# Statistical Analysis Plan for Interventional Studies

**Sponsor Name:** Prestige BioPharma Pte Ltd

**Protocol Number: TROIKA-1**
**Protocol 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 Version and Date: Version Final, 17 Jan 2019**

**Syneos Health Project Code: 7002750**

**Author:** Siva Durga Prasasd Sattu, Sr.Statistician

**Notice of Confidential and Proprietary Information:**

The information contained in this document is confidential belonging to Prestige BioPharma Pte Ltd. Acceptance of this document constitutes agreement by the recipient that no information contained herein will be published or disclosed without prior written authorization from an official of Prestige BioPharma Pte Ltd. However, this document may be disclosed to appropriate Institutional Review Board and Ethics Committees or duly authorized representatives of a national regulatory authority under the condition that they are requested to keep it confidential. In the event of an actual or suspected breach of this obligation, Syneos Health should be notified promptly.

## Revision History

| **Version #** | **Date** (DD-Mmm-YYYY) | **Document Owner** | **Revision Summary** |
|---|---|---|---|
| Final 1.0 | 10-Apr-2019 | Siva Durga Prasad Sattu | |

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

## Approvals

### Syneos Health Approval

| Siva Durga Prasad, Sr. Statistician | | 11 Apr 2019 |
|---|---|---|
| Name, Title<br>Lead Biostatistician | Signature | Date (DD-Mmm-YYYY) |

| Sean T. Marume, Principal Statistician | | 16-Apr-2019 |
|---|---|---|
| Name, Title<br>Senior Reviewing Biostatistician | Signature | Date (DD-Mmm-YYYY) |

### Prestige BioPharma Pte Ltd Approval

| Felica Ang, Project Manager | felica | 11-Apr-2019 |
|---|---|---|
| Name, Title<br>Sponsor Contact | Signature | Date (DD-Mmm-YYYY) |

## Table of Contents

Revision History ..... 2
**Approvals** ..... 3
1. Glossary of Abbreviations ..... 7
2. Purpose ..... 9
   2.1. Responsibilities ..... 9
   2.2. Timings of Analyses ..... 9
3. Study Objectives ..... 10
   3.1. Primary Objective ..... 10
   3.2. Secondary Objective ..... 10
   3.3. Brief Description ..... 10
   3.4. Subject Selection ..... 11
   3.5. Determination of Sample Size ..... 11
   3.6. Treatment Assignment & Blinding ..... 11
4. Endpoints ..... 12
   4.1. Pharmacokinetic Endpoints ..... 12
   4.2. Safety, Tolerability, and Immunogenicity Endpoints ..... 12
5. Analysis Populations ..... 13
   5.1. Safety Population ..... 13
   5.2. Intent-to-Treat Population ..... 13
   5.3. Pharmacokinetic Concentration Population ..... 13
   5.4. Pharmacokinetic Parameters Population ..... 13
   5.5. PK Similarity Population ..... 13
   5.6. Protocol Deviations ..... 13
6. General Aspects for Statistical Analysis ..... 14
   6.1. General Methods ..... 14
   6.2. Key Definitions ..... 14
   6.3. Missing Data ..... 15
   6.4. Handling of the Below the Lower Limit of Quantitation (BLQ) and the No Reportable Concentration Values ..... 15
   6.5. Handling of the Difference Between the Scheduled and the Actual Sampling Times ..... 15

This document is confidential.

6.6. Visit Windows ....15
7. Demographic and Baseline Characteristics ....16
7.1. Subject Disposition and Withdrawals ....16
7.2. Demographic and Baseline Characteristics....16
7.3. Medical History ....16
8. Analysis Of Pharmacokinetics ....17
8.1. PK Sampling Schedule ....17
8.2. Immunogenicity Sampling Schedule ....17
8.3. Derived PK Parameters ....18
8.4. Summary of PK Variables....19
8.5. Statistical Analyses of Pharmacokinetic Data ....19
8.6. Treatments Comparisons....20
8.7. Criteria for Pharmacokinetic Similarity Acceptance ....20
9. Safety....22
9.1. Adverse Events....22
9.2. Laboratory Evaluations ....22
9.3. Vital Signs....23
9.4. 12-Lead ECG....23
9.5. Echocardiogram....23
9.6. Infusion Site Evaluation ....23
9.7. Medication ....24
9.8. Immunogenicity analysis....24
9.9. Other Safety ....24
10. Interim Analyses....25
11. Changes from Analysis Planned in Protocol....26
12. Programming Considerations ....27
12.1. General Considerations ....27
12.2. Table, Listing, and Figure Format ....27
12.2.1. General ....27
12.2.2. Headers....27
12.2.3. Display Titles....28
12.2.4. Column Headers ....28

This document is confidential.

12.2.5. Body of the Data Display ..... 28
12.2.6. Footnotes ..... 31
13. Quality Control ..... 32
14. Index of Tables, Listings and Figures ..... 33
15. Appendices ..... 35
16. Reference List ..... 36

This document is confidential.

# 1. Glossary of Abbreviations

| Abbreviation | Description |
|---|---|
| AE | Adverse event |
| ANOVA | Analysis of variance |
| ATC | Anatomical Therapeutic Chemical |
| AUC | Area under the curve |
| BMI | Body mass index |
| BQL | Below the quantification limit |
| CI | Confidence interval |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| GLM | Generalized linear model |
| HIV | Human immunodeficiency virus |
| ICF | Informed consent form |
| IP | Investigational Product |
| ITT | Intent-to-Treat |
| IV | Intravenous |
| LLOQ | Lower limit of quantification |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MTD | Maximum tolerated dose |
| OLS | Ordinary least squares |
| PK | Pharmacokinetic(s) |
| PT | Preferred term |
| RTF | Rich text format |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SAS | Statistical Analysis System |
| SD | Standard deviation |
| SOC | System organ class |
| SOP | Standard Operating Procedure |
| TEAE | Treatment Emergent Adverse Event |

This document is confidential.

| Abbreviation | Description |
|---|---|
| TLF | Table, Listing and Figure |
| WHO | World Health Organization |

# 2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

## 2.1. Responsibilities

Syneos Health will perform the statistical analyses and are responsible for the production and quality control of all tables, listings and figures. Pharmacokinetic (PK) analysis will be performed by PK analyst.

## 2.2. Timings of Analyses

*Final Analysis:*

The primary analysis of safety, immunogenicity and PK is planned after all subjects complete the final study visit or terminate early from the study. Bioanalysis of all samples should be completed prior to the initiation of the PK and statistical analyses.

This document is confidential.

# 3. Study Objectives

## 3.1. Primary Objective

The primary objective of this study is:

- 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.

## 3.2. Secondary Objective

The secondary objective of this study is:

- 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.

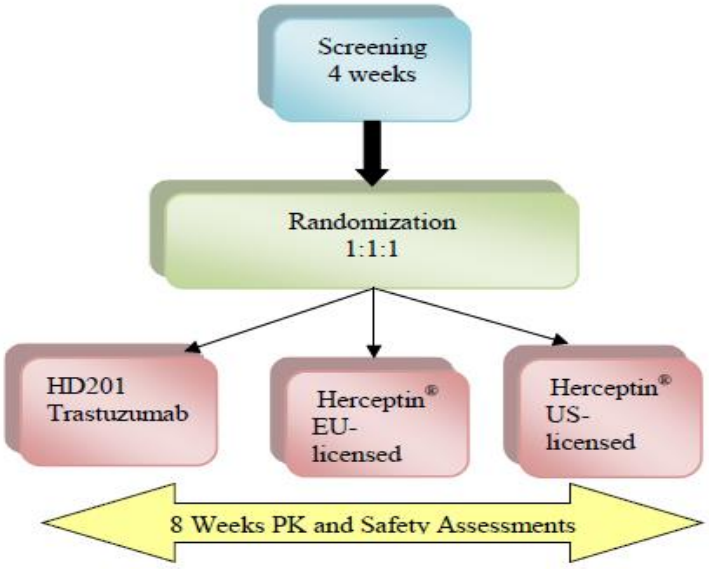
## 3.3. Brief Description

This will be a 2-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, PK, 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**



### 3.4. Subject Selection

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.

### 3.5. Determination of Sample Size

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 PK biosimilarity. In order to account for possible dropouts, 35 subjects will be included in each group

In view of the above, it is planned to enroll 105 subjects in a 1:1:1 ratio to ensure that there are enough evaluable subjects.

### 3.6. Treatment Assignment & 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.

**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.

All doses will be administered at 6 mg/kg i.v. infusion.

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 AEs 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.

This document is confidential.

# 4. Endpoints

## 4.1. Pharmacokinetic Endpoints

The PK endpoints are:

**Primary Parameters:**

- $AUC_{0\text{-}inf.}$

**Secondary Parameters:**

- $AUC_{0\text{-}t}$, $C_{max}$, Residual area, $T_{max}$, $T_{½\ el}$, $K_{el}$, Cl, and $V_d$.

Additional PK analysis may be performed as secondary parameters.

## 4.2. 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.

This document is confidential.

# 5. Analysis Populations

All subjects' inclusion status into each analysis population will be determined after database lock and prior to unblinding for the final analysis.

## 5.1. Safety Population

The safety population is defined as all subjects who received at least 1 dose of the study medication.

## 5.2. 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.

## 5.3. Pharmacokinetic Concentration Population

The PK Concentration Population will comprise all subjects who receive any amount of IP and have at least 1 quantifiable PK concentration (≥LLOQ), and will be based on the actual treatment received, if this differs from that to which the subject was randomized.

## 5.4. 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 analysis of variance (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).

## 5.5. PK Similarity Population

The PK similarity Population will include all subjects from the PK Parameters Population who have at least $AUC_{0\text{-}inf}$ available from at least one treatment and are without any major protocol deviations that would affect the analysis.

The inferential analysis will be carried out for all subjects in the PK similarity Population.

## 5.6. Protocol Deviations

Subject data will be examined for evidence of protocol deviations in order to assess how well the protocol was followed. Possible protocol deviations will be independently reviewed and acknowledged by Prestige BioPharma Pte Ltd.

All protocol deviations will be detailed in a listing, and summarized by randomized treatment.

This document is confidential.

# 6. General Aspects for Statistical Analysis

## 6.1. General Methods

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

All data in the database will be presented in the data listings. Unless otherwise stated, all listings will be sorted by randomized treatment group (HD201, Herceptin-US or Herceptin-EU), subject number and assessment date/time.

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

- HD201 6 mg/kg (A)
- Herceptin-EU 6 mg/kg (B)
- Herceptin-US 6 mg/kg (C)

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

For the serum PK data, summary statistics will also include the geometric mean and geometric coefficient of variation (%) (excluding $T_{max}$, $T_{½\ el}$, Residual area and $K_{el}$).

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

## 6.2. Key Definitions

*Baseline*:

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

*Study Day*:

Study day will be calculated using study drug administration date as the reference date. If the date of interest occurs on or after the study drug administration date, study day will be calculated as (date of interest – study drug administration date) + 1. If the date of interest occurs prior to the study drug

This document is confidential.

administration date, study day will be calculated as (date of interest – study drug administration date). There will be no study day 0.

### 6.3. Missing Data

All withdrawals will be included in all summaries up to the time of withdrawal., except for PK data where rules of inclusion are defined in Section 5.4.

Only observed data will be used in the data analysis except for concentration values below the lower limit of quantitation (BLQ) and samples with no reportable value occurring prior to dosing as described in Section 6.4. No attempt will be made to extrapolate or interpolate estimates for missing data.

### 6.4. Handling of the Below the Lower Limit of Quantitation (BLQ) and the No Reportable Concentration Values

All concentrations values BLQ will be set to zero as well as for PK parameter calculations for samples with no reportable value occurring prior to the dosing for a given period. For tabulation, graphical representation and calculation purposes, all samples with no reportable value observed after dosing will be set to missing.

### 6.5. Handling of the Difference Between the Scheduled and the Actual Sampling Times

For all sampling times, the actual sampling times will be calculated as the difference between the sample collection actual clock time and the actual clock time of the start of infusion. The actual post-dose sampling times expressed in hours and rounded off to three decimal digits will be used to calculate the PK parameters, except for pre-dose samples occurring prior to the start of infusion, which will always be reported as zero (0.000), regardless of the time difference. In the PK section of the report, scheduled sampling times will be presented in concentration tables and mean graphs while actual times are presented for the individual graphs. A listing of the actual times for PKs will be provided for PK samples.

### 6.6. Visit Windows

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

This document is confidential.

# 7. Demographic and Baseline Characteristics

## 7.1. Subject Disposition and Withdrawals

Subject enrollment and disposition, including reasons for early withdrawal from the study, will summarized by randomized treatment.

All subject disposition parameters will be presented for individual subjects in the listings.

## 7.2. Demographic and Baseline Characteristics

Demographic and baseline characteristics (including gender, age, race, ethnicity, child bearing potential, height, weight and body mass index [BMI] will be summarized by randomized treatment and overall.

All demographic and baseline characteristics (and other screening data) will be listed.

## 7.3. Medical History

Medical history, urine drug screen and alcohol breath test will be listed only.

This document is confidential.

# 8. Analysis Of Pharmacokinetics

All serum concentration summaries will be conducted on the PK Concentration Population. All serum PK parameter summaries will be conducted on the PK Parameters Population. PK analysis will be performed using Phoenix WinNonlin® version 8.0.

Analysis of PK similarity will be conducted on the PK Similarity Population.

## 8.1. PK Sampling Schedule

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 pharmacokinetic and statistical analyses.

## 8.2. Immunogenicity Sampling Schedule

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.

This document is confidential.

### 8.3. Derived PK Parameters

*Serum PK parameters*:

| Parameter | Definition | Method of Determination |
|---|---|---|
| $AUC_{0-t}$ | Area under the serum concentration-time curve, from time zero to the last non-zero concentration | Linear trapezoidal method |
| $AUC_{0-inf}$ | Area under the serum concentration-time curve, from time zero extrapolated to infinity | *$AUC_{0-t}$ + last measurable concentration/* $K_{el}$ |
| Residual area | Percentage of $AUC_{0-inf}$ due to extrapolation from the time of last concentration to infinity. | $(1 - AUC_{0-t}/ AUC_{0-inf})*100$ |
| $C_{max}$ | Maximum observed serum concentration | Observed directly from data |
| $T_{max}$ | Time to reach $C_{max}$. If the maximum value occurs at more than 1 timepoint, $T_{max}$ is defined as the first timepoint with this value | Observed directly from data |
| $T_{½\ el}$ | Apparent first-order terminal elimination half-life | $ln(2)/K_{el}$ |
| $K_{el}$ | Apparent first-order terminal elimination rate constant | Estimated by linear regression of the terminal elimination phase of the log-linear drug concentration-time curve |
| Cl | Apparent total body clearance | Estimated as $Dose/AUC_{0-inf}$. |
| $V_d$ | Apparent volume of distribution | Estimated as $Dose/(K_{el} \times AUC_{0-inf})$. |

Note1: $K_{el}$ will be the negative of the estimated slope of the linear regression of the log-transformed concentration (natural logarithm) versus time profile in the terminal elimination phase. At least three concentration points will be used in estimating $K_{el}$. The time point where log-linear $K_{el}$ calculation begins ($K_{el}$ Lower), and the actual sampling time of the last quantifiable concentration used to estimate the $K_{el}$ ($K_{el}$ Upper) will be reported with the correlation coefficient from the linear regression to calculate $K_{el}$.

Note2: Additional PK analysis may be performed.

This document is confidential.

### 8.4. Summary of PK Variables

*Concentration:*

Serum concentrations will be listed and summarized, by nominal sampling time, and actual treatment. The below the quantification limit (BQL) will be set to zero in summary tables. BQL will be displayed in listings.

Individual subject and mean ± SD profiles of the serum concentration-time data will be plotted by treatment using actual and nominal times, respectively. These profiles will be presented on both linear-linear and log-linear scales.

*Parameters*:

Serum PK parameters will be listed and summarized descriptively by actual treatment.

For plots and derivation of serum pharmacokinetic parameters, the BQL values that occur in a profile before the first measurable concentration will be set to zero. The BQL values that occur after first measurable concentration will be set to missing.

### 8.5. 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 $T_{max}$.

This document is confidential.

**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 $C_{max}$.

## 8.6. Treatments Comparisons

Treatments Comparisons analysis of PK parameters will be undertaken for $AUC_{0-t}$, $AUC_{0-inf}$, and $C_{max}$, based on the PK similarity Population. These parameters will be statistically compared across each treatment group (i.e. each pairwise comparison for HD201, Herceptin-US and Herceptin-EU). The estimated ratio of geometric means will be used to perform these comparisons.

The linear model will be specified as follows. The response variable will be the natural-log transformed PK Parameter, and the model will include Treatment as a fixed effect. The model parameters will be estimated by ordinary least squares (OLS).

The model has the form:

ln(PK Parameter) = μ + Treatment + ϵ,

where μ represents the overall mean, Treatment is a fixed effect with three factors, and ϵ represents the associated model error.

From this model, the difference in means will be estimated for each pairwise comparison, accompanied by a corresponding (two-sided) 90% confidence interval (CI). These point estimates and confidence endpoints will be exponentiated using base *e* in order to obtain a point and interval estimate for the ratio of geometric means (presented to three decimal places). If this transformed CI is wholly contained within the range (0.8,1.25), then PK similarity will be concluded.

The SAS code to fit the model will follow the format given below (using the Mixed Procedure). The input variables, datasets and labels are depicted in slanted red text and have been given generic names.

```
proc mixed data = dataset order = data;
  class treat(ref = 'Herceptin-EU');
  model ln_pk_parameter = treat;
  estimate 'HD201 vs. Herceptin-EU' treat 1 -1 0 / cl alpha = 0.1;
  estimate 'HD201 vs. Herceptin-US' treat 1 0 -1 / cl alpha = 0.1;
  estimate 'HD201 -EU vs. Herceptin-US' treat 0 1 -1 / cl alpha = 0.1;
  ods output estimates = estimates;
run;
```

## 8.7. 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%.

This document is confidential.

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

This document is confidential.

# 9. Safety

Summaries of safety, tolerability and immunogenicity data will be based on the Safety Population.

## 9.1. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or higher. AEs will be grouped by system organ class (SOC) and preferred term (PT) and summarized by actual treatment. The summary tables will present the number and percentage of total subjects and number of events by SOC and by PT.

All AE summaries will be restricted to TEAEs only. Treatment emergent AEs are defined as AEs that commence on or after the time of study drug administration. Adverse events without an onset date or time or AEs with an onset date of the date of study drug administration but without an onset time will be defined as treatment emergent, except if an incomplete date (e.g., month and year) clearly indicates that the event started prior to administration of study drug or if the AE stop date indicates that the event started and stopped prior to administration of study drug.

Treatment-emergent AEs will be summarized by actual treatment. The number and percentage of subjects experiencing AEs and the number of TEAEs will be tabulated. Subjects who experience the same AE (in terms of MedDRA PT) more than once will only be counted once for that event, however, the total number of events will also be counted per category. This also applies to sub-categories displayed in the summaries.

The following summaries will be presented:

- Overall summary of TEAEs
- TEAEs by SOC and PT
- TEAEs by SOC, PT, and severity
- TEAEs by SOC, PT, and relationship to study drug
- Serious TEAEs by SOC and PT

All AEs will be listed. This will include a separate listing of serious adverse events (SAEs), and Non-TEAEs

## 9.2. Laboratory Evaluations

Laboratory data (hematology, clinical chemistry and urinalysis) will be summarized at each protocol scheduled visit, by actual treatment. Actual values and actual changes from baseline will be presented.

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

Abnormal results will be flagged in the listings.

This document is confidential.

### 9.3. Vital Signs

Vital signs will be summarized at each protocol-scheduled time point, by actual treatment. Actual values and actual changes from baseline will be presented.

### 9.4. 12-Lead ECG

ECG values will be summarized at each protocol-scheduled visit, by actual treatment. Actual values and actual changes from baseline will be presented.

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

Abnormal results will be flagged in the listings.

### 9.5. Echocardiogram

Echocardiogram values will be summarized at each protocol-scheduled visit, by actual treatment. Actual values and actual changes from baseline will be presented.

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

Abnormal results will be flagged in the listings.

### 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 AEs.

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 2 dimensions. Reactions < 10 mm will not be listed as an AE 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

This document is confidential.

end of infusion.

### 9.7. Medication

Concomitant medications will be coded using the latest version of the World Health Organisation (WHO) Drug coding dictionary. The version will be presented in the table/listing footnotes.

Prior and concomitant medications will be grouped by Anatomical Therapeutic Chemical (ATC) class and PT. The summary tables will show the number and percentage of subjects by ATC class, PT and by actual treatment. Prior medications are those medications that were stopped prior to study drug administration. Concomitant medications are medications taken at least once after study drug administration. Medications stopped on the same day as study treatment will be considered as concomitant medications. Only concomitant medications will be summarized. Concomitant medications will be summarized by actual treatment and class. Prior medications will be listed only. For the summaries of concomitant medications, subjects who take the same medication (in terms of PT and ATC) more than once will only be counted once for that medication.

### 9.8. Immunogenicity analysis

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. Immunogenicity assessments will be summarized by treatment group.

### 9.9. Other Safety

Physical examination and serology data will be listed only.

This document is confidential.

# 10. Interim Analyses

None.

# 11. Changes from Analysis Planned in Protocol

None.

# 12. Programming Considerations

All tables, data listings, figures (TLFs), and statistical analyses will be generated using SAS® for Windows, Release 9.4 (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

For all PK analyses, Phoenix® WinNonlin® version 8.0 or higher (Certara USA, Inc., Princeton, NJ) will be used.

## 12.1. General Considerations

- One SAS program can create several outputs.
- Each output will be stored in a separate file.
- Output files will be delivered in rich text format (RTF) that can be manipulated in MS Word.
- Numbering of TLFs will follow ICH E3 guidance.

## 12.2. Table, Listing, and Figure Format

### 12.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8
- The data displays for all TLFs will have a minimum 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

### 12.2.2. Headers

- All output should have the following header at the top left of each page:

- Prestige BioPharma Pte Ltd Protocol TROIKA-1 (Syneos Health study number 7002750)

This document is confidential.

- All output should have Page n of N at the top or bottom right corner of each page. TLFs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).

- The date output was generated should appear along with the program name as a footer on each page.

12.2.3. Display Titles

- Each TLF are identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended, but sponsor preferences are obtained before final determination A decimal system (x.y and x.y.z) are used to identify TLFs with related contents. The title is centered. The analysis set are identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the

- Column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed

12.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.

- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.

- For numeric variables, include “unit” in column or row heading when appropriate.

- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis set.

- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

12.2.5. Body of the Data Display

**12.2.5.1.** *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left-justified;

- Whole numbers (e.g., counts) are right-justified; and

This document is confidential.

- Numbers containing fractional portions are decimal aligned.

**12.2.5.2.** *Table Conventions*

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

| Severity Rating | N |
|---|---|
| severe | 0 |
| moderate | 8 |
| mild | 3 |

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups are included.
- An Unknown or Missing category are added to each parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values are printed out to one more significant digit than the original values, and standard deviations are printed out to two more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

| | |
|---|---|
| N | XX |
| Mean | XXX.X |
| Std Dev | X.XX |
| Median | XXX.X |
| Minimum | XXX |
| Maximum | XXX |

- P-values are output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If the p-value is returned as >0.999, then present as >0.999
- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero

This document is confidential.

counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.

- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of AE data are presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by PT), drugs (by ATC1 code), and AEs (by PT) are displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated are reported as "-".

- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject are included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

#### 12.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.

- Missing data are represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.

- Dates are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.

- Units will be included where available

#### 12.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

This document is confidential.

### 12.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with “Note:” if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line, where possible.
- Subject specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display and date the program was run (i.e., ‘Program : myprogram.sas’).

This document is confidential.

# 13. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health SOP Developing Statistical Programs (3907).

Syneos Health SOPs Developing Statistical Programs (3907) and Quality Deliveries (SDTM, ADaM, TLF) (3908) describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

This document is confidential.

# 14. Index of Tables, Listings and Figures

| Number | Name | Analysis Set |
|---|---|---|
| Table 14.1.1.1 | Enrolment and Disposition | ITT |
| Table 14.1.3.1.1 | Demographic Characteristics | ITT |
| Table 14.1.4.1 | Concomitant Medications | Safety |
| Table 14.2.1.1.1 | Serum Concentrations | Pharmacokinetic Concentration |
| Figure 14.2.1.2.1 | Individual Serum Concentrations by Treatment Group | Pharmacokinetic Concentration |
| Figure 14.2.1.2.2 | Individual Serum Concentrations (Log-Scale) by Treatment Group | Pharmacokinetic Concentration |
| Figure 14.2.1.2.3 | Mean Trastuzumab Serum Concentrations | Pharmacokinetic Concentration |
| Figure 14.2.1.2.4 | Mean Trastuzumab Serum Concentrations (Log-Scale) | Pharmacokinetic Concentration |
| Table 14.2.1.3.1 | Trastuzumab Serum Pharmacokinetic Parameters | Pharmacokinetic Parameters |
| Table 14.2.1.3.2 | Analysis of PK Similarity Between Formulations for Trastuzumab | PK similarity |
| Figure 14.2.1.4.1 | Plots of Individual and Geometric Mean for $AUC_{0-t}$ of Trastuzumab for Each Treatment Group | Pharmacokinetic Parameters |
| Figure 14.2.1.4.2 | Plots of Individual and Geometric Mean for $AUC_{0-inf}$ of Trastuzumab for Each Treatment Group | Pharmacokinetic Parameters |
| Figure 14.2.1.4.3 | Plots of Individual and Geometric Mean for $C_{max}$ of Trastuzumab for Each Treatment Group | Pharmacokinetic Parameters |
| Table 14.3.1.1 | Treatment Emergent Adverse Events – Overall Summary | Safety |
| Table 14.3.1.2 | Treatment Emergent Adverse Events | Safety |
| Table 14.3.1.3 | Treatment Emergent Adverse Events by Severity | Safety |
| Table 14.3.1.4 | Treatment Emergent Adverse Events by Relationship to Study Drug | Safety |
| Table 14.3.1.5 | Serious Treatment Emergent Adverse Events | Safety |
| Table 14.3.4.1.1 | Hematology | Safety |
| Table 14.3.4.1.2 | Hematology Shifts from Baseline | Safety |
| Table 14.3.4.1.3 | Chemistry | Safety |
| Table 14.3.4.1.4 | Chemistry Shifts from Baseline | Safety |
| Table 14.3.4.1.5 | Urinalysis | Safety |
| Table 14.3.4.1.6 | Urinalysis Shifts from Baseline | Safety |
| Table 14.3.4.1.7 | Urinalysis Categorical Results Evaluation | Safety |
| Table 14.3.4.2.1 | Vital Signs | Safety |
| Table 14.3.4.3.1 | 12-Lead Electrocardiogram | Safety |
| Table 14.3.4.3.2 | 12-Lead Electrocardiogram Shifts from Baseline | Safety |
| Table 14.3.4.4.1 | Echocardiogram | Safety |
| Table 14.3.4.4.2 | Echocardiogram Shifts from Baseline | Safety |
| Table 14.3.4.5.1 | Immunogenicity | Safety |
| Listing 16.1.9-1 | ANOVA for Treatment Comparisons (A/B, B/C and A/C) | ITT |

This document is confidential.

| Number | Name | Analysis Set |
|---|---|---|
| Listing 16.1.9-2 | Wilcoxon Rank Sum Test for $T_{max}$ for Treatment Comparisons (A/B, B/C and A/C) | ITT |
| Listing 16.2.1.1 | Subject Enrolment | ITT |
| Listing 16.2.1.2 | Subject Disposition | ITT |
| Listing 16.2.3.1 | Inclusion/Exclusion Criteria | ITT |
| Listing 16.2.4.1 | Demographic Characteristics | ITT |
| Listing 16.2.4.2 | Medical History | ITT |
| Listing 16.2.4.3 | Alcohol Test | ITT |
| Listing 16.2.4.4 | Urine Drug Test | ITT |
| Listing 16.2.4.5 | Serology | ITT |
| Listing 16.2.4.6 | Prior and Concomitant Medications | ITT |
| Listing 16.2.5.1 | Study Drug Administration | Safety |
| Listing 16.2.5.2 | Randomization | ITT |
| Listing 16.2.7.1 | Adverse Events | Safety |
| Listing 16.2.7.2 | Serious Adverse Events | Safety |
| Listing 16.2.7.3 | Non-Treatment-Emergent Adverse Events | Safety |
| Listing 16.2.8.1.1 | Hematology | Safety |
| Listing 16.2.8.1.2 | Chemistry | Safety |
| Listing 16.2.8.1.3 | Urinalysis | Safety |
| Listing 16.2.8.2.1 | Vital Signs | Safety |
| Listing 16.2.8.2.2 | 12-Lead Electrocardiogram | Safety |
| Listing 16.2.8.2.3 | Echocardiogram | Safety |
| Listing 16.2.8.2.4 | Physical Examination | Safety |
| Listing 16.2.8.2.5 | Brief Physical Examination | Safety |
| Listing 16.2.8.2.6 | Oral Temperature | Safety |
| Listing 16.2.8.2.7.1 | Trastuzumab Serum Concentrations by Time point | Safety |
| Listing 16.2.8.2.8.1 | Trastuzumab Serum Pharmacokinetic Parameters | Safety |
| Listing 16.2.8.2.9.1 | Immunogenicity | Safety |
| Listing 16.2.8.2.9.2 | Injection Site Evaluation | Safety |

This document is confidential.

# 15. Appendices

None.

# 16. Reference List

None.

| | |
|---|---|
| Syneos Health | **Note to File #1** |

| | |
|---|---|
| **Project**: 7002750 | **Sponsor**: Prestige BioPharma Pte Ltd. |
| **CC**: Statistical Analysis Plan | **Date**: 03-Oct-2019 |
| **Title**: A double-blind, randomized, 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. | |

RE:

This note to file intends to bring the following changes/clarifications to the final version of above-mentioned statistical analysis plan (SAP) dated 10-Apr-2019:

---

**Description of Study Design**

**Current Text Section 3.3**

This will be a 2-center, Phase 1, double-blind, randomized, single-dose, 3-arm, parallel study.

**Revised Text Section 3.3:**

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

---

**Analysis Populations – Related to PK**

**Current Text Section 5.3 to 5.4**

**5.3. Pharmacokinetic Concentration Population**
The PK Concentration Population will comprise all subjects who receive any amount of IP and have at least 1 quantifiable PK concentration (≥LLOQ), and will be based on the actual treatment received, if this differs from that to which the subject was randomized.

**5.4 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 analysis of variance (ANOVA) if the pre-dose concentration is greater than 5% of the Cmax value for that subject.
Data (concentrations and PK parameters) from subjects excluded due to a pre dose concentration greater than 5% of their Cmax or from subjects withdrawn due to AEs will be presented but excluded from the statistical analyses (i.e., descriptive statistics and ANOVA).

This document is confidential.

**Revised Text Sections 5.3 to 5.4**

**5.3. Pharmacokinetic Concentration (PKC) Population**
The PK Concentration Population will comprise all subjects who receive a complete dose of study drug, have at least 1 quantifiable PK concentration (≥LLOQ), and do not have any major protocol violation which may significantly affect the PK assessment. The analysis on this population will be based on the actual treatment received, if this differs from that to which the subject was randomized.

The statistical analysis of the PK concentrations, including descriptive statics and graphical representations, will be performed based upon the PKC Population. Any pre-dose concentration will be considered in the analysis.

**5.4 Pharmacokinetic Parameters (PKP) Population**
The PKP population will include all subjects of the PKC Population 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 PK list but excluded from descriptive statistics and analysis of variance (ANOVA) if the pre-dose concentration is greater than 5% of the Cmax value for that subject.

The statistical analysis of the PK parameters, including descriptive statistics, graphical representations, and the inferential analysis, will be performed based upon the PKP Population.

---

**General Methods**

**Current Text Section 6.1**

The minimum and maximum values will be presented to the same number of decimal places as recorded in the CRF, mean and median will be presented to one more decimal place than the raw data and the SD will be presented to two more decimal places than the raw data.

**Revised Text Section 6.1:**

The minimum and maximum values will be presented to the same number of decimal places as recorded in the CRF, mean, median and SD will be presented to one more decimal place than the raw data.

---

**General Methods**

**Current Text Section 6.2:**

In general, baseline will be defined for each subject and will be defined as the last available, non-missing assessment prior to study drug administration.

This document is confidential.

**Revised Text Section 6.2:**

In general, baseline will be defined for each subject and will be defined as the last available scheduled, non-missing assessment prior to study drug administration.

---

**General Methods**

**Current Text Section 6.5:**

For all sampling times, the actual sampling times will be calculated as the difference between the sample collection actual clock time and the actual clock time of the start of infusion.

**Revised Text Section 6.5:**

For all sampling times, the actual sampling times will be calculated as the difference between the sample collection actual clock time and the actual clock time of the start of infusion, and referred to as 'Post-dose sampling time'.

---

**The rules for the handling of BLQ concentrations were not clear in section 6.4 (Handling of the Below the Lower Limit of Quantitation (BLQ) and the No Reportable Concentration Values) and section 8.4 (Summary of PK Variables).**

**Current Text Section 6.4:**
All concentrations values BLQ will be set to zero as well as for PK parameter calculations for samples with no reportable value occurring prior to the dosing for a given period. For tabulation, graphical representation and calculation purposes, all samples with no reportable value observed after dosing will be set to missing.

**Revised Text Section 6.4:**
Concentration:
Serum concentrations will be summarized based on the PKC population using descriptive statistics for each treatment. Concentrations that are below the limit of quantification (BLQ) will be treated as zero for the computation of descriptive statistics. For tabulation and graphical representations, all samples with no reportable value (e.g. sample with non-valid bioanalytical results due to sample assay issues) observed after dosing will be set to missing.

Parameters:
For PK parameter calculations, predose samples that are BLQ or missing will be replaced by zero. BLQ concentrations occurring before the first measurable concentration will be replaced by zero. BLQ concentrations embedded between 2 measurable data points will be treated as missing when calculating PK parameters. If a BLQ value occurs at the end of the collection interval (after the last measurable concentration), it will be set to zero.

This document is confidential.

**Current Text Section 8.4:**
Concentration:
Serum concentrations will be listed and summarized, by nominal sampling time, and actual treatment. The below the quantification limit (BQL) will be set to zero in summary tables. BQL will be displayed in listings.
Individual subject and mean ± SD profiles of the serum concentration-time data will be plotted by treatment using actual and nominal times, respectively. These profiles will be presented on both linear-linear and log-linear scales.

Parameters:
Serum PK parameters will be listed and summarized descriptively by actual treatment.
For plots and derivation of serum pharmacokinetic parameters, the BQL values that occur in a profile before the first measurable concentration will be set to zero. The BQL values that occur after first measurable concentration will be set to missing.

**Revised Text Section 8.4:**
Concentration:
Serum concentrations will be listed and summarized, by nominal sampling time, and actual treatment based on the PKCpopulation. Concentrations that are below the limit of quantification (BLQ) will be treated as zero for the computation of descriptive statistics.

Individual subject and mean ± SD profiles of the serum concentration-time data will be plotted by treatment using actual and nominal times, respectively. These profiles will be presented on both linear-linear and log-linear scales.

Parameters:
Serum PK parameters will be listed and summarized descriptively by actual treatment on the PKP population.

---

**Current Text Section 8.6:**
Treatments Comparisons analysis of PK parameters will be undertaken for $AUC_{0-t}$, $AUC_{0-inf}$, and Cmax, based on the PK similarity Population.

**Revised Text Section 8.6:**
Treatments Comparisons analysis of PK parameters will be undertaken for $AUC_{0-t}$, $AUC_{0-inf}$, and $C_{max}$, based on the PKP Population.

---

**Programming Considerations**

**Current Text Section 12 - The entire text is to be replaced by:**

The statistical analysis will be performed using SAS, Version 9.2. Tables, listings and figures will be generated as per DICE templtes.

---

## Index of Tables, Listings and Figures

## Current Text Section 14:

| Number | Name | Analysis Set |
|---|---|---|
| Table 14.2.1.3.2 | Analysis of PK Similarity Between Formulations for Trastuzumab | PK similarity |
| Table 14.3.4.1.1 | Haematology | Safety |
| Table 14.3.4.1.2 | Haematology Shifts from Baseline | Safety |
| Table 14.3.4.1.3 | Chemistry | Safety |
| Table 14.3.4.1.4 | Chemistry Shifts from Baseline | Safety |
| Table 14.3.4.1.5 | Urinalysis | Safety |
| Table 14.3.4.1.6 | Urinalysis Shifts from Baseline | Safety |
| Table 14.3.4.3.1 | 12-Lead Electrocardiogram | Safety |
| Table 14.3.4.3.2 | 12-Lead Electrocardiogram Shifts from Baseline | Safety |
| Table 14.3.4.4.1 | Echocardiogram | Safety |
| Table 14.3.4.4.2 | Echocardiogram Shifts from Baseline | Safety |

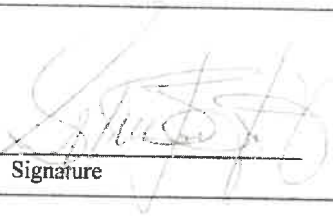
## Revised Text Section 14:

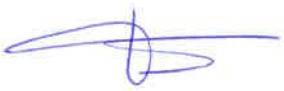
| Number | Name | Analysis Set |
|---|---|---|
| Table 14.2.1.3.2 | Analysis of PK Similarity Between Formulations for Trastuzumab | Pharmacokinetic Parameters |
| Table 14.3.4.1.1 | Descriptive Statistics for Haematology results and Shifts from Baseline | Safety |
| Table 14.3.4.1.3 | Descriptive Statistics for Chemistry results and Shifts from Baseline | Safety |
| Table 14.3.4.1.5 | Descriptive Statistics for Urinalysis results and Shifts from Baseline | Safety |
| Table 14.3.4.3.1 | 12-Lead Electrocardiogram and Shifts from Baseline | Safety |
| Table 14.3.4.4.1 | Echocardiogram and Shifts from Baseline | Safety |

This document is confidential.

**Note to File**
Sponsor: Prestige BioPharma Pte Ltd; Protocol No.: TROIKA-1

| **Created by:** | | |
|---|---|---|
| Siva Durga Prasad Sattu,<br>Sr.Statistician |  | 03-Oct-2019 |
| Printed Name, Title | Signature | Date (DD-Mmm-YYYY) |

| **Reviewed by:** | | |
|---|---|---|
| Sylvie Boudreault,<br>Manager, Pharmacokinetics |  | 03-OCT-2019 |
| Printed Name, Title | Signature | Date (DD-Mmm-YYYY) |

| **Reviewed by:** | | |
|---|---|---|
| Marie-Paule Derde<br>Head of Biometrics, DICE NV |  | 04-OCT-2019 |
| Printed Name, Title | Signature | Date (DD-Mmm-YYYY) |

| **Sponsor Approval:** | | |
|---|---|---|
| Felica Ang<br>Project Manager,<br>Prestige BioPharma Pte Ltd |  | 25 Oct 2019 |
| Printed Name, Title | Signature | Date (DD-Mmm-YYYY) |