Statistical Analysis Plan

RICHMOND Pharmacology

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STATISTICAL ANALYSIS PLAN

A Randomized, Open-label, Parallel-group, Ethno-bridging Study Comparing the Pharmacokinetics and Safety of a Single Dose of UPB-101 in Healthy Japanese and Non-Japanese Non-East Asian Adults

FINAL VERSION 1.0 16 MAY 2023

Issued by: [redacted]
Richmond Pharmacology
Biostatistician

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Date.....

Approved by: [redacted]
Upstream Bio
VP of Biometrics

Signature.....

Date.....

Reviewed by: [redacted]
Richmond Pharmacology
Sub-Investigator

Signature. [redacted] SignNow e-signature ID: ecae62ff3c... [redacted]

Date.....

Reviewed by: [redacted]
TranScrip
Senior Medical Writer

Signature.....

Date.....

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
%AUCextrap	percentage of AUC that is due to extrapolation from t_{last} to infinity
β-HCG	Beta Human Chorionic Gonadotropin
ADA	Antidrug Antibodies
AE	Adverse Event
AUC	Area under the Concentration Time Curve
AUC_{0-inf}	Area under the Serum Concentration versus Time Curve from Time Zero Extrapolated to Infinity
AUC_{0-t}	Area under the Serum Concentration versus Time Curve from Time Zero to the Last Quantifiable Concentration
BLQ	Below the Level of Quantification
BMI	Body Mass Index
CL/F	Total clearance after extravascular administration
C_{max}	Maximum Observed Serum Concentration
C_{min}	Minimum Observed Serum Concentration
CS	Clinically Significant
CSR	Clinical Study Report
DB	Database
DBP	Diastolic blood pressure
ECG	Electrocardiogram
ET	Early Termination
ICF	Informed Consent Form
IMP	Investigational medicinal product
LOQ	Limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
Nab	Neutralizing antibodies
NCA	Non-Compartmental Analysis
NCI CTCAE Criteria	National Cancer Institute's Common Terminology Criteria for Adverse Events
NCS	Not clinically significant
NJNEA	Non-Japanese Non-East Asian Adults
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PR	Pulse Rate
PROC	Programmed Random Occurrence
QRS	Ventricular Conductance Time
QTcF	QT interval corrected using Fridericia's formula
RPL	Richmond Pharmacology Ltd
RR	RR interval
SAD	Single Ascending Dose
SAE	Serious adverse events
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure

SC	Subcutaneous
SD	Standard Deviation
SOC	System Organ Class
SOM	Study operations manual
$t_{½}$	Terminal Elimination Half-Life
TEAE	Treatment-Emergent Adverse Event
TFLs	Tables, Figures and Listings
T_{max}	Time to Maximum Observed Serum Concentration
TSLP	Thymic stromal lymphopoietin
V_z/F	Apparent Volume of Distribution after extravascular administration
WOCBP	Women of Childbearing Potential

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1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to define the variables and analysis methodology to address the study objectives.

The protocol dated 17th October 2022, Version 1.0, was used to prepare this SAP.

All analyses listed in this SAP, including but not limited to the pharmacokinetic (PK) parameter calculations and statistical analyses of PK data, will be the responsibility for Richmond Pharmacology Ltd.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study objectives

The objectives of this study are:

Primary

- To characterize and compare the PK of single doses of UPB-101 in healthy Japanese and Non-Japanese Non-East Asian Adults (NJNEA).

Secondary

- To assess and compare the safety and tolerability of UPB-101 in healthy Japanese and NJNEA adults.
- To assess and compare the immunogenicity of UPB-101 when administered to Japanese and NJNEA adults.

Exploratory

- To assess the pharmacodynamic (PD) effect of UPB-101 on biomarkers related to inflammation, specifically the thymic stromal lymphopoietin (TSLP) pathway.

2.2 Endpoints

Primary

- Serum UPB-101 concentrations and analyses including C_{max}, t_{max}, AUC_{0-t} will be assessed. If appropriate, AUC_{0-inf}, $t_{1/2}$, apparent total body clearance after dosing (CL/F), and apparent volume of distribution during the terminal elimination phase after dosing (Vz/F) will also be analysed. These endpoints will be assessed from baseline through Day 85 ± 5 days in the PK Set.

Secondary

- The safety endpoints will include adverse events (AEs), serious adverse events (SAEs), physical examinations, clinical laboratory assessments, vital signs, electrocardiograms (ECGs) including telemetry, withdrawal of participants, and early terminations. These endpoints will be assessed from baseline through Day 85 ± 5 days in the Safety Set.
- The immunogenicity endpoint includes UPB-101 anti-drug antibodies (ADAs) and presence of neutralizing antibodies (Nabs). These endpoints will

be assessed from baseline through Day 85 ± 5 days in the Immunogenicity Set.

Exploratory

- Specific PD biomarkers for exploratory analysis will be selected based on relevant data from ongoing clinical studies.

3. TRIAL DESIGN

3.1 Overall Trial Design

This is a randomized, open-label, parallel-group, PK study comparing the PK and safety of a single dose of UPB-101 in healthy Japanese and NJNEA adults. Japanese participants must have been born in Japan, with parents and grandparents born in Japan, and lived for < 5 years outside of Japan.

Each participant will receive verbal and written information about the study, followed by signing of the Informed Consent Form (ICF) prior to any Screening procedures taking place. Following signing of the informed consent, participants will be evaluated for eligibility during the Screening Days -21 to -2. Participants who are eligible at the end of the Screening assessments will be admitted on Day -1 for confirmation of eligibility, then dosed on Day 1, and discharged on Day 15. All assessments performed during the study are detailed in the study Schedule of Assessments. The study will be conducted at a single site in the UK.

The study consists of 4 treatment groups. Three treatment groups will include Japanese healthy adult volunteers and 1 treatment group will include NJNEA healthy adult volunteers.

The 4 treatment groups will be assigned as few cohorts as operationally feasible to avoid period bias, and each cohort will attempt to contain at least two participants from each treatment group.

Each participant will receive one of the following dosing regimens in parallel:

Table 1: Planned treatment groups

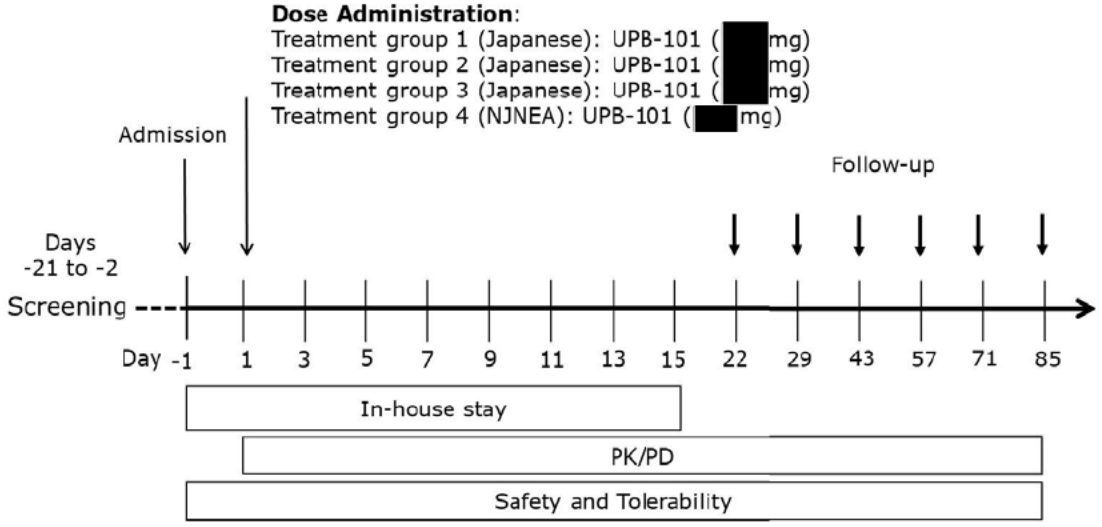
Planned Treatment Groups	Participant Ethnicity (N Participants)	Treatment	Number of Injections to Achieve Dose	Number of Doses
1	Japanese (8)	UPB-101 [redacted]mg SC	[redacted]	Single dose
2	Japanese (8)	UPB-101 [redacted]mg SC	[redacted]	
3	Japanese (8)	UPB-101 [redacted]mg SC	[redacted]	
4	Non-Japanese Non-East Asian (8)	UPB-101 [redacted]mg SC	[redacted]	

N: number; SC: subcutaneous

Screening will commence with the informed consent process. After signing of the approved ICF, participants will be assigned a Screening number, and then undergo the scheduled Screening assessments to allow for assessment of safety and the study eligibility criteria. All women of childbearing potential (WOCBP) will undergo a serum beta human chorionic gonadotropin (β-HCG) pregnancy test. The assessments to be conducted on all treatment groups during the Screening Period (Day -21 to Day -2) are found in the Schedule of Assessments in the study protocol.

On Day 1 the final pre-dose safety assessments will be reviewed by a Research Physician and a final decision on each participant's study eligibility will be made. Following completion of these reviews, participants who remain eligible for enrolment will be randomly assigned to treatment group 1, 2, or 3 for Japanese participants, while NJNEA participants will be automatically allocated to treatment group 4.

Figure 1: Study Flow Chart



3.2 Analysis Sets

The analysis of data will be based on different analysis sets according to the purpose of analysis. Subject eligibility for each analysis set will be finalised before the database hard lock. A subject who withdraws prior to the last planned observation in a study period will be included in analyses up to the time of discontinuation.

The following data sets will be used for analysis and presentation of the study data:

Safety set

The Safety set will consist of all randomized participants who received at least one injection of the UBP-101. The safety set will be used for the safety analyses.

The Safety set will be used for the presentation of demographic summaries.

PK Set

The PK set will consist of those participants in the safety set who have sufficient blood samples taken for at least one of the PK variables to be calculated. The PK set will be used for the PK analyses. *Immunogenicity Set*

The Immunogenicity set will consist of those participants in the safety set who have blood samples taken for at least one timepoint where ADA or Nabs are measured post-dose. The Immunogenicity set will be used for the Immunogenicity analyses.

3.3 Sample Size

The primary objective of the study is to characterize and compare the PK of single doses of UPB-101 in Japanese and NJNEA adults. A sample size of 8 Japanese participants enrolled in each of treatment groups 1, 2, and 3 to be administered [redacted], [redacted], and [redacted] mg of UPB-101, respectively, and 8 NJNEA participants assigned [redacted] mg of UPB-101 to treatment group 4, is considered adequate to accomplish the primary objectives of the study. The sample size is not based on formal statistical hypothesis testing.

3.4 Randomisation and Blinding

All participants of Japanese ethnicity will be assigned to a treatment regimen according to a randomization schedule generated by a statistician using PROC Plan (treatment groups 1-3). Randomization does not occur for participants in treatment group 4 as all NJNEA participants are assigned to the same treatment ([redacted]mg UPB-101). Details regarding the unique Screening and participant number will be included in the study operations manual (SOM).

Eligible participants will be randomly assigned on Day 1 at the point of dosing. 8 participants will be randomized per treatment group. Thus, a total of approximately 32 male and female participants will be enrolled in the study with

approximately 24 Japanese participants in treatment groups 1-3 and 8 NJNEA participants in treatment group 4.

4. STATISTICAL ANALYSES

4.1 General Notes for Statistical Analyses

In general, descriptive statistics for continuous variables will include number of non-missing values (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum.

Descriptive statistics for PK parameters will include N - the number of participants, n – the number of samples, n(LLOQ) - the number of samples <LLOQ (lower limit of quantification), arithmetic mean, SD - standard deviation, CV - coefficient of variation, geometric mean, median, minimum, maximum.

Categorical variables will be summarized using frequency counts and percentages.

For all tables, except PK parameter tables, descriptive statistics for minimum and maximum will be presented with the same decimal digits as the original data, and with 1 more decimal place than the original data for mean and median; SD will be reported with 2 more decimal places than the original data. Degrees of freedom based on the Kenward Roger approximation will be presented with one decimal (where applicable).

All collected data will be presented in by-subject listings. Listings will be ordered by treatment group and subject number and will include all randomized subjects.

Unless otherwise stated, baseline will be defined as the last non-missing value prior to first administration of study drug. Changes from baseline values will be calculated as the post-baseline assessment value minus the baseline value. If repeated measurements are made at a time point, the first scheduled value will be used for summary analysis, unless otherwise stated in relevant section of this SAP.

Deviations from the planned analyses will be described in the final clinical study report (CSR).

Page layout of the TFLs will be in landscape mode and will be provided as individual RTF format. Further details of page layout will be provided in the TFL shell document.

4.2 Interim Analysis

No interim analysis is planned for this study.

4.3 Subject Disposition

All subjects will be included in the summary of subject disposition. This will present the overall number of subjects, the frequency and percentage of subjects randomized and treated, and who completed or discontinued from the study, along with reason for discontinuation.

Furthermore, the number and percentage of subjects in each analysis set will be tabulated. Discontinued subjects will be listed. Subject assignment to analysis sets will be listed. Screen Failures will not be listed or included in summary tables.

4.4 Demographic Characteristics

Individual subject demographics (including age, gender, and race) and body measurement data (height, body weight and body mass index [BMI]) at screening will be listed and summarized by each treatment group and by each population group (i.e., Japanese vs NJNEA). Height will be measured in centimetres and weight in kilograms, BMI will be given in kg/m^2. For repeated height/weight measurements the last measurement prior to dosing will be presented. Date of birth and ethnicity will be included in the listing only.

4.5 Inclusion and Exclusion Criteria

Violated Inclusion and Exclusion criteria for each randomised subject will be listed.

4.6 Protocol Deviations

The final review of protocol deviations will be performed at the Data Review Meeting prior to database lock. The major protocol deviations will be listed.

4.7 Medical and Surgical History

Medical and Surgical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary Version 25.0 (or higher) and listed individually. Surgical history data will be listed separately. Medical and Surgical history data will be summarised together using frequency and percentage by system organ class (SOC) and preferred term.

4.8 Study Drug Administration

Study drug administration data will be listed by subject, including treatment received, dose level (unit), study day, date, and time of administration.

4.9 Prior and Concomitant Medications

All prior and concomitant medications will be coded using the World Health Organization Drug Dictionary version 2022 (or higher) and will be listed individually. The frequency and percentage of prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical and Preferred Name. Separate tables will be given for prior and concomitant medications. Prior medications are defined as those taken within 3 months of informed consent for which the end date and time is prior to the date, and time of first study drug administration. Concomitant medications are defined as those with start date and time on or after the date and time of first study drug administration and those with start date and

time prior to the first study drug administration but with end date and time on or after the date and time of first study drug administration.

If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

4.10 Safety Analysis

Safety analyses will be performed on the safety set.

Safety analyses will include an analysis of all AEs, ECGs, clinical laboratory data and vital sign measurement results and will be presented using descriptive statistics. No formal statistical analysis will be performed.

4.10.1 Adverse Events

A Treatment Emergent Adverse Event (TEAE) is any adverse event that commences after the start of administration of study drug.

AEs with unknown start date/time will be assumed to be treatment-emergent unless the end date/time is known to be before the first administration of study drug. Otherwise, missing, or partial dates will be listed as such.

The incidence of TEAEs (after dosing) will be summarized using the safety set. The MedDRA dictionary Version 25.0 (or higher) will be used to classify all AEs reported during the study by SOC and Preferred Term.

A summary of TEAEs including the incidence of subjects who experienced TEAEs (number and percentage of subjects) and incidence of TEAEs (number of events) will be presented for each treatment group, and by population group (i.e., Japanese vs NJNEA) and overall, by maximum intensity (NCI CTCAE Criteria) and by relationship to study drug.

Serious TEAEs, TEAEs leading to withdrawal will be summarized by SOC and Preferred Term for each treatment group and overall, and by relationship to study drug.

Subjects having multiple AEs within a category (e.g., overall, SOC and Preferred Term) will be counted once in that category. In each table, SOC and Preferred Term will be presented in descending order of overall incidence rate (alphabetical order will be used in case of equal rates).

All AEs will be listed.

4.10.2 Laboratory Data

Biochemistry (including chemistry, serology, FSH, Total Ige, CRP and serum pregnancy results where available), haematology and coagulation will be listed with abnormal parameters being flagged as high (H) or low (L) (where defined) and as being clinically significant or not. Normal ranges, absolute (observed) values and changes from baseline (continuous variables) will also be presented in these listings

for each parameter and scheduled time point. Clinically significant values for these laboratory parameters will be presented again in a separate listing.

Urinalysis will also be listed with their result, evaluation (normal/abnormal and CS/NCS) and any additional comments, where available.

The quantitative laboratory data for biochemistry, haematology, and coagulation, along with changes from baseline will be summarized using descriptive statistics (n, mean, median, standard deviation, minimum, maximum). Change from baseline values at each assessment will be calculated as the assessment value minus the baseline value. The qualitative urinalysis data and immunogenicity will be summarised and listed.

The number of volunteers presenting out-of-range and clinically significant values will be summarised by treatment group. The scheduled lab value will be used for summary analysis if repeated measurements are made at any time point.

For summary statistics, a lab value with "<" sign will be removed with the numeric value being used. In the listings, the values will be displayed as originally reported by the laboratory.

4.10.3 Vital Signs

Vital signs data (SBP, DBP, Pulse rate, respiratory rate and tympanic temperature) will be listed for individual subjects. Summary statistics of absolute (observed) values and changes from baseline will be calculated for each parameter and scheduled timepoint by treatment group. Clinically significant values for vital signs will be presented again in a separate listing.

Out-of-reference-range values will be flagged as high (H) or low (L) and as being clinically relevant or not: the number of subjects presenting out-of-range and clinically relevant values will be summarised.

The normal range for vital signs is displayed below:

Parameter	Normal Range
Temperature (tympanic)	35-38°C
Systolic Blood Pressure (Supine)	90–130 mmHg
Diastolic Blood Pressure (Supine)	40–90 mmHg
Pulse Rate (supine)	40–90 bpm
Respiratory Rate	8-20 breaths per min

4.10.4 Telemetry and Holter

Cardiac telemetry and Holter data (Start / End Date time and evaluation) will be listed by subject.

4.10.5 Physical Examination

The physical examination performed at screening and at the Final Visit (Day 85) will be listed only and include an assessment of the following: general appearance, skin, eyes/ears/nose, neck, lymph nodes, throat, heart, lungs, abdomen, musculoskeletal system, and extremities. Symptom-directed physical examinations will be performed at all other time-points as needed, these will be included in the listings where available.

4.10.6 Electrocardiograms

Triplicate ECGs are performed at each timepoint ensuring the following criteria:
- Three consecutive evaluable ECGs;
- With maximum HR of 2 bpm difference;
- Triplicate is obtained between 1.5 to 4.5 minutes.

Due to above criteria, up to 10 ECGs can be acquired for a given timepoint. Typically, in most cases, the last 3 ECGs represent the triplicate which will be transferred to Clario for adjudication. If a triplicate could not be obtained (e.g. due to variable heart rate) then the last 3 ECGs are transferred for adjudication.

Adjudicated ECGs (Clario) will be used for analyses in the TFLs. Un-adjudicated ECGs (internal RPL) will be listed only. Details are as below.

Un-adjudicated ECGs

All un-adjudicated ECG data (PR, QRS, QT, QT_cB, QT_cF and HR) including H/L flags and overall ECG evaluation will be listed only. Out-of-reference-range values will be flagged as clinically relevant or not. Reference ranges for RPL ECGs are as follows:

Parameter	Normal Range
Heart Rate (Supine)	40-90 bpm
PR Interval	120–200 ms
QRS duration	≤120 ms
QTcF	≤450 ms (Males & Females)

Clario's Reference Ranges are as follows:

Parameter	Normal Range
RR	600-1200
PR Interval	120–200 ms
QRS	60–109 ms

QT	320 – 450 ms
QTcF or QTcB	320–450 ms (Males & Females)

Adjudicated ECGs

All below analyses will be performed on adjudicated ECGs.

Adjudicated ECG parameters will be listed separately with above flags, with Clario evaluations where available.

For summary statistics an arithmetic mean value of the adjudicated triplicate ECG (where available) parameters will be used at each time-point. All below analyses will be performed using this set.

ECG data and changes from baseline will be summarised using descriptive statistics.

The change from baseline will be derived using the arithmetic mean value of each time-point triplicate minus baseline value, where baseline is the arithmetic mean of the pre-dose values of Day 1.

Furthermore, categorical analysis of QTcF data will be presented as follows:

- Absolute QTcF interval prolongation
  - QTcF interval > 450 ms to ≤ 480 ms
  - QTcF interval > 480 ms to ≤ 500 ms
  - QTcF interval > 500 ms
- Change from baseline in QTcF interval
  - QTcF interval increases from baseline > 30 msec to ≤ 60 msec
  - QTcF interval increases from baseline > 60 ms

The mean absolute value of QTcF will be plotted by treatment group and by time-point. The number of subjects presenting out-of-range and clinically relevant values will be summarised.

4.11 Pharmacokinetic Data Reporting

PK analyses from blood samples will be performed on the PK set and will be reported at each time point by treatment group (dose level). PK parameters will be presented as follows in the listing: C_{max} and t_{max} will be presented as given in the raw data; other PK parameters will be presented with 3 significant figures. Descriptive statistics for PK parameters will be presented with decimal places as appropriate for the particular parameter and treatment group. PK parameters with the exception of

T_{max} and $t_{½}$ will be reported to 3 significant figures. T_{max} and $t_{½}$ will be reported to 2 decimal places.

Standard non-compartmental PK parameters for serum samples of UBP-101 will be estimated, and study drug exposure to UBP-101 will be summarised using continuous summary statistics. Concentrations will be listed and summarised by dose level and time point. Values excluded from table summaries will be flagged and included in the listing. Figures will present the individual and mean ± SD concentration curves on both a linear and log scale. Figures will be presented by treatment group (dose level). The PK parameters will be listed for each subject and summarised for each dose level using descriptive statistics.

Summary Statistics

In the case that quantifiable measurements are observed, serum concentrations will be listed and summarised by time point including the number of patients (N), number of samples (n), number of samples <below the limit of quantification (BLQ) (n(BLQ)), arithmetic mean, standard deviation (SD), coefficient of variation (CV), geometric mean, median, minimum, and maximum. If all the values are BLQ, then the arithmetic mean, arithmetic SD, median, minimum, and maximum will be presented as 1, and the geometric mean and geometric CV will be denoted as zero.

In addition, concentration figures over time will be presented by subject (combined in one figure and may also be presented as one figure per subject) and as mean (± SD) concentration, both on linear and logarithmic scale. Figures will be presented by treatment dose level. BLQ values will be set to 0 on the linear scale, and LLOQ x 0.5 on the logarithmic scale.

PK parameters will be listed for each patient and summarized for each treatment dose level using descriptive statistics (number of patients, arithmetic mean, SD, CV, geometric mean, median, minimum, maximum).

For the calculation of summary statistics of PK parameters, all not reported values will be set to missing.

4.11.1 Values Below the Limit of Quantification and Missing Values

If a BLQ value occurs in a profile before the first measurable concentration, it will be assigned a value of zero concentration. If a BLQ value (or consecutive BLQ values) occurs after a measurable concentration in a profile and is followed by a value above the lower level of quantification, then the appropriateness for omission of the BLQ value will be assessed following visual inspection of the plasma concentration versus time profile and set to missing. If a BLQ value (or consecutive BLQ values) occurs at the end of a collection profile (after the last quantifiable

concentration), it will be assigned a value of" missing". If consecutive BLQ values occur at the start of a collection profile, the first will be assigned a value of zero and all subsequent BLQ values will be omitted.

4.11.2 Pharmacokinetic Parameters

The following PK parameters for UBP-101 will be calculated.

Parameter	Description
C_{max}	Maximum observed serum concentration
T_{max}	Time at which the maximum serum concentration occurs
$t_{1/2}$	Terminal half-life
λ_z	Terminal elimination rate constant obtained from linear regression of time vs log-concentration during the terminal elimination phase; using at least three time-points during the terminal elimination phase.
$AUC_{0\text{-}inf}$	Area under the serum concentration-time curve from time 0 extrapolated to infinite time
$AUC_{0\text{-}t}$	Area under the serum concentration curve from time zero up to the last quantifiable concentration
$AUC_{\%extrap}$	Percentage of AUC that is due to extrapolation from t last to infinity $((AUC_{0\text{-}inf} - AUC_{0\text{-}tlast})/AUC_{0\text{-}inf}) \times 100$
CL/F	Serum clearance after extravascular administration calculated as $Dose/AUC_{0\text{-}inf}$
V_z/F	Apparent Volume of distribution after extravascular administration; calculated as…$Dose/(\lambda_z * AUC_{0\text{-}inf})$

The individual serum concentration data, and the actual time for UBP-101 administration and blood sampling will be used in the derivation of the PK parameters. If there is any doubt in the actual time a sample was taken, or if the actual sampling or dosing times are missing, then the scheduled time will be used.

$AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ will be calculated using the linear/log trapezoidal method, applying the linear trapezoidal rule up to C_{max} and the log trapezoidal rule for the remainder of the curve. Samples below lower limit of quantification (LLOQ) prior to the first quantifiable concentration will be set to zero. Samples with concentrations

LLOQ after the first quantifiable concentration will be set to 'missing' and omitted from the analysis.

In the determination of λ_z (and $AUC_{0\text{-}inf}$), the following conditions should be met:

- A minimum of at least 3 data points in the terminal elimination phase, in which Cmax is not included;
- The Adj-Rsq should be ≥ 0.8, and
- %AUCextrap < 20%.

If these conditions are not met, the PK parameter will be flagged in the listings (together with those dependent on λ_z, such as $t_{1/2}$, CL/F and V_z/F) and they may be excluded from the summary statistics. The decision to include these parameters will be based on the decision of the Sponsor with input from the pharmacokineticist. The following flags/footnotes may be applied to the PK parameters:

Flag	Footnote
a	Adj-Rsq of regression was <0.8
b	Extrapolated portion of $AUC_{0\text{-}inf}$ >20%
c	Insufficient post-C_{max} data points for estimation of lambda-z
d	Entire profile BLQ, no pharmacokinetic parameters could be calculated
e	Regression line could not be fitted

Descriptive statistics for PK parameters will include number of observations, arithmetic mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum. Median and range will only be presented for Tmax.

If serum concentrations are all BLQ, then PK parameter estimation and all subsequent statistical summaries will not be possible.

4.12 Pharmacodynamic Analyses

The analysis of pharmacodynamic (PD) data falls outside the scope of this SAP.

4.13 Immunogenicity Analyses

Immunogenicity (ADA) to UPB-101 will be explored (incidence and duration) for each treatment group using a three-tiered approach of screening, confirmatory, and titer.

ADA data will be listed for each participant. Samples which screen ADA-positive in the screening assay, will undergo a confirmatory assay to confirm the presence of ADA. Once confirmed as ADA-positive, the samples will be run in a titration assay to determine the level of ADA response. Summaries of positive ADA test results over time may be provided.

4.14 Methods for Withdrawals, Missing Data and Outliers

Unrecorded values will be treated as missing. The appropriateness of the method(s) for handling missing data may be reassessed at the data review prior to DB lock.

4.15 Deviations from Protocol Specified Analysis

PD analysis was originally planned as an exploratory objective and endpoint in the protocol, however, biomarkers related to inflammation were deemed to be poor predictors of PD effects of UPB-101 in healthy subjects. Hence, a decision was made to remove this analysis from the current study.

Nab sample was collected and listed as a secondary endpoint; however, this will not be included in the analysis and the secondary objective of immunogenicity assessment of UPB-101 will be supported only by the ADA data, as the Nab assay was still under development at the time of study completion.

5 REFERENCES

1. Garnett C, Bonate P, Dang Q, Ferber G, Huang D, Liu J, Mehortra D, Riley P, Sager P, Tornoe C, Wang Y. Scientific white paper on concentration-QTc modelling. Journal of Pharmacokinetics and Pharmacodynamics. 2018;45, 383-397. https://link.springer.com/article/10.1007%2Fs10928-017-9558-5.

2. Darpö B, Ferber G, Siegl P, Laurijssens B, Macintyre F, Toovey S, Duparc S. Evaluation of the QT effect of a combination of piperaquine and a novel anti-malarial drug candidate OZ439, for the treatment of uncomplicated malaria. British Journal of Clinical Pharmacology. 2015;80(4):706-15.