the study is $AUC_{0\text{-}inf}$. PK similarity of HD201 to each reference product will be concluded if the 90% confidence interval for the ratio of geometric means is within the conventional equivalence margin of 80 to 125%.

The study will also allow gathering safety and tolerability data, as well as evaluating the production of anti-trastuzumab antibodies, in order to evaluate potential differences between the proposed biosimilar and the EU and US-licensed products in the incidence and severity of adverse events and human immune responses.

5.1.1 Choice of the Dose

Prestige BioPharma proposes a single-dose of 6 mg/kg i.v. to demonstrate PK similarity in this study. As stated in the FDA draft *"Guidance to Industry: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product"* (May 2014)[9], the dose selected for the PK study should be one most likely to provide clinically meaningful and interpretable data. Therefore, the dose of 6 mg/kg was chosen since it represents the recommended maintenance dose for treatment of EBC, and for MGC.

5.1.2 Rationale for the Study Population

According to EMA guidelines and FDA guidance on similar biological medicinal products, [6,7,8,9] human PK studies should be conducted in healthy volunteers if the product can be safely administered to this population. A study in healthy volunteers is considered to be more sensitive in evaluating the product similarity because it is likely to produce less PK variability compared with that in patients with potentially confounding factors such as underlying and/or concomitant disease and concomitant medications. Additionally, in the light of the trastuzumab safety profile, it is anticipated that the use of a dose of 6 mg/kg will be well tolerated by healthy volunteers.

Males only are proposed in this Phase I PK biosimilarity study due to the fact that male volunteers represent the most homogeneous population for a PK biosimilarity study and to avoid the formation of neutralizing anti-trastuzumab antibodies in individuals who are more likely to require trastuzumab for the treatment of breast cancer at some point in their life. Since there was no prior experience of trastuzumab PK in healthy females in the literature, only males will be included.

For safety reasons, a limit on age from 18 to 55 inclusive was selected.

6. Objectives

Primary objective:

- To demonstrate the PK similarity of HD201 to the EU and US reference products Herceptin, following a single i.v. infusion of 6 mg/kg in healthy volunteers.

Secondary objectives:

- To evaluate the safety, tolerability and immunogenicity of HD201 and the EU and US reference products Herceptin, following a single i.v. infusion of 6 mg/kg in healthy volunteers.
- To evaluate the PK similarity between the EU and US reference products Herceptin, following a single i.v. infusion of 6 mg/kg.

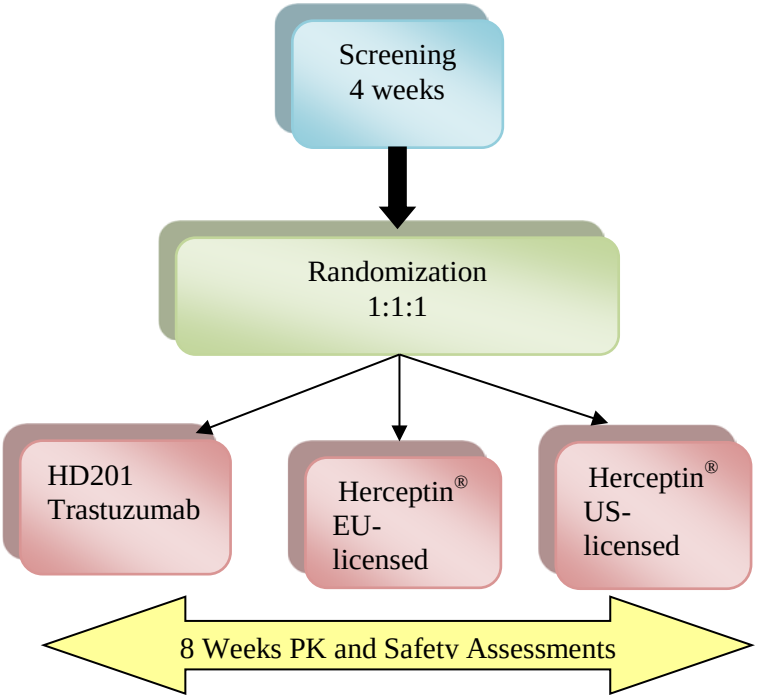
7. Study Design

This will be a two-center, Phase 1, double-blind, randomized, single-dose, 3-arm, parallel study.

Subjects eligible for the study will be randomized to one of 3 treatment arms. After a single 6 mg/kg i.v. infusion, pharmacokinetic, safety, tolerability, and immunogenicity data will be collected for a total of 54 days.

This study is intended for filing under FDA and EMA regulations.

Figure 1. Study Design



8. Study Population

8.1 Sample Size

A total of 105 healthy adult male volunteers will be dosed; 35 subjects per treatment group, randomly assigned to one of the 3 treatment arms.

Based on data from literature and sponsor data, the inter-subject coefficients of variation should be 17% and 19% for AUC and C_{max}, respectively. Thus, with these expected coefficients of variation and assuming a ratio of AUC and C_{max} between 0.925-1.08 and a power of at least 85%, 29 evaluable subjects per group for a total of 87 subjects are required to show pharmacokinetic biosimilarity. In order to account for possible dropouts, 35 subjects will be included in each group.

8.2 Inclusion Criteria

Subjects enrolled in this study will be members of the community at large. The recruitment advertisements may use various media types (e.g. radio, newspaper, clinical sites Web site, clinical sites volunteer database). Subjects must meet all of the following criteria to be included in the study:

1) Male, non-smoker (no use of tobacco products within 3 months prior to screening), ≥ 18 and ≤ 55 years of age, with BMI ≥ 18.5 and ≤ 30.0 kg/m^2 and body weight ≥ 50.0 kg.
2) Healthy as defined by:

    a) the absence of clinically significant illness and surgery within 4 weeks prior to dosing. Inclusion pre-dosing is at the discretion of the Principal Investigator.

    b) the absence of clinically significant history of neurological, endocrinal, cardiovascular, pulmonary, hematological, immunologic, psychiatric, gastrointestinal, renal, hepatic, and metabolic disease.

    c) a LVEF within the normal range (≥60%) as measured by echocardiogram (ECHO) within 4 weeks prior to randomization.

    d) the absence of clinically significant history of anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome.

3) Male subjects who are not vasectomized for at least 6 months, and who are sexually active with a female partner of child bearing potential/non-sterile female partner [sterile female partners include post-menopausal women (absence of menses for 12 months prior to drug administration) or women who have had a tubal ligation, hysterectomy, or bilateral oophorectomy (at least 6 months prior to drug administration)] must be willing to use one of the following acceptable contraceptive methods throughout the study and for 90 days after the last study drug administration:

    a) simultaneous use of condom, and for the female partner hormonal contraceptives (used since at least 4 weeks) or intra-uterine contraceptive device (placed since at least 4 weeks);

    b) simultaneous use of male condom, and for the female partner, diaphragm.

4) Male subjects with a pregnant partner, including subjects who have had a vasectomy must agree to use a condom throughout the study and for 90 days after the last study drug administration.

5) Male subjects must be willing not to donate sperm until 90 days following the last study drug administration.

6) Capable of consent.

8.3 Exclusion Criteria

Subjects to whom any of the following applies will be excluded from the study:

1) Any clinically significant abnormality or abnormal laboratory test results found during medical screening or positive test for hepatitis B, hepatitis C, or HIV found during medical screening or hemoglobin < 12.8 g/dL and hematocrit < 0.37 L/L at screening.

2) Positive urine drug screen at screening.

3) History of allergic reactions to trastuzumab, benzyl alcohol, murine proteins, or other related drugs.

4) Any reason which, in the opinion of the Principal Investigator, would prevent the subject from participating in the study.

5) Clinically significant ECG abnormalities (QTc >450 ms) and or vital sign abnormalities (systolic blood pressure lower than 90 or over 140 mmHg, diastolic blood pressure lower than 40 or over 90 mmHg, or heart rate less than 40 or over 100 bpm) at screening.

6) History of significant alcohol abuse within one year prior to screening or regular use of alcohol within six months prior to the screening visit (more than fourteen units of alcohol per week [1 unit = 150 mL of wine, 360 mL of beer, or 45 mL of 40% alcohol]).

7) History of significant drug abuse within one year prior to screening or use of soft drugs (such as marijuana) within 3 months prior to the screening visit or hard drugs (such as cocaine, phencyclidine [PCP], crack, opioid derivatives including heroin, and amphetamine derivatives) within 1 year prior to screening.

8) Previous use of trastuzumab or another monoclonal antibody for a medical condition or in the context of another clinical trial in the 6 months prior to screening.

9) Participation in a clinical research study involving the administration of an investigational or marketed drug or device within 30 days prior to the first dosing, administration of a biological product in the context of a clinical research study within 90 days prior to the first dosing, or concomitant participation in an investigational study involving no drug or device administration.

10) Use of medication other than topical products without significant systemic absorption:

    a) prescription medication within 14 days prior to dose administration; sporadic use of prescription medication such as benzodiazepines and codeine can be accepted at the discretion of the Investigator;

b) over-the-counter products including natural health products (e.g. including herbal remedies, homeopathic and traditional medicines, probiotics, food supplements such as vitamins, minerals, amino acids, essential fatty acids, and protein supplements used in sports) within 7 days prior to dosing, with the exception of the occasional use of acetaminophen (paracetamol - up to 4 g daily);

c) a depot injection or an implant of any drug within 3 months prior to dose administration.

11) Donation of plasma within 7 days prior to dosing. Donation or loss of blood (excluding volume drawn at screening) of 50 mL to 499 mL of blood within 30 days, or more than 499 mL within 56 days prior to the first dosing.

9. Clinical Procedures

Unless otherwise specified, procedures, data collection and evaluation will be conducted as per clinical sites SOPs.

9.1 Screening Procedures

Subject screening procedures will be performed within 28 days preceding administration of study medication. Subjects must provide written informed consent prior to initiation of any screening procedures. The consent to perform some general screening procedures may be obtained on a consent document other than the Informed Consent Form (ICF) specific to this study, and therefore, some screening test results could be obtained before signature of the ICF specific to this study. The study-specific ICF must be signed and dated by the subject before participation to study-specific procedures.

Screening procedures will include: demographic data, medical and medication histories, physical examination, body measurements, ECG (12-lead), echocardiogram, vital signs (BP, HR, RR, and OT), hematology, biochemistry, HIV, hepatitis B and C tests, urinalysis, and urine drug screen.

For eligibility purposes, abnormal laboratory or vital signs results may be repeated once if abnormal result is observed at the initial reading. Moreover, abnormalities found in the ECG may need to be confirmed by repeated measurements. In the event that the participation of a subject in the study is delayed and some screening procedures had been performed outside the prescribed screening window, outdated screening procedures can be repeated.

9.2 Confinement and Visits

Subjects will be confined from at least 10 hours before dosing until after the 48-hour post-dose blood draw. Subjects will come back for all subsequent blood draws. The duration of the study for each subject will be approximately 14 weeks: 4 weeks for screening, and approximately 8 weeks for single dose pharmacokinetic and safety assessments.

9.3 Randomization and Blinding

Subjects eligible for the study will be administered Treatment A, B, or C according to the 1 period, 3-arm, block randomization scheme produced by Syneos Health.

Both study subjects and the clinical personnel involved in the collection, monitoring, revision, or evaluation of AEs or personnel who could have an impact on the outcome of the study will be blinded to treatment allocation until the clinical phase of the study is completed (i.e. when investigation and reporting of all adverse events have been completed). Designated pharmacy personnel at the clinical sites not directly involved with the clinical aspects of the study will prepare and dispense the study medication and will be aware of the randomization code.

In the event of an emergency, an envelope for each subject containing his treatment assignment will be available. The Principal Investigator or other attending study physician will make every effort to contact the Sponsor prior to unblinding a subject's treatment assignment and will record the date and reason for the unblinding in the study source documents.

The bioanalytical laboratory will also remain blinded until the clinical phase and analysis of PK samples of the study have been completed. For immunogenicity analysis, since separate assays will be used for test product vs. the reference products, the immunogenicity portion will be unblinded to the subject's treatment assignment, but only after the PK samples analysis has been completed.

9.4 Study Medication

Treatment A (Test): Trastuzumab (Prestige BioPharma Pte, Ltd., Singapore), 150 mg powder for concentrate for solution for i.v. infusion.

Treatment B (Reference 1): Herceptin (EU-licensed trastuzumab, Roche Pharma AG, Germany), 150 mg powder for concentrate for solution for i.v. infusion.

Treatment C (Reference 2): Herceptin (US-licensed trastuzumab, Genentech, USA), 150 mg powder for concentrate for solution for i.v. infusion.

Dose: 6 mg/kg, i.v. infusion

9.5 Drug Supplies and Accountability

It is the responsibility of the Sponsor to ensure that study medication provided for this study are manufactured under Good Manufacturing Practices (GMP) and are suitable for human use. It is the responsibility of the Sponsor to ship a sufficient amount of dosage units to allow the clinical sites to conduct the study. In addition to the amount required for the study, an appropriate number of dosage units of the Test and Reference products must also be sent to the clinical sites for drug retention purposes, as per applicable EMA and FDA regulation (21 CFR 320.38, 320.63). Clinical sites will store the retention samples on site for a minimum of 5 years following the application approval or, if not approved, at least 5 years after the completion of the study (in accordance with FDA regulation 21 CFR 320.38), unless documented by the Sponsor that the study will not be submitted to the FDA.

Study medication will be stored by the clinical sites as per applicable requirements. The management of investigational drugs is under the supervision of the Principal Investigator. The medications will be stored in a locked, environmentally-controlled medication room with restricted access. Container(s) will bear a label containing at least the name of the study drug, lot

and/or batch number, and manufacturing and/or expiry/retest date. Individual subject doses will be dispensed according to the randomization scheme in appropriate infusion bags indicated with at least the project number and the subject number/spare number. The medications will be dispensed according to clinical sites SOP. Whenever possible, dispensing will occur not more than 24 hours prior to dosing.

All study drug received at the site will be inventoried and accounted for throughout the study and the result recorded in the drug accountability/retention record according to clinical sites appropriate SOP.

9.6 Drug Administration

All subjects will be randomized to one of the three treatment arms, and receive a single dose of either the Test product Prestige BioPharma trastuzumab or one of the two Reference products Herceptin (EU or US), administered as an intravenous infusion over 90 minutes in sodium chloride 9 mg/mL (0.9%) solution for injection. Infusions will be required to be completed in approximately 90 minutes but not exceeding 3 hours (± 10 minutes). For subject safety reasons, initiation of infusion of each subject could be separated by at least 30 minutes.

The dose will be calculated with body weight measured at check-in. All doses will be prepared by the Research Pharmacy Unit and administered using aseptic techniques in accordance with the pharmacy instructions in the form of a project specific procedure (PSP).

The complete dose should be administered wherever possible. Dosing time (Hour 0) is considered as the start of infusion. The time the infusion begins and ends should be documented in the source data and reported in the CRF. Subjects who do not receive a complete dose are not to be included in the statistical analyses. The end of infusion includes the flush.

Unused infusate will be disposed of per appropriate procedures and local laws.

9.7 Study Restrictions

9.7.1 Food and Fluids

For standardisation purposes, the study drug will be administered in all subjects approximately 0.5 to 2 hours after a light breakfast.

There will be no fluid restrictions during the study; water will be provided *ad libitum.*

Subjects will be required to abstain from:

- food or beverages containing xanthine derivatives or xanthine-related compounds or energy drinks from 48 hours prior to dosing until after the 168-hour post-dose sample collection;
- food containing poppy seeds within 24 hours prior to admission;
- natural health products (including herbal remedies, homeopathic and traditional medicines, probiotics, food supplements such as vitamins, minerals, amino acids,

essential fatty acids, and protein supplements used in sports) from 7 days prior to dosing until after the last PK blood sample collection of the study.

9.7.2 Tobacco, Alcohol, and Illicit Drugs

Subjects will be required to abstain from using soft or hard drugs or any tobacco or nicotine products from screening and throughout the study.

Consumption of alcohol-based products will be prohibited from 24 hours prior to admission until after the 168-hour post-dose sample collection.

9.7.3 Medications

Prescription and over-the-counter medications will be prohibited throughout the study. No concomitant drug therapy will be allowed during the study except one(s) required for the medical management of an adverse event. Any concomitant medication use other than the occasional use of acetaminophen (paracetamol - up to 4 g/day) will be evaluated on a case-by-case basis by the Principal Investigator or a physician. All concomitant medication use will be documented.

9.7.4 Posture and Physical Activity

For safety reasons, subjects will be required to remain seated or semi-reclined during the infusion and for at least 4 hours after the start of infusion. However, failure of subjects to comply with these requirements does not constitute a deviation from the protocol if it is medically necessary, procedurally required, or to go to the bathroom. When appropriate, subjects will be accompanied by a staff member during ambulations. Vigorous activity will be prohibited at all times during the confinement.

9.8 Sample Collection and Processing

9.8.1 Pharmacokinetic Samples

A total of 13 blood samples will be drawn from each subject for PK analyses. Blood samples will be collected prior to drug administration (0 hour within 45 min), 1.5* (within 2 minutes before the end of infusion), 3** (1.5 hours post end of infusion), 8, 24, 48 (Day 3), 96 (Day 5), 168 (Day 8), 336 (Day 15), 504 (Day 22), 672 (Day 29), 1008 (Day 43), and 1272 hours (Day 54) post-dose (4 mL for each sampling time).

*If the infusion duration is more than 90 minutes, this timepoint will be taken within 5 minutes before the end of infusion.

** This timepoint will be taken 1.5 hours post end of infusion.

The time tolerance window for blood samples collected during the confinement period will be as follow:

During confinement:		
± 45 min	Predose sample: 45 min prior	before dosing
+ 2 min	If between 0 and 4 hr, inclusive	after dosing
+ 5 min	If greater than 4 hr and up to and including 14 hr	after dosing
+ 15 min	If greater than 14 hr and up to and including 16 hr	after dosing
± 30 min	If greater than 16 hr	after dosing
Sample collection during outpatient visit:		
± 60 min	If 24 hr or greater	after dosing

Blood sample collections beyond 168 (Day 8) time point are allowed to be performed with a maximum deviation of 24 hours from the scheduled time points. Actual sampling times will be used for statistical analyses.

9.8.2 Immunogenicity Samples

A total of 5 blood samples (10 mL for each sampling time) will be collected for anti-trastuzumab antibodies detection: pre-dose (0 hour), 336 (Day 15), 672 (Day 29), 1008 (Day 43), and 1272 hours (Day 54) post-dose.

9.8.3 Sample Processing

Unless otherwise specified or for subject safety, when blood draws and other procedures coincide, blood draws will have precedence. Intravenous cannulas may be used for blood collection to avoid multiple skin punctures, when appropriate. Otherwise, blood samples will be collected by direct venipuncture.

The total volume of blood including that collected for eligibility and safety purposes should not exceed 180 mL for the whole study.

Samples will be collected and processed as per the instructions provided by the laboratories responsible for the analysis.

9.9 Subject Monitoring

Subjects will be monitored throughout the study by clinical sites staff for adverse events. The Principal Investigator or Sub-Investigator will be on site for drug administration and until 4 hours after administration of the study medication to the last subject. The Principal Investigator or Sub-Investigator will also be on call for the remainder of the study. If necessary, a physician, either at the clinical sites or in a nearby hospital will administer treatment for any adverse event(s). A crash cart or emergency bag containing the necessary rescue material and appropriate medications will be available in the clinic to allow rapid intervention in case of emergency.

Safety parameters, including laboratory results and ECG, will be assessed by the Principal Investigator or delegate, using clinical sites criteria for biomedical laboratory and ECG acceptance ranges as suggested guidelines in making the medical assessment.

Scheduled safety measurements will be repeated according to appropriate clinical sites SOPs or upon request from a physician. Any abnormal repeated measurement will be evaluated by a

physician and repeated if judged necessary. Further action may be taken upon physician's request.

Unless otherwise specified or for subject safety, when the timing of some assessments coincide with other assessments or procedures, the following priority order and sequence should be adhered to, whenever possible: blood samples for PK, ECG, vital signs, clinical laboratory samples, and physical examination. If these procedures are performed out of this order, this will not be a protocol deviation.

Subjects will be advised to notify their health care professional(s) (e.g., physician, dentist, and/or pharmacist) that they are participating in a clinical research study on a drug called trastuzumab before taking any medicines or undergoing any medical procedure.

9.9.1 Vital Signs

BP, RR, and HR will be measured in a sitting position (after a resting time of minimum 3 minutes,except for safety reasons) at screening and at study exit. BP and HR will also be measured at check-in, before dosing, and approximately 1, 6, 12, 24, and 48 hours post-dose, and at each visit. Oral temperature will be measured at screening, at check-in, prior to dosing, and approximately 4, 8, 12, 24, 36, and 48 hours post-dose, at each visit, and at study exit. A window of 60 minutes will be allowed for all vital signs measurement.

Oral temperature measurement will be repeated for initial reading ≥ 38.0°C or upon request from a physician. An AE of fever will be documented for confirmed oral body temperature ≥ 38.0°C.

9.9.2 ECG

Supine ECG will be performed (after a resting time of minimum 3 minutes) at screening, prior to dosing, and approximately 1, 6, 12, and 24 hours post-dose, and at study exit. A window of 60 minutes will be allowed for all ECG measurement.

9.9.3 Echocardiograms

Evaluation of LVEF will be measured by an echocardiogram at screening, and at study exit. It will also be measured on study only if a subject experiences a cardiac AE that would require echocardiographic evaluation.

9.9.4 Physical Examination

A complete physical examination will be performed at screening. A complete physical examination includes assessments of the following: head, eyes, ears, nose, throat (HEENT), neck, chest, lungs, abdomen, musculoskeletal, dermatological, cardiovascular/peripheral vascular, and general neurological examination.

A brief physical examination will be done at check-in. A brief physical examination includes assessments of the following: HEENT, chest, lungs, abdomen, dermatological, cardiovascular/peripheral vascular, and areas of note elicited from the subject.

9.9.5 Body Measurement

Height and body weight will be measured and BMI will be calculated at screening. Body weight will also be measured at check-in.

9.9.6 Infusion Site Evaluation

The infusion site reaction assessment will be done before dosing, and approximately 1, 1.5* (at the end of infusion), 2, 4, and 24 hours post-dose by the Investigator or a delegate who will be blinded to treatment assignment using an infusion site reaction score. It consists of rating the severity of each reaction for the infusion site. A global severity rating for infusion site reactions will be included in the assessment of adverse events.

Infusion site reaction scores:

None	0	No reaction
Mild	1	Easily tolerated erythema and/or light bruising and/or mild pain
Moderate	2	Distributing erythema with swelling and/or distributing bruising and/or distributing pain
Severe	3	Almost intolerable symptoms, or clinically definite skin necrosis, characterized by any of the following: oozing, weeping, skin breakdown, ulceration, scar formation

In addition, bleeding or fluid loss at the infusion site will be documented. The diameter of any erythema or swelling will be measured (mm) in two dimensions. Reactions < 10 mm will not be listed as an adverse event unless it persists for more than 24 hours.

*If the infusion duration is more than 90 minutes, this timepoint will be taken within 5 minutes before the end of infusion.

9.9.7 Drug and Alcohol Screen

A urine drug screen (amphetamines, methamphetamines, barbiturates, benzodiazepines, tetrahydrocannabinol, cocaine, opiates, PCP, MDMA, methadone) will be performed at screening. A urine drug screen and an alcohol test will also be performed at check-in.

9.9.8 Laboratory Assessments

9.9.8.1 Hematology

Hematology will be performed at screening, on Day -1, Day 3, Day 8, Day 29, and at study exit. The following will be assessed: complete blood count with differential, hemoglobin, and hematocrit.

9.9.8.2 Biochemistry

Biochemistry will be performed after a fasting time of 8 hours at screening, on Day -1, Day 3, Day 8, Day 29, and at study exit. The following will be assessed: albumin, alkaline phosphatase, AST, ALT, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, total

cholesterol, urea, calcium, chloride, glucose, phosphorus, potassium, creatinine, sodium, total bilirubin, and total protein.

9.9.8.3 Serology

Hepatitis B (HBs Ag, HBsAb, and HBcAb), Hepatitis C (HCV) antibody, and HIV antigen and antibody detection will be performed at screening.

9.9.8.4 Urinalysis

Urinalysis will be performed at screening, on Day -1, Day 3, Day 8, Day 29, and at study exit. The following will be assessed: macroscopic examination, pH, specific gravity, protein, glucose, ketones, bilirubin, occult blood, nitrite, urobilinogen, and leukocytes. Unless otherwise specified, microscopic examination will be performed on abnormal findings upon Investigator judgment.

9.10 Emergency Event Management

Subjects will be closely monitored by a medical team during drug infusion and in the hours following the end of infusion, for the presence of symptoms of infusion-related reactions. Subjects will be also encouraged to quickly report any symptoms at any time they occur during the confinement. The necessary rescue material, equipment and appropriate medications will be available in the clinic to allow rapid intervention in case of emergency including, but not limited to:

tourniquet

oxygen

epinephrine 1:1000 solution for i.v. or endotracheal injection

antihistamines

corticosteroids

i.v. infusion solutions, tubing, catheters, and tape

The following procedures will be followed in the event of a suspected anaphylactic reaction during study drug infusion:

Stop the study drug infusion.

Disconnect from the cannula and aspirate 10 mL blood from the dosing cannula if the infusion is to be ceased immediately.

Maintain an adequate airway.

Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the Principal Investigator or a Sub-Investigator.

Continue to observe the patient and document observations.

9.11 Study Exit Procedures / Early Termination Procedures

Study exit procedures are scheduled to be performed at the last study visit, on Day 54 after the infusion. If not possible, or in case of early termination, all efforts will be made to complete study exit / early termination procedures within 14 days after the last participation of the subject in the study.

The study exit procedures include hematology, biochemistry, urinalysis, vital signs (BP, HR, RR, and OT), ECG, echocardiogram*, and adverse event monitoring will be performed on the last study day.

*Echocardiogram should be completed up to ±7 days after at the last study visit.

9.12 Data Collection and Evaluation

All clinical raw data will be recorded promptly, accurately, legibly, and indelibly by the clinical staff on raw data sheets and/or recorded electronically using validated software(s) and reported into Case Report Forms (CRFs). All raw data will be conserved in order to maintain data integrity. The Investigator and/or the clinical staff will assume the responsibility of ensuring the completeness and accuracy of the clinical data.

9.13 Subject Withdrawal and Replacement

Subjects will be advised that they are free to withdraw from the study at any time. Over the course of the study, the Sponsor and the Investigator or a delegate may withdraw any subject from the study for one of the reasons described below; subject withdrawal will be done in accordance with clinical sites SOP:

- safety reason;
- non-compliance with protocol requirements;
- significant protocol deviation;
- positive alcohol test or drug screen;

Clinical laboratory results will be reviewed by a Medical Sub-Investigator prior to dosing; subjects will be withdrawn from the study if it is deemed that the subject's safety may be at risk on the basis of these test results.

Subjects who withdraw or are withdrawn from the study after dosing will not be replaced. However, in the event that the number of drop-outs exceeds initial expectations, subjects who withdraw or are withdrawn might be replaced at the discretion of the Sponsor. Such replacement resulting in dosing more subjects than planned in this protocol would be documented in a protocol amendment.

Subjects who withdraw or are withdrawn will be asked to remain at the clinic until the Investigator or a delegate agrees that the subject is fine and can be discharged. As soon as subject withdrawal is confirmed, blood sampling will be stopped. A PK blood draw may be collected at the time of withdrawal if deemed required by the Investigator. Study exit procedures will be performed at the time of withdrawal from the study or as soon as possible thereafter.

9.14 Stopping Rules

The Principal Investigator will review the safety data on a regular basis in order to make a decision regarding continuation of the study based on consideration of the clinical significance of safety and tolerability parameters. For guidance, the study could be temporarily halted if one of the conditions described below occurs:

- New toxicological or pharmacological findings that invalidate the initial positive benefit-risk assessment.
- The occurrence of any specific related serious adverse event (SAE).
- The occurrence of any unexpected severe related AE.

In the event of related SAE or severe related AE, the subject's treatment assignment may be unblinded if judged appropriate. Then, the event warranting suspension will be thoroughly evaluated by the Principal Investigator and the Sponsor, and a decision will be made to discontinue the study or resume study drug administration.

Serious infusion reaction will stop dosing for an individual subject, but as it is an expected AE it would not meet the study stopping criteria.

9.15 Pregnancy

Should a pregnancy occur in a female partner of a male subject from the time of first investigational product administration until 60 days after, it must be reported and recorded on a pregnancy form provided by Syneos Health Safety and Pharmacovigilance. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed and documented even if the subject was withdrawn from the study. The follow-up period will be deemed to have ended when the health status of the child has been determined at birth and followed for 8 weeks after the birth for any potential abnormalities.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

9.16 Adverse Events

9.16.1 Adverse Event Definition

An AE is defined as any untoward medical occurrence in a clinical study subject administered a medicinal product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not it is related to the medicinal (investigational) product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the indication under investigation that is not recorded elsewhere in the CRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

9.16.2 Recording of Adverse Events

It is the responsibility of the Investigator to document all AEs that occur during the study (Study begins at the informed consent signature). Adverse events will be elicited by asking the subject a nonleading question, for example, “Have you experienced any new or changed symptoms since we last asked/since your last visit?”. Adverse events should be reported on the appropriate page of the CRF. AEs will be recorded and evaluated for their seriousness, severity, and relationship to the study medication. AEs will be collected and documented during the course of the study as specified in the Schedule of Events (Section 3). For a period of 54 days following the last study drug administration, AEs will also be documented if reported. AEs will be followed-up until complete resolution, or until the Investigator judges safe to discontinue follow-up.

The severity of all AEs will be graded according to criteria described in section 9.16.3. The relationship to the study medication will be classified according to section 9.16.4.

9.16.3 Assessment of Severity

The severity of AEs will be described and documented using the following definitions:

Severity	Description
Mild	Awareness of signs and symptoms, but are easily tolerated; are of minor irritant type; causing no limitations of usual activities. Signs or symptoms may require minor action.
Moderate	Discomfort sufficient to cause some limitations of usual activities and may require action.
Severe	Incapacitating with inability to carry out usual activities or significantly affects clinical status, and requires specific action and/or medical attention.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Definition of Serious Adverse Event. An AE of severe intensity may not be considered serious.

9.16.4 Assessment of Relationship to the Study Drug

Each AE must be classified based on medical judgment and according to the following categories: probably related, possibly related, unlikely related, and unrelated (not related).

The definitions for the causality assessments are as follows:

- **PROBABLY RELATED** (must have first three points)**:** This category applies to AEs that are considered, with a high degree of certainty, to be related to the investigational product. An AE may be considered probable, if:

  1) It follows a reasonable temporal sequence from the administration of the drug.
  2) It cannot be reasonably explained by the known characteristics of the subject’s clinical state, environmental or toxic factors or other modes of therapy administered to the subject.

3) It disappears or decreases on cessation or reduction in dose (there are important exceptions when an AE does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists; e.g., (1) bone marrow depression, (2) tardive dyskinesias).

4) It follows a known pattern of response to the suspected drug.

5) It reappears upon re-challenge.

- **POSSIBLY RELATED** (must have first two points)**:** This category applies to AEs in which the connection with the investigational product administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possible if, or when:

  1) It follows a reasonable temporal sequence from the administration of the drug.

  2) It may have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.

  3) It follows a known pattern of response to the suspected drug.

- **UNLIKELY RELATED** (must have first two points)**:** In general, this category is applicable to an AE that meets the following criteria:

  1) It does not follow a reasonable temporal sequence from the administration of the investigational product.

  2) It may readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.

  3) It does not follow a known pattern of response to the suspected drug.

  4) It does not reappear or worsen when the investigational is re-administered.

- **UNRELATED (NOT RELATED):** This category is applicable to AEs that are judged to be clearly and incontrovertibly due only to extraneous causes (disease, environment, etc.), and do not meet the criteria for medication relationship listed under unlikely, possible, or probable.

Determination of the Relationship of AEs to the Study Drug

	Probable	**Possible**	**Unlikely**	**Unrelated**
Clearly due to extraneous causes	–	–	–	+
Reasonable temporal association with drug administration	+	+	–	–
May be produced by subject clinical state, etc.	–	+	+	+
Known response pattern to suspected drug	+	+	–	–
Disappears or decreases on cessation or reduction of the dose	+	–	–	–

Reappears on re-challenge	+	–	–	–

9.16.5 Serious Adverse Events

9.16.5.1 Definition of Serious Adverse Event

A SAE is any event that meets any of the following criteria:

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject
- Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are:
  - ✓ Intensive treatment in an emergency room or at home for allergic bronchospasm
  - ✓ Blood dyscrasias or convulsions that do not result in inpatient hospitalization
  - ✓ Development of drug dependency or drug abuse

Expected and Unexpected Adverse Events

Expected AEs are those that are listed in the most recent versions of reference safety information (e.g. IB, summary of product characteristics (SmPC)).

Unexpected AEs are events not previously reported in nature, severity, or incidence in the applicable reference safety information.

If the relationship between the SAE and the investigational product is determined to be "Probably related" or "Possibly related", the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

9.16.6 Serious Adverse Events Reporting Procedures

Any serious adverse event (SAE) will be reported to the Sponsor's safety representative Syneos Health Safety and Pharmacovigilance via e-mail (preferred) or fax, within 24 hours of first knowledge by the Investigator, regardless of presumed causal relationship. The notification must be directed to:

Syneos Health Safety and Pharmacovigilance
Fax Number: 001-877-464-7787
Local Toll-Free Fax Number Australia: 1800 256 952

Email: safetyreporting@syneoshealth.com

For medical emergencies, contact:
Medical Monitor: David Fuller, MBBS, BPharm (Hons)
Mobile: +61 (0)4 5096 5709
Email: david.fuller@syneoshealth.com

Information on SAEs will be recorded on the SAE Report Form. Blank copies are included in the study Investigator's file. It is not acceptable for the Investigator to send photocopies of the patient's medical records to the Sponsor company or its representative in lieu of completion of the appropriate AE eCRF page or SAE Report Form. However, there may be instances when copies of medical records for certain cases are requested by the Sponsor or its representative. In this instance, all subject identifiers will be blinded on the copies of the medical records before submission to the Sponsor or its representative.

The completed SAE Form and SAE cover sheet should be sent via fax or email immediately upon completion to Syneos Health Safety and Pharmacovigilance. If the Investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before completing and sending the form.

Additional relevant information or clinical follow-up should be sent via fax or email to Syneos Health Safety and Pharmacovigilance as soon as it becomes available.

The Investigator should follow the subject with the event until resolution or stabilization of the condition.

Follow-up reports (as many as required) should be completed and faxed/emailed following the same procedure above.

A final report is required once the condition is resolved or stabilized and no more information about the event is expected. The final report should be completed and faxed/emailed following the same procedure above.

The Investigator must keep a copy of all documentation related to the event in the study site's files.

If the Investigator learns of any SAE, including death, at any other time after a subject completes the study, and he/she considers the event reasonably related to the study drug, the Investigator will promptly notify the Sponsor/Medical Monitor.

9.16.6.1 Serious Adverse Event Reporting to Regulatory Agency(ies)

The Sponsor (or Sponsor's safety representative) is responsible for notifying regulatory agencies of suspected, unexpected, serious adverse drug reactions (SUSARs) observed during conduct of studies in which the investigational drug is administered.

Notifications of fatal or life-threatening suspected, unexpected, serious adverse drug reaction must be made as soon as possible, but no later than 7 calendar days after becoming aware of the

information. Notifications of all other suspected, unexpected, serious adverse drug reactions that are neither fatal nor life-threatening must be made as soon as possible, but no later than 15 calendar days after becoming aware of the information.

The Sponsor is responsible to comply with any other applicable regulatory requirement(s) related to the reporting of SAE to regulatory authority(ies).

9.16.6.2 Serious Adverse Event Reporting to the Human Research Ethics Committee (HREC)

In addition to reporting the SAE to the Sponsor (or Sponsor's safety representative), the Investigator must also notify the Human Research Ethics Committee (HREC) that approved the study according to their requirements.

It is the responsibility of each clinical site to report as soon as possible, but no later than 7 calendar days after first knowledge by the Investigator, fatal or life-threatening suspected, unexpected, serious adverse drug reactions occurring at its site to the HREC responsible for the study.

It is the responsibility of each clinical site to report to the HREC all other suspected, unexpected, serious adverse drug reactions that are neither fatal nor life-threatening, as soon as possible, but no later than 15 calendar days after first knowledge by the Investigator.

Investigators and HRECs will also be notified of all significant safety issues (SSIs) that occur during the clinical trial. Each site is responsible for notifying its Research Governance Office (RGO)/Institution of these SSIs.

Copies of all correspondence relating to reporting of any SAE should be maintained in the study site files and will be checked routinely by the Study Monitor.

9.16.7 Adverse Events of Special Interest

Adverse events of special interest should be reported in the CRF. Adverse events of special interest for this study include the following:

Adverse events associated with suspected cases of infusion-related reactions (IRR) which occur within 24 hours of study drug administration and may show the following signs and symptoms:

- Fever and/or shaking chills
- Flushing and/or itching
- Alterations in heart rate and blood pressure
- Dyspnea or chest discomfort
- Back or abdominal pain
- Nausea, vomiting, and/or diarrhea
- Various types of skin rashes
- Anaphylaxis

Anaphylaxis due to IV drugs most often presents with the following signs and symptoms:

- Cutaneous symptoms: flushing, itching, urticarial, and/or angioedema (usually of face, eyelids, or lips)

- Respiratory symptoms: repetitive cough, sudden nasal congestion, shortness of breath, chest tightness, wheeze, sensation of throat closure or choking, and/or change in voice quality due to laryngeal edema
- Cardiovascular symptoms: faintness, tachycardia (or less often bradycardia), tunnel vision, chest pain, hypotension, sense of impending doom, and/or loss of consciousness
- Gastrointestinal symptoms: nausea, vomiting, abdominal cramping, and diarrhea

10. Study Termination

The study may be terminated by the Principal Investigator following consultation with the Sponsor, by the Sponsor or by the regulatory authorities. Following a decision to discontinue the trial, the Principal Investigator will immediately inform the active study subjects and the IEC responsible for this trial, stating the reasons for discontinuation of the study and, furthermore, advise them in writing of any potential risks to the health of study subjects or other persons. It is the Sponsor's responsibility to report the premature termination of the study to the regulatory authority(ies), when required by the applicable regulatory requirement(s).

11. Analytical Methodology

When applicable, samples will be transported to the bioanalytical facility in at least two separate shipments, with each set of aliquots in separate shipments. Once the bioanalytical laboratory confirms receipt of the first shipment, the second set of aliquots may be sent. The samples should be packed on sufficient dry ice to keep them frozen for at least 72 hours.

CPR Pharma Services will analyse trastuzumab in serum samples using an ELISA assay.

ADA samples will be analyzed using a validated immunoassay with tiered approaches (screening, confirmatory and titrations) by CPR Pharma Services.

Samples confirmed to be positive for ADA will be further tested for NAb using a validated non-cell based antibody neutralization assay.

Samples from subjects included in the pharmacokinetic population (see section12.2) and from subjects who were withdrawn from the study due to adverse events will be analyzed.

The bioanalytical work in support to the study will be conducted in compliance with the GCP using the SOPs in place in each bioanalytical laboratory performing analyses. Those SOPs should be written in accordance with the current regulations in place in the industry: Guidelines on Bioanalytical Method Validation, Good Laboratory Practices (GLP) and Guideline for GCP ICH E6 (R2).

12. Pharmacokinetic and Statistical Analyses

Pharmacokinetic analysis will be performed using Phoenix® WinNonlin®, which is validated for bioequivalence/bioavailability studies. Inferential statistical analyses will be performed using SAS® according to EMA and FDA guidelines.

Bioanalysis of all samples should be completed prior to the initiation of the PK and statistical analyses.

12.1 Pharmacokinetics

The following PK parameters will be calculated by standard non-compartmental methods for trastuzumab:

Primary parameter:

1) $AUC_{0\text{-}inf}$: area under the concentration-time curve from time zero to infinity (extrapolated)

Secondary parameters:

1) $AUC_{0\text{-}t}$: area under the concentration-time curve from time zero to the last non-zero concentration
2) C_{max}: maximum observed concentration
3) Residual area: calculated as $100*(1- AUC_{0\text{-}t} / AUC_{0\text{-}inf})$
4) T_{max}: time of observed C_{max}
5) $T_{½\ el}$: elimination half-life
6) K_{el}: elimination rate constant
7) Cl: apparent body clearance, calculated as $Dose/AUC_{0\text{-}inf}$
8) V_d: apparent volume of distribution, calculated as $Dose/(K_{el} \times AUC_{0\text{-}inf})$

Additional PK analysis may be performed.

12.2 Analysis Populations

12.2.1 Safety Population

The safety population is defined as all subjects who received at least one dose of the study medication.

12.2.2 Intent-to-Treat Population

The Intent-to-Treat Population will comprise all randomized subjects and will be based on the randomized dose, regardless of which treatment the subject actually received.

12.2.3 Pharmacokinetic Concentration Population

The PK Concentration Population will comprise all subjects who receive any amount of IP and have at least one quantifiable PK concentration (≥LLOQ), and will be based on the actual treatment received, if this differs from that to which the subject was randomized.

12.2.4 Pharmacokinetic Parameters Population

The PK population will include all subjects who received a complete dose of study drug within the maximum prescribed time (i.e. 3 hours (± 10 minutes)) and for whom the PK profile can be adequately characterized.

Any subject with pre-dose concentrations will be presented in the concentrations and PK tables but excluded from descriptive statistics and ANOVA if the pre-dose concentration is greater than 5% of the C_{max} value for that subject.

Data (concentrations and PK parameters) from subjects excluded due to a pre dose concentration greater than 5% of their C_{max} or from subjects withdrawn due to AEs will be presented but excluded from the statistical analyses (i.e., descriptive statistics and ANOVA).

12.3 Statistical Analyses of Pharmacokinetic Data

Individual and mean serum concentration versus time curves will be presented for both linear and semi-log scales. Descriptive statistics (arithmetic and geometric means, standard deviation [SD], coefficient of variation [CV (%)], minimum [min.], maximum [max.], and median) of the serum concentrations versus time will be presented as well for the PK parameters.

The study will be dosed in more than one group. Considering that all subjects will have similar demographics and will be recruited from the same general population (i.e., same regional/city location), and that the same protocol requirements and procedures will be followed within each group, no group terms will be included in the primary analysis.

The analysis for each comparison (A vs. B, A vs. C, and B vs. C) will be conducted excluding the data from the treatment that is not relevant for the comparison in question.

EMA (A vs. B):

As primary analysis, using GLM procedures in SAS, ANOVA will be performed on untransformed K_{el} and $T_{½\,el}$ and on ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} at the alpha level of 0.05. The factor Treatment will be incorporated in the model. Coefficient of variation (CV%) will be estimated for AUC_{0-t}, AUC_{0-inf} and C_{max}. The ratio of geometric means (A/B) and 90% confidence interval for the ratio of geometric means, based on least-squares means from the ANOVA of the ln-transformed data, will be calculated for AUC_{0-t}, AUC_{0-inf}, and C_{max}. Wilcoxon's test will be performed on T_{max}.

References comparison for EMA bridging (B vs. C):

As primary analysis, using GLM procedures in SAS, ANOVA will be performed on untransformed K_{el} and $T_{½\ el}$ and on ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} at the alpha level of 0.05. The factor Treatment will be incorporated in the model. Coefficient of variation (CV%) will be estimated for AUC_{0-t}, AUC_{0-inf} and C_{max}. The ratio of geometric means (B/C) and 90% confidence interval for the ratio of geometric means, based on least-squares means from the ANOVA of the ln-transformed data, will be calculated for AUC_{0-t}, AUC_{0-inf}, and C_{max}. Wilcoxon's test will be performed on T_{max}.

FDA (A vs. C):

As primary analysis, using GLM procedures in SAS, ANOVA will be performed on untransformed T_{max}, K_{el} and $T_{½\ el}$ and on ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} at the alpha level of 0.05. Factor incorporated in the model will include only the Treatment. Coefficient of variation (CV%) will be estimated for AUC_{0-t}, AUC_{0-inf} and C_{max}. The ratio of geometric means (A/C) and 90% confidence interval for the ratio of geometric means, based on least-squares means from the ANOVA of the ln-transformed data, will be calculated for AUC_{0-t}, AUC_{0-inf}, and C_{max}.

A complete description of the statistical analyses to be performed with the PK parameters will be presented in the Statistical Analysis Plan. Additional statistical analysis may be performed.

12.4 Criteria for Pharmacokinetic Similarity Acceptance

EMA (A vs. B; B vs. C**):**

The 90% confidence intervals for the ratio of geometric means (A/B) based on least-squares means from the ANOVA of the ln-transformed AUC_{0-inf} must be within 80.00% to 125.00%.

The 90% confidence intervals for the ratio of geometric means (B/C) based on least-squares means from the ANOVA of the ln-transformed $AUC_{0\ inf}$ must be within 80.00% to 125.00%.

FDA (A vs. C):

The 90% confidence intervals for the ratio of geometric means (A/C) based on least-squares means from the ANOVA of the ln-transformed AUC_{0-inf} must be within 80.00% to 125.00%.

13. Safety, Tolerability, and Immunogenicity Evaluation

13.1 Analyses of Safety, Tolerability, and Immunogenicity Data

Demographic parameters will be summarized descriptively. Safety, tolerability, and immunogenicity data will be reported using descriptive statistics (arithmetic mean, SD, CV%, min., max., and median). No inferential statistical analysis of safety data is planned.

AEs will be summarized by treatment group, and will be categorized in subsets of all treatment-emergent AEs, and of all treatment-related AEs.

Clinical laboratory and vital signs will be summarized by treatment and change from baseline.

Immunogenicity assessments will be summarized by treatment group.

A complete description of the descriptive statistics to be performed with the safety, tolerability and immunogenicity data will be presented in the Statistical Analysis Plan.

14. Final Report

A final report including clinical and statistical sections will be the responsibility of Syneos Health. The bioanalytical laboratory will provide its bioanalytical section of the report.

In the event that the study is prematurely terminated, Syneos Health will produce an abbreviated safety report. In such an event, raw data will not be submitted with the abbreviated report but will be archived at the clinical sites, unless requested by the Sponsor.

15. Regulatory Considerations and Quality Assurance

15.1 Independent Ethics Committee Approval of Protocol and Other Study Documents

The Investigator(s) agree to provide the IEC with all appropriate documents, including a copy of the protocol/amendments, ICFs, advertising text (if any), Investigator's Brochure (if any) and any other written information provided to study subjects. The trial will not begin until the Investigators have obtained the IEC favourable written approvals for the above-mentioned study documents. A properly executed written ICF shall be read, signed, and dated by each subject prior to entering the trial or prior to performing any study procedure. The original signed and dated ICF will be kept at the clinical sites, and a copy will be given to the subject.

In the event that the protocol is amended, the revised protocol must be approved by the IEC prior to its implementation, unless the changes involve only logistical or administrative aspects of the trial. If a revised ICF is introduced during the study, each subject's further consent must be obtained. The new version of the ICF must be approved by the IEC, prior to subsequently obtaining each subject's consent.

The Investigators and the Sponsor's representative must sign the protocol and its amendments (if any) before initiating the study.

It is the Sponsor's responsibility to submit the protocol and its amendments (if any), and the ICFs to regulatory authorities when necessary.

15.2 Compliance

This study will be conducted in compliance with the protocol, GCP, the requirements of Directive 2001/83/EC Annex I, as amended by Directive 2003/63/EC and Directive 2001/20/EC, and all applicable regulations, including the Federal Food, Drug and Cosmetic Act, U.S. applicable Code of Federal Regulations (title 21), and any IEC requirements relative to clinical studies. The study will also be conducted in compliance with the recommendations laid down in the most recent version of the Declaration of Helsinki, with the exception that registration of such Phase 1 trials in a publicly accessible database is not mandatory.

15.3 Liability

If a bodily injury is sustained, resulting directly from the use of the study drug, the Sponsor will reimburse for reasonable physician fees and medical expenses necessary for diagnosis and treatment of only the bodily injury which is not covered by the subject's medical or hospital insurance, provided that the injury is not due to a negligent or wrongful act or omission by the study doctor and his/her staff, in which case the clinical site would cover associated fees.

15.4 Quality Assurance Program

The clinical sites have established Quality Control (QC) and Quality Assurance (QA) systems with written SOPs to ensure that the study will be conducted and data will be generated, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirements. A rigorous QC program is applied to ensure accuracy of all data and reports.

15.5 Audits, Inspections and Monitoring

In accordance with the principles of GCP and GLP, the study may be inspected by the QA unit of the clinical sites, regulatory authorities, the Sponsor and Syneos Health. The Sponsor is entitled to access information about the status of the study and to review the original documents of the study.

16. Confidentiality and Retention of Study Records

This document contains trade secrets and commercial information that is confidential and may not be disclosed to third parties. Persons to whom this study protocol is disclosed must be informed that all the information herein is confidential and may not be further divulged. These restrictions will apply as well to all future communications if deemed privileged or confidential. Publication of the study results may only be allowed with written permission from the Sponsor.

All information on a subject obtained during the conduct of the study will be kept confidential. Subjects will be identified by an anonymized identifier on all samples and study records provided to the Sponsor or designee. In compliance with ICH GCP, the Sponsor's authorized representatives, monitor(s), auditor(s), IEC, and regulatory authority(ies) will be granted direct access to the subject's original trial-related records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations. Consent from the subject for disclosure of such information will be obtained in writing in the ICF. In addition, should a subject requires medical care or hospitalization during the course of the study, the clinical site's representatives may contact the treating physician with the subject's consent, except that consent may not be requested if there is an emergency situation. If the results of the study are published, the subject's identity will remain confidential.

The clinical site will maintain adequate study records for 25 years after completion or termination of study. The Sponsor will be notified prior to the destruction of study records.

17. References

1. Herceptin®, Annex I. Summary of Product Characteristics. Version last updated on 2017-04-19. Available online at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000278/WC500074922.pdf
2. Herceptin®, Prescribing Information. Version revised on 10/2018. Available online at: http://www.gene.com/download/pdf/herceptin_prescribing.pdf
3. HD201 Investigator's Brochure, Prestige BioPharma Pte Ltd. Version 2.0, 28.07.2017
4. EMA Assessment report Ontruzant, EMA/CHMP/9855/2018, 14 September 2017
5. Yin, et al. A randomised phase 1 pharmacokinetic trial comparing the potential biosimilar PF-05280014 with trastuzumab in healthy volunteers (REFLECTIONS B327-01). Br J Clin Pharmacology. 2014 Dec; 78(6):1281-90.
6. EMA «Guideline on Similar Biological Medicinal Products», CHMP/437/04 Rev. 1, October 2014.
7. EMA «Guideline on similar biological medicinal products containing monoclonal antibodies», EMA/CHMP/BMWP/403543/2010, May 2012.
8. FDA Final « Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product», April 2015
9. FDA Draft « Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product», May 2014

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PRESTIGE BIOPHARMA

Protocol Clarification Letter

Date: 28 February 2019

Study Title: A DOUBLE-BLIND, RANDOMISED, PARALLEL GROUP STUDY TO DEMONSTRATE THE EQUIVALENT PHARMACOKINETIC PROPERTIES OF A SINGLE INTRAVENOUS DOSE OF HD201 VERSUS EU-HERCEPTIN®AND US-HERCEPTIN® IN HEALTHY MALE SUBJECTS

Protocol Number: TROIKA-1

Clinical Trial Protocol Version: 17 January 2018 / Version 1.0

There is one item in the current TROIKA-1 protocol dated 17 January 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
There is an inconsistency on page 14 and 30 regarding assessments being done at the start or end of infusion time:

Page 14:

5. Injection site evaluation: before dosing, at the end of infusion (1.5) and approximately 1, 2, 4, and 24 hours after the start of infusion.
6. PK Samples: pre-dose and 1.5 (within 5 minutes before the end of infusion), 3 (1.5 hours post-end of infusion), 8, 24, 48 (Day 3), 96 (Day 5), 168 (Day 8), 336 (Day 15), 504 (Day 22), 672 (Day 29), 1008 (Day 43), and 1272 hours (Day 54) post-dose.

Page 30:

9.9.6 Infusion Site Evaluation

The infusion site reaction assessment will be done before dosing, and approximately 1, 1.5* (at the end of infusion), 2, 4, and 24 hours post-dose by the Investigator or a delegate who will be blinded to treatment assignment using an infusion site reaction score. It consists of rating the severity of each reaction for the infusion site. A global severity rating for infusion site reactions will be included in the assessment of adverse events.

This letter is to clarify the abovementioned query.

Injection site should be evaluated as follow:

1. Before dosing – prior start of infusion
2. 1.5 hrs – at the end of infusion (90 mins from dosing start time)
3. 1,2,4 and 24 hours – after end of infusion

PK sampling should be as follow:

1. Pre-dose – before dosing start

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Tel +65 6863 9575, Fax +65 6863 4834

2. 1.5 hour timepoint – within 5 mins before end of infusion
3. 3,8,24,48,96,168,336,504,672,1008 and 1272 hours – after end of infusion.

Signed:



Peggy Feyaerts,
Clinical Operations Director