STATISTICAL ANALYSIS PLAN

Study: UP0073

Product: UCB0599

A 2-PART STUDY TO EVALUATE THE RELATIVE BIOAVAILABILITY OF 2 NEW FORMULATIONS OF UCB0599 AND THE EFFECT OF ESOMEPRAZOLE ON THE PK OF UCB0599 IN HEALTHY PARTICIPANTS (PART A, OPEN-LABEL) AND TO ASSESS THE SAFETY/TOLERABILITY AND PK OF UCB0599 IN HEALTHY PARTICIPANTS OF JAPANESE AND CHINESE ORIGINS (PART B, DOUBLE-BLIND)

A randomized, 2-part single-dose crossover Phase 1 study to assess 2 new formulations of UCB0599 in healthy participants (Part A, open-label) and to assess UCB0599 with the new formulation in healthy participants of Japanese and Chinese origins (Part B, double-blind)

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Confidentiality Statement

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VERSION HISTORY

SAP Version	Approval Date	Change	Rationale
1	05 SEP 2023	Not Applicable	Original version

LIST OF ABBREVIATIONS

List of Abbreviations

AE	Adverse Event
ANOVA	Analysis of Variance
ASPS	All Study Participants Set
BP	blood pressure
BLQ	below the limit of quantification
BMI	body mass index
BW	body weight
CDE	Center for Drug Evaluation
CI	Confidence Interval
CSR	clinical study report
CRF	clinical report form
CTR	Clinical Trials Registry (CTR)
CV	coefficient of variation
D	dose
DBP	diastolic blood pressure
DEM	Data Evaluation Meeting
ECG	electrocardiogram
FSH	follicle-stimulating hormone
geometric cv	geometric coefficient of variation
hCG	human chorionic gonadotropin
HLT	high level term
ICF	informed consent form
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IQR	interquartile range
IPD	Important protocol deviations
LLOQ	Lower limit of quantification

List of Abbreviations

ln	natural logarithm
LSMEAN	least square mean
MedDRA	Medical Dictionary for Regulatory Activities
msec	milliseconds
NC	not calculable
NE	not estemable
PK	Pharmacokinetic
PKS	Pharmacokinetic Set
PMDA	Pharmaceuticals and Medical Devices Agency
PPI	proton pump inhibitor
PT	preferred term
QD	once daily
REML	restricted maximum likelihood
RS	Randomized Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SBP	systolic blood pressure
SD	Single Dose
sd	standard deviation
SFU	Safety Follow-Up
SMC	Safety Monitoring Committee
SMQ	Standardized MedDRA Query
SOC	system organ class
SS	Safety Set
TEAE	Treatment-Emergent Adverse Event
TFLs	tables, figures and listings
TOST	two 1-sided ratio of means tests
WHO-DRL	World Health Organization Drug Reference List
WHODD	World Health Organization Drug Dictionary
WO	Washout Period

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide all necessary information to perform the statistical analyses and defines the summary tables, figures and listings (TFLs) to be included in the final clinical study report (CSR) of study UP0073, according to the protocol and using UCB Standard TFL Shells.

The SAP is based on the following study documents:

- Protocol UP0073, 02Mar2023
- Clinical report form (CRF), 20Jun2023

1.1 Objectives and Endpoints

Table 1-1: Objectives and Endpoints for Part A

Objectives	Endpoints
Primary	
• To estimate the relative bioavailability of 2 new UCB0599 formulations versus reference 'granules in capsule' formulation under elevated gastric pH and under normal condition in healthy participants	PK endpoints of UCB0599 • C_{max} • AUC_{0-t} • AUC_{inf}
Secondary	
• To evaluate for each formulation the safety and tolerability of single dose UCB0599 alone under elevated gastric pH and under normal condition in healthy participants	Safety endpoints • Incidence of TEAEs • Incidence of treatment-emergent SAEs • Incidence of TEAEs leading to withdrawal from study
Other	
• To estimate the relative bioavailability of UCB0599 under elevated gastric pH versus normal gastric pH for each tested formulation • To further evaluate the PK of UCB0599 and its CCI [redacted] metabolites after single dose UCB0599 alone and co-administrated with esomeprazole in healthy participants	Other PK endpoints • For UCB0599: – C_{max}, AUC_{0-t}, and AUC_{inf} – t_{max}, $t_{½}$, CL/F, and Vz/F (if possible but not limited) • For CCI [redacted] metabolites: – C_{max}, t_{max}, AUC_{0-t}, and AUC_{inf} – metabolite/parent C_{max} and AUC ratio (corrected for the molecular weight of the entities), as appropriate

Table 1-1: Objectives and Endpoints for Part A

Objectives	Endpoints

AUC_{inf}=area under the plasma concentration-time curve from time zero to infinity; AUC_{0-t}=area under the plasma concentration-time curve from time zero to t; CL/F=apparent total body clearance; C_{max}=maximum observed plasma concentration; PK=pharmacokinetic(s); SAE=serious adverse event; $t_{½}$=apparent terminal elimination half-life; TEAE=treatment emergent adverse event; t_{max}=time of occurrence of C_{max}; Vz/F=apparent volume of distribution

Table 1-2: Objectives and Endpoints for Part B

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of UCB0599 after administration of a single dose of an oral formulation in healthy participants of Japanese and Chinese origins	<u>Safety endpoint</u> • Incidence of TEAEs • Incidence of treatment-emergent SAEs • Incidence of TEAEs leading to withdrawal from study
• To evaluate the plasma PK of UCB0599 after administration of a single dose of an oral formulation in healthy participants of Japanese and Chinese origins	<u>Co-primary PK endpoints for UCB0599</u> • Cmax • AUC_{0-t} • AUC_{inf}
Other	
• To assess additional safety and tolerability characteristics of UCB0599 in healthy participants of Japanese and Chinese origins	<u>Other safety endpoints</u> • Changes from Baseline in vital signs (pulse rate, blood pressure [BP], respiratory rate, and body temperature) • Changes from Baseline in safety laboratory data (hematology, clinical chemistry, urinalysis) • Changes from Baseline in 12-lead electrocardiogram (ECG) assessment • Physical examination findings

Table 1-2: Objectives and Endpoints for Part B

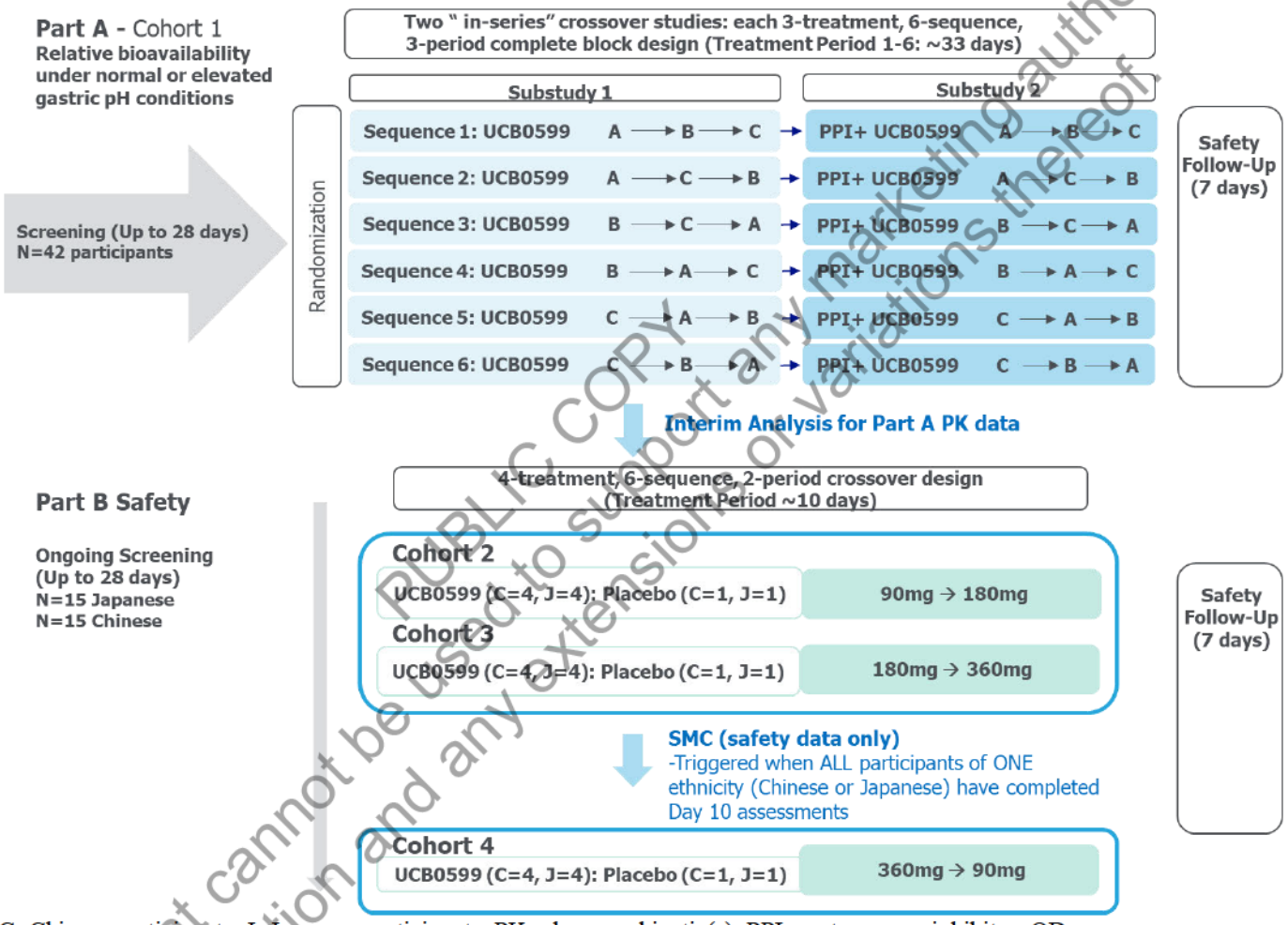
Objectives	Endpoints
• To further evaluate the PK of UCB0599 and its CCI [redacted] metabolites after a single dose of an oral formulation in healthy participants of Japanese and Chinese origins	Other PK endpoints 1. For UCB0599: – t_{max}, CL/F, Vz/F, $t_{1/2}$, C_{max}/BW/D, AUC_{0-t}/BW/D, and AUC_{inf}/BW/D • For CCI [redacted] metabolites: – C_{max}, t_{max}, AUC_{0-t}, and AUC_{inf} – Metabolite/parent C_{max} and AUC ratio (corrected for the molecular weight of the entities), as appropriate – Metabolite/parent C_{max} and AUC ratio (corrected for the molecular weight of the entities) per population, as appropriate

AUC_{inf}=area under the plasma concentration-time curve from time zero to infinity; AUC_{0-t}=area under the plasma concentration-time curve from time zero to t; BW=body weight; CL/F=apparent total body clearance; C_{max}=maximum observed plasma concentration; D=dose; ECG= electrocardiogram; PK=pharmacokinetic(s); SAE=serious adverse event; $t_{½}$=apparent terminal elimination half-life; TEAE=treatment emergent adverse event; t_{max}=time of occurrence of C_{max}; Vz/F=apparent volume of distribution

1.2 Study design

UP0073 is a randomized, 2-part single-dose crossover Phase 1 study. The study will enroll approximately 42 healthy participants into open-label Part A and 30 healthy participants (15 of Japanese origin and 15 of Chinese origin) into double-blind Part B at a single study site. A study overview of UP0073 is provided in Figure 1-1. Part A and Part B design are provided in Table 1-3 and Table 1-4, respectively.

Figure 1-1: Overall study schematic



C=Chinese participants; J=Japanese participants; PK=pharmacokinetic(s); PPI=proton pump inhibitor; QD=once daily; SMC=Safety Monitoring Committee

Note: A: 180mg (90mg x 2 granules in capsule) current clinical formulation (reference formulation); B: 180mg non-encapsulated tablet containing [redacted]; C: 180mg encapsulated tablet containing [redacted].

Note: The PPI esomeprazole 40mg QD will be administrated on 20-consecutive days during substudy 2.

Table 1-3: Part A design: Relative bioavailability of UCB0599 under normal or elevated gastric pH condition in healthy participants (3-treatment, 6-period complete block design)

Sequence (Duration)	**Period 1** (D1)	**WO** (D2-5)	**Period 2** (D6)	**WO** (D7-10)	**Period 3** (D11)	**WO**[a] (D12-18)	**Period 4** (D19)	**WO** (D20-23)	**Period 5** (D24)	**WO** (D25-28)	**Period 6** (D29)	**WO** (D30-33)
1 (ABC)	A		B		C	PPI start (D14)	A		B		C	
2 (ACB)	A		C		B	PPI start (D14)	A		C		B	
3 (BCA)	B		C		A	PPI start (D14)	B		C		A	
4 (BAC)	B		A		C	PPI start (D14)	B		A		C	
5 (CAB)	C		A		B	PPI start (D14)	C		A		B	
6 (CBA)	C		B		A	PPI start (D14)	C		B		A	

D=day; PPI=proton pump inhibitor; QD=once daily; WO=Washout Period.

Note: A: 180mg (90mg x 2 granules in capsule) current clinical formulation (reference formulation); B: 180mg non-encapsulated tablet containing CCI [redacted]; C: 180mg encapsulated tablet containing CCI [redacted].

Note: The washout of UCB0599 will take place after each period and last for 4 days.

Note: All 6 dosing days will be in a fasted state. In Treatment Period 1 through Period 3, study participants will fast overnight for at least 10 hours prior to study medication administration on Day 1, Day 6, and Day 11, and will continue to fast for at least 4 hours post-study medication administration. In Treatment Period 4 through Period 6, study participants will fast overnight for at least 9 hours prior to esomeprazole administration on Day 19, Day 24, and Day 29, and will continue to fast prior to study medication administration, which will be taken 1 hour following esomeprazole administration, and for at least 4 hours post-study medication administration. No fluid intake, apart from the fluid given at the time of study medication intake, is allowed from 2 hours before until 2 hours after dosing of study medication (Protocol Section 5.3.1).

[a] The PPI esomeprazole will be administrated at a dose of 40mg QD starting at the Washout Period and for 20-consecutive days (D14-D33).

Table 1-4: Part B design: The PK of UCB0599 in healthy Japanese and Chinese participants under normal gastric pH condition (4-treatment, 6-sequence, 2-period crossover design)

Sequence (Duration)	**Period 1** (D1)	**WO** (D2-5)	**Period 2** (D6)	**WO** (D7-10)
1	Placebo 90mg SD		Placebo 180mg SD	
2	UCB0599 90mg SD		UCB0599 180mg SD	
3	Placebo 180mg SD		Placebo 360mg SD	
4	UCB0599 180mg SD		UCB0599 360mg SD	
5	Placebo 360mg SD		Placebo 90mg SD	
6	UCB0599 360mg SD		UCB0599 90mg SD	

D=day; PK=pharmacokinetic(s); SD =single dose; WO=Washout Period.

Note: Of the 30 study participants enrolled in Part B, 15 participants of each ethnic origin will be randomized to the 4 treatments (placebo SD, UCB0599 90mg SD, UCB0599 180mg SD, and UCB0599 360mg SD) following a UCB0599:placebo 4:1 ratio. All participants will be dosed under fasting conditions. Study participants will fast overnight for at least 10 hours prior to study medication administration and will continue to fast for at least 4 hours post-study medication administration. No fluid intake, apart from the fluid given at the time of study medication intake, is allowed from 2 hours before until 2 hours after dosing of study medication (Protocol Section 5.3.1). The Washout Period will take place after each period and last for 4 days.

1.2.1 Part A

Part A is an open label, randomized, 2 in-series crossover substudies, each with a fixed sequence complete block design of 3 treatment periods in healthy male and female participants.

Part A consists of the following (for a total duration of up to 68 days):

- A 28-day Screening Period (2 to 28 days before administration of study medication)
- A Baseline health status on admission to study site on Day -1.
- 6 treatment periods (each treatment period is followed by a 4-day Washout Period)
  - The first 3 periods include the evaluation of UCB0599 PK following its single-dose administration (180mg) of each formulation under normal gastric pH condition.
  - The second 3 periods include the evaluation of UCB0599 PK following its single-dose administration (180mg) of each formulation under the condition of elevated gastric pH. The elevated gastric pH will be achieved by co-administering esomeprazole 40mg once daily (QD) over the duration of the 3 treatment periods (Day 14 to Day 33; see Table 1-3).
- A 7-day Safety Follow-Up (SFU) Period

After completion of Part A, an interim analysis will be performed on key PK endpoints for all available PK data, to support the decision on selection of the Part B formulation.

1.2.2 Part B

Part B of this study is an ethnobridging study evaluating the safety, tolerability, and PK of a single oral dose of the new UCB0599 formulation selected in Part A at 3 dose levels (90mg, 180mg, and 360mg) under normal gastric pH condition in healthy participants of Japanese and Chinese origins. Each group of ethnic origin (N=15 total for each) will be randomized to a 4-treatment, 6-sequence, 2-period crossover study using UCB0599:placebo in a 4:1 ratio, as shown below and in the Overall study schematic (Figure 1-1). Sequences 3 and 4 (Cohort 3) will only commence after Sequences 1 and 2 (Cohort 2) have been completed for all 5 participants; Sequences 5 and 6 (Cohort 4) will only commence after Sequences 3 and 4 have been completed for all 5 participants allowing the SMC review to be carried out before the start of Sequence 5 and 6.

- Sequence 1: placebo 90mg, followed by placebo 180mg (N=1)
- Sequence 2: UCB0599 90mg followed by UCB0599 180mg (N=4)
- Sequence 3: placebo 180mg, followed by placebo 360mg (N=1)
- Sequence 4: UCB0599 180mg, followed by UCB0599 360mg (N=4)
- Sequence 5: placebo 360mg, followed by placebo 90mg (N=1)
- Sequence 6: UCB0599 360mg, followed by UCB0599 90mg (N=4)

No participant will ever receive both UCB0599 and placebo, and therefore no intra-participant comparison will be possible; the crossover aspect of the Part B design refers to the dose level over 2 periods in order to limit the number of participants to be recruited into this study. This design will allow the collection of UCB0599 data at each dose level for 8 study participants of

each ethnic origin and the collection of dose-matching placebo data for 2 study participants of each ethnic origin for each dose. Participants will be blinded to the treatment (ie, UCB0599 or placebo), but not to the dosage within a sequence.

Part B consists of the following periods (for a total duration of up to 45 days):

- A 28-day Screening Period (2 to 28 days before administration of study medication)
- 2 treatment periods (for a total duration of up to 10 days)
  - Eligible study participants will commence the Treatment Period on Day -1. Each participant enrolled will receive a single oral dose of UCB0599 (formulation selected in Part A) or placebo on Day 1 (90mg or 180mg or 360mg of UCB0599 or matching placebo), in accordance with the randomization schedule (see Table 1-4). Study participants will be administered the second single oral dose of UCB0599 or placebo on Day 6. In between each Treatment Period, participants will undergo a 4-day Washout Period.
- A SFU Period (7 days after the last study medication administration)

2 STATISTICAL HYPOTHESES

Not Applicable.

3 SAMPLE SIZE DETERMINATION

3.1 Part A

To assess the relative bioavailability of 2 new formulations (film-coated tablet or encapsulated tablet) to the reference formulation (capsule) under condition of normal or elevated gastric pH with the desired power of 90%, the study was estimated to require approximately 36 completers with a maximum of 42 randomized participants. No replacements are planned.

The assessment was based on two 1-sided ratio of means tests (TOST) for a 3-treatment, 6-sequence, 3-period complete Williams' square crossover design for continuous response data with significance level of 0.05 (5%), assuming:

- a ratio of means between any of the 2 new formulations and the reference formulation under the alternative hypothesis (H1) of 1.0
- lower and upper limits of 0.8 and 1.25, respectively
- a geometric intra-participant coefficient of variation of 28.5% based on the mean estimate of the residual variance obtained from the linear mixed effect model of the log-transformed C_{max} data from the UP0078 study (σ^2=0.0782), a trial with similar participants demographics (males and female aged 18 to 55), and which used a crossover design.

For more details, please refer to the UCB0599 UP0073 sample size calculation documentation form (eTMF: "UCB0599_UP0073_Sample_size_calculation_documentation_form.doc").

3.2 Part B

A formal sample size calculation has not been performed; the group sizes are based upon historical precedent and regulatory requirements.

In order to estimate PK and safety profiles in 2 ethnic groups (Japanese and Chinese origins), it is considered that a group size of at least 10 participants in each ethnicity (8 participants on active drug at each dose and 2 participants on placebo) is appropriate. Chinese Center for Drug Evaluation (CDE) guidance suggests 8 to 12 participants per dose, whereas Japanese Pharmaceuticals and Medical Devices Agency (PMDA) guidance suggests 6 participants per dose for PK studies; both suggest 2 participants on placebo.

The Asian Pacific cohort participants will be recruited from the same clinical center as the participants from Part A (based on prior recommendation, see PMDA report on Opicapone, 2020 https://www.pmda.go.jp/files/000243472.pdf); and therefore, the Part A cohort of healthy participants can be used for assessment alongside the Japanese and Chinese cohorts, using the Part A PK data for the new formulation of choice.

4 POPULATIONS FOR ANALYSIS

Separate Analysis Sets will be generated for Part A and Part B using the definitions in Table 4-1

Table 4-1: Definition of analysis sets

Population	Definition/Criteria	Randomized vs. Actual Treatment
ASPS	All Study Participants Set includes all study participants who signed the ICF.	ASPS will be analyzed as randomized. Non-randomized participants will be defined as "Screen Failures"
RS	Randomized Sets includes all study participants who are randomized.	RS will be analyzed as randomized
SS	The Safety Sets includes all study participants who are randomized and receive full or partial study medication. Study participants will be classified according to the treatment that the participants actually received.	SS will be analyzed according to the treatment actually received.
PKS	The Pharmacokinetic Set includes all participants of the SS, who received at least 1 total dose of study medication and have at least 1 observable PK measurement without important protocol deviations that would affect the PK. If a study participant in the PKS is missing individual time points or individual time points are otherwise non-evaluable, the study participant will be included in the PKS, but those individual time points will be identified as missing in listings. All study participants in the PKS will be included in the listings and derivation of PK parameters. Note: some	PKS will be analyzed according to the treatment actually received.

Table 4-1: Definition of analysis sets

Population	Definition/Criteria	Randomized vs. Actual Treatment
	participants may have missing PK parameters if there are insufficient concentrations to derive them.	

ASPS=All Study Participants Set; ICF=Informed Consent Form; PK=pharmacokinetic(s); PKS=Pharmacokinetic Set; RS=Randomized Set; SS=Safety Set

5 STATISTICAL ANALYSIS

5.1 General Considerations

Statistical analysis and generation of tables, figures, and study participant data listings will be performed using SAS Version 9.4. The PK noncompartmental analysis will be performed using Phoenix WinNonlin® Version 8.0 or higher (Certara L.P., Princeton, NJ, USA) for PK parameters estimation.

A complete set of listings containing both all documented data and all calculated data will be generated by parts and treatment sequence, unless otherwise specified. Missing data will not be imputed, unless otherwise specified. Outlier detection and statistical analysis of outliers will not be performed.

Descriptive statistics will be displayed to provide an overview of the study results. For categorical endpoints, the number and percentage of study participants in each category will be presented. The denominator for percentages will be based on the number of study participants appropriate for the purpose of the analysis. For continuous endpoints, descriptive statistics will include number of study participants, mean, standard deviation (sd), median, interquartile range (IQR), minimum, and maximum. The descriptive statistics for plasma concentrations and PK parameters will be described in Appendix 2 (Section 6.2.1).

Unless otherwise noted, the denominator for percentages should be based on the number of participants included in the respective analysis set. For summaries of demographics and Baseline characteristics: summarize percentages based on all participants in the relevant analysis set and include a potential "Missing" category (corresponding to participants with missing data at the time of the variable being summarized) as the last row in the list of categories being summarized.

Percentages for frequency tables will be presented to 1 decimal place. If the percentage is 100%, do not present a decimal. If the percentage is 0, do not present the percentage. Typically, the % sign should be presented in the column header, but not with each individual value.

Decimal places for descriptive statistics will always apply the following rules, unless otherwise stated:

- "n" will be an integer
- Mean, sd, median, and IQR will use one additional decimal place compared to the original data
- Coefficient of variation (CV) [%] will be presented with one decimal place

- Minimum and maximum will have the same number of decimal places as the original value.

Derived variables in general will display the mean, sd, median, and IQR to 1 more decimal place than the variables used in the derivation. If the number of decimal places reported in the raw data is varied then use either the maximum raw number of reported decimal places or 3, whichever is the lowest, as a guide for the descriptive statistics. If participants have more than one observation for a given time point, the observation closest to the intended time point will be used. If both observations are equidistant from the intended time point, then the later value will be used.

Refer to Appendix 2 (Section 6.2.1 and Section 6.2.2) for standard reporting procedures of PK concentrations and parameters in listings, tables, and figures.

5.1.1 General study level definitions

5.1.1.1 Analysis Time Points

5.1.1.1.1 Relative day

Relative day will be derived with the date of treatment in each Period (treatment and washout) as reference for that specific Period.

- Relative Day 1 is the date of treatment.
- For days prior to first treatment:

  Relative day = Current date – Date of first treatment.
- For days after the day of treatment in Period:

  Relative day = Current date - Date of treatment within the same Dosing Period +1.
- For days after the day of last treatment:

  Relative day = Current date - Date of last treatment +1.

There is no Relative day 0. Relative day will not be calculated for partial dates. Relative day for partial days will be displayed as '--' to distinguish it from missing values which are displayed as blanks.

5.1.1.1.2 End date of the Treatment Period

Treatment periods are specified in Section 5.1.1.1.3.

5.1.1.1.3 Study periods

The total duration of the study for an individual study participant is up to 68 days for Part A and up to 45 for Part B, and includes a Screening Period, Dosing Periods, Washout Periods, and a Safety Follow up Period as given in Table 5-1.

Table 5-1: Study Periods Duration

Study Part	Period	Duration	Relative Day
Part A	Screening Period	Day -28 to Day -2	Relative Day -28 to -2

Table 5-1: Study Periods Duration

Study Part	Period	Duration	Relative Day
	Treatment Period 1	Day -1 to Day 1	Relative Day -1 to 1
	Washout Period 1	Day 2 to Day 5	Relative Day +2 to +5
	Treatment Period 2	Day 6	Relative Day 1
	Washout Period 2	Day 7 to Day 10	Relative Day +2 to +5
	Treatment Period 3	Day 11	Relative Day 1
	Washout Period 3	Day 12 to Day 18	Relative Day +2 to +7
	Treatment Period 4	Day 19	Relative Day 1
	Washout Period 4	Day 20 to Day 23	Relative Day +2 to +5
	Treatment Period 5	Day 24	Relative Day 1
	Washout Period 5	Day 25 to 28	Relative Day +2 to +5
	Treatment Period 6	Day 29	Relative Day 1
	Washout Period 6	Day 30 to 33	Relative Day +2 to +5
	Safety Follow-Up	Day 34 to 39	Relative Day +6 to +10
Part B	Screening Period	Day -28 to -2	Relative Day -28 to -2
	Treatment Period 1	Day -1 to 1	Relative Day -1 to 1
	Washout Period	Day 2 to 5	Relative Day +2 to +5
	Treatment Period 2	Day 6	Relative Day 1
	Washout Period 2	Day 7 to 10	Relative Day +2 to +5
	Safety Follow-Up	Day 11 to 15	Relative Day +6 to +10

5.1.1.1.4 Mapping of assessments performed at Early Termination Visit

Safety assessments made at an early termination visit that correspond to a scheduled visit will be summarized at the scheduled visit to corresponding to the early termination visit if the assessment was scheduled to occur at that visit. Such assessments at the early termination visit will also be considered for safety follow up/ termination visit.

5.1.1.1.5 Definition of Baseline values

Unless otherwise stated, a Baseline value refers to the last non-missing value collected prior to the first treatment. Scheduled or unscheduled measurements can be used as the Baseline value. If a Baseline measurement is repeated and is obtained prior to the first treatment, then the last available measurement will be used as the Baseline value. If an unscheduled measurement occurs

after the planned Baseline measurement time point but before the first treatment, then the unscheduled measurement will be used.

Table 5-2: Definition of Baseline for Part A and Part B

Procedure	Baseline Day
Vital sign	Predose on Day 1 or if missing then the Baseline data will be missing.
Single 12-lead ECG	
Laboratory assessments (hematology, clinical chemistry, and urinalysis)	Baseline is defined as the value on Day -1. If this value is missing, the most recent value obtained prior to Day 1 will be used as Baseline.

ECG= electrocardiogram

5.1.1.2 Protocol Deviations

Protocol deviations are specified in Appendix 1 (Section 6.1.2).

All protocol deviations will be reviewed at the Data Cleaning Meetings (DCM) and decisions made on whether they should be considered important or not.

Important protocol deviations (IPDs) are deviations from the protocol which could potentially have a meaningful impact on study conduct or on either the primary or key secondary outcome(s) for an individual study participant. The criteria for identifying such protocol deviations will be defined within the IPD specifications document.

Important protocol deviations will be categorized as follows:

2. Inclusion/exclusion criteria deviations
3. Incorrect treatment or dose administered
4. Procedural non-compliance
5. Prohibited concomitant medication use
6. Withdrawal criteria deviation

All IPDs will be reviewed as part of the ongoing data cleaning process and data evaluation. At least one Data Evaluation Meeting (DEM) will be performed prior to the final database lock after all data have been verified/coded/entered into the database to discuss exclusion of study participants from analysis populations.

Participants may be excluded from the safety set if they do not pass the inclusion/exclusion criteria. However, should a participant be mistakenly dosed despite failing the inclusion/exclusion criteria, then their safety data would need to be reported as part of the safety analysis. Participants may be excluded from other analysis sets, but this will be determined on a case-by-case basis. If the deviation is deemed to have the potential to bias the analyses for the duration of the study then the whole participant may be removed in a sensitivity analysis on the key endpoints. The removal of the participant and the rationale will be clearly documented within the relevant TFLs.

Important protocol deviations will be identified and classified by the deviation types in the IPD document. A listing of all IPDs identified at the DCMs will be presented for all participants based on the safety set and will include the deviation type and description.

The IPDs will be tabulated using the SS, separately for Part A and Part B and will present the deviation type and description by treatment group.

5.1.1.3 Treatment assignment and treatment groups

It is expected that participants will receive treatment as randomized; hence safety analyses will be based on the SS-as randomized. However, if after unblinding it is determined that participants received treatment other than what they were randomized to, then for PK and safety analyses purposes participants will be allocated to the actual treatment they received (SS-as treated).

5.1.1.4 Definition of Analysis by Variables

Table 5-3: Definition of Analysis by Variables for Part A

Term	Variables
Sequence	Sequence 1 (ABC)
	Sequence 2 (ACB)
	Sequence 3 (BCA)
	Sequence 4 (BAC)
	Sequence 5 (CAB)
	Sequence 6 (CBA)
Formulation	180mg (90mg x 2 granules in capsule)
	180mg non-encapsulated tablet containing PPD
	180mg encapsulated tablet containing PPD
Gastric condition	Normal gastric pH
	Elevated gastric pH

Note: A: 180mg (90mg x 2 granules in capsule) current clinical formulation (reference formulation); B: 180mg non-encapsulated tablet containing PPD; C: 180mg encapsulated tablet containing PPD.

Table 5-4: Definition of Analysis by Variables for Part B

Term	Variables
Sequence	Sequence 1 (C=1, J=1; 90mg → 180mg)
	Sequence 2 (C=4, J=4; 90mg → 180mg)

Table 5-4: Definition of Analysis by Variables for Part B

Term	Variables
	Sequence 3 (C=1, J=1; 180mg → 360mg)
	Sequence 4 (C=4, J=4; 180mg → 360mg)
	Sequence 5 (C=1, J=1; 360mg → 90mg)
	Sequence 6 (C=4, J=4; 360mg → 90mg)
Dose level	Pooled Placebo
	90mg
	180mg
	360mg
Participant group	Japanese participants
	Chinese participants
	Part A healthy participants under normal gastric pH condition on the formulation chosen for Part B

C=Chinese participants; J=Japanese participants.

Table 5-5: Analysis Performed by "by Variables"

Analysis	Part A by Variable	Part B by Variable
Disposition	Sequence	Sequence
Medical History		
Concomitant Medications		
Important Protocol Deviations		
PK Concentration	Formulation and gastric condition	Dose level and participant group
Adverse Events	Formulation	Dose level and participant group
Laboratory Values	Time Point and Sequence	Time Point Sequence
Vital Signs		
ECG		

ECG= electrocardiogram; PK=pharmacokinetic.

5.1.1.5 Center pooling strategy

This is a single center study.

5.1.1.6 Coding dictionaries

Medical history and adverse events (AEs) will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA) at time of database lock. Medications will be coded using the current version of World Health Organization Drug Reference List (WHO-DRL) at time of database lock. Medical procedures will not be coded.

5.1.1.7 Handling of repeated and unscheduled measurements

All repeated and unscheduled measurements will be presented in the data listings, where applicable. Repeated measurements are defined as more than 1 measurement at same time point. The following general rules will apply to all repeated and unscheduled measurements:

- For repeated measurements obtained prior to the first dose of study medication the latest value (which may be scheduled or unscheduled) will be used in the calculation of the descriptive statistics.
- For repeated measurements obtained for the designated Baseline value, the latest value (which may be scheduled or unscheduled) will be defined as the Baseline provided that this occurred prior to the first dose of study medication.
- Unscheduled measurements and repeated measurements after the first one at a given time point will not be used in the descriptive statistics at time points after first dose of study medication.
- Unscheduled measurements performed for the Early EOS/WD visit will be assigned to the EOS Visit and analyzed accordingly as an EOS Visit.

5.2 Participant Dispositions

Participant screening and primary reason for screen failure will be summarized using the ASPS, separately for Part A and Part B. The summaries will include the following:

- Number of participants screened
- Number and proportion of participants rescreened
- Number and proportion of participants with screen failures (Not counting successfully rescreened participants)
- Number and proportion of screen failures by primary reason for screen failure (Based on the later screening visit)

By-participant listings of rescreened participants will be presented using the ASPS.

Participant disposition will be summarized using the ASPS, separately for Part A and Part B. Each summary will include the following:

- Date of first screening visit
- Date of last visit for last participant
- Number of participants screened
- Number of participants in each analysis set, by treatment sequence (according to randomized treatment).

Disposition of analysis sets will be tabulated using the ASPS, separately for Part A and Part B. Each table will present the total number of participants in the ASPS, as well as the number and percentage of participants in each analysis set by treatment sequence.

Study completion/discontinuation and primary reason for discontinuation will be summarized using the RS, separately for Part A and Part B. Each table will present the following, by treatment sequence:

- Number and percentage of participants that started the study
- Number and percentage of participants completing the study
- Number and percentage of participants discontinuing the study
- Number and percentage of participants discontinuing the study by primary reason for discontinuation.
- Part A only:
  - Number and percentage of participants that started substudy 1 and substudy 2
  - Number and percentage of participants completing substudy 1 and substudy 2
  - Number and percentage of participants discontinuing substudy 1 and substudy 2

Participants that started the study are defined as participants that were randomized. Participants completing the study are those participants completing the SFU visit AND who did not discontinue dosing or withdraw from the study for any reason before the SFU.

Participants that started substudy 1 and substudy 2 are defined as participants who started treatment period 1 and 4, respectively. Participants completing the substudy 1 and substudy 2 are those participants completing Washout period 3 and 6, respectively.

Study discontinuation due to AEs will be tabulated using the RS, separately for Part A and Part B. Each table will present the number and percentage of participants who discontinued the study due to AE by treatment sequence.

By-participant listings of participant who did not meet study eligibility criteria will be presented by study part and treatment sequence, using the ASPS. The listing will include inclusion criteria that were not met and the exclusion criteria that were met.

By-participant listings of participant disposition will be provided using the ASPS, by study part and treatment sequence. The listings will include:

- Study termination/completion status
- Date of informed consent
- Date of randomization
- Date and time of first study treatment (first start date and time)
- Date and time of last study treatment (last stop date and time)
- Date of last contact

- Date of premature study termination for successfully screened participants dropping out of the study.
- Date of screen failure for screen failure participants (based on the last screening visit in case of rescreen)
- Primary reason for premature study termination
- Primary reason for screen failure (Based on the last screening visit in case of rescreen)

By-participant listings of participant inclusion in each analysis set will be presented by study part and sequence, using the ASPS.

By-participant listings of study discontinuation will be presented by study part and sequence, using the RS.

5.3 Pharmacokinetics

Unless otherwise stated, PK analysis will be performed on the PKS.

5.3.1 Analysis of Concentration Measures

The plasma concentration-time profiles will be summarized for Part A by formulation and gastric condition, and for Part B by dose level and group using descriptive statistics (number of available observations, arithmetic mean, sd, geometric mean, geometric coefficient of variation (geometric cv), median, IQR, minimum, and maximum).

Individual concentration-time profiles will be displayed graphically on a linear-linear scale and semilogarithmic scale. For Part A, individual concentration-time profiles for a given formulation and gastric condition will be presented on the same plot; for Part B, individual concentration-time profiles will be presented separately for each participant (both doses on the same plot).

Overall geometric mean plasma concentrations-time curves and corresponding 95% CIs will be displayed for Part A by formulation and gastric condition, and for Part B by dose level and participant group.

Individual concentrations will be listed for Part A by formulation and gastric condition, and for Part B by dose level and participant group.

Standard reporting procedures of individual values and descriptive statistics for plasma concentration data in listings, tables, and figures are described in Appendix 2 (Section 6.2.1).

5.3.2 Pharmacokinetic Parameters

The following PK parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin® (Version 8 or higher), as applicable: C_{max}, t_{max}, AUC_{last}, AUC_{inf}, AUC%Extrap, $t_{½}$, Lambda z (λ_z), CL/F (UCB0599 only), Vz/F (UCB0599), MRC_{max}, and $MRAUC_{inf}$ from the plasma concentration-time data.

Table 5-6: Non-compartmental PK parameters for UCB0599 in plasma

PK Parameter	Definition
AUC_{inf}	The AUC from time zero to infinity (mass * time * volume^{-1}).
AUC_{last}	The AUC from time zero to the last measurable drug concentration sampling time (t_{last}) (mass * time * volume^{-1}).
C_{max}	The maximum (peak) observed drug concentration following a single dose administration (mass * volume^{-1}).
t_{max}	The time to reach maximum (peak) drug concentration following a single dose administration (time).
$t_{½}$	The elimination half-life associated with the terminal slope (λ_z) of a semilogarithmic concentration-time curve (time).
CL/F[a]	The total apparent body clearance of drug (volume/time).
Vz/F[a]	The apparent volume of distribution during terminal phase (associated with λ_z) (volume).
Lambda_z (λ_z)	Terminal elimination rate constant (1/time).
AUC%Extrap[b]	Area under the <matrix> concentration-time curve extrapolated from the time t to infinity as a percentage of total AUC.
Rsq_adj[c]	Square of the correlation coefficient (adjusted for the number of data points included) associated with λz.
MRC_{max}[d]	C_{max} metabolite to parent ratio.
$MRAUC_{inf}$[d]	$AUC_{0\text{-}inf}$ metabolite to parent ratio.

[a] For UCB0599 only
[b] AUC%Extrap is listed if AUCinf is presented
[c] Rsq_adj is listed only
[d] Metabolites only

PK parameters of UCB0599 will be listed and summarized using descriptive statistics similarly to the plasma concentrations.

Standard reporting procedures of individual values and descriptive statistics for PK parameters in listings, tables, and figures are described in Appendix 2 (Section 6.2.2).

5.4 PK Endpoints Analysis

5.4.1 Definition of endpoint(s)

PK endpoints are based on the definitions in Table 5-6.

The primary endpoints for PK objectives in both parts are:

- $AUC_{0\text{-}t}$
- AUC_{inf}
- C_{max}

The other PK endpoints for Part A are defined as follows:

- For UCB0599:
  - t_{max}, $t_{½}$, CL/F, and Vz/F (if possible but not limited)
- For CCI [redacted] metabolites:
  - C_{max}, t_{max}, AUC_{0-t}, and AUC_{inf}
  - metabolite/parent C_{max} and AUC ratio (corrected for the molecular weight of the entities), as appropriate

The other PK endpoints for Part B are defined as follows:

7. For UCB0599:
   - t_{max}, CL/F, Vz/F, $t_{1/2}$, C_{max}/BW/D, AUC_{0-t}/BW/D, and AUC_{inf}/BW/D
- For CCI [redacted] metabolites:
  - C_{max}, t_{max}, AUC_{0-t}, and AUC_{inf}

5.4.2 Part A

5.4.2.1 Analyses required for Primary Objective (on Primary PK endpoints)

The 2 new UCB0599 formulations will be compared with reference 'granules in capsule' formulation and compared against each other under normal gastric pH condition, and under elevated gastric pH condition, separately. The primary comparisons of interest are:

- non-encapsulated tablets vs granules in capsule under normal pH condition
- encapsulated tablets vs granules in capsule under normal pH condition
- non-encapsulated tablets vs granules in capsule under elevated pH condition
- encapsulated tablets vs granules in capsule under elevated pH condition
- non-encapsulated tablets vs encapsulated tablets under normal pH condition
- non-encapsulated tablets vs encapsulated tablets under elevated pH condition

In order to estimate these comparisons, the primary analysis model will be applied to the 2 sets of data separately; namely, the data under normal gastric pH condition (first 3-period crossover design substudy, ie substudy 1) and the data under elevated gastric pH condition (second 3-period crossover design substudy, ie substudy 2).

The PK parameters C_{max}, AUC_{0-t}, and AUC_{inf} will be evaluated according to a univariate model of analysis of variance (ANOVA), adapted to crossover designs. The model will include a random intercept term for participant within sequence and fixed effect categorial terms for sequence, period, and formulation (Model 1.1 and Model 1.2 in Table 6-10).

The dependent variables will be logarithmically transformed by natural logarithms (ln) prior to statistical testing, following the usual recommendations.

The linear mixed model is given as following:

$$\ln(Y) = Q + S_i + P + T + \varepsilon, \text{ where} \quad \textbf{(1)}$$

- *ln(Y)* is the log transformed PK parameter value,

- Q is the fixed effect term for the sequence,
- S_i is the fixed effect term of the participant nested to the sequence,
- P is the fixed effect term for the period,
- T is the fixed effect term for the treatment,
- ε is the random error.

The PROC MIXED procedure in the Statistical Analysis Software (SAS) will be used for this analysis. For estimation based on a linear mixed model, covariance matrix applied to the within-subject error will be estimated by restricted maximum likelihood (REML). The Kenward-Roger approximation will be used to estimate the degree of freedom. Variance component structure will be used as covariance in this linear mixed model.

For each PK parameter and set of substudy data separately (ie, gastric pH condition), the least square mean (LSMEAN) for each formulation and 95%CI of LSMEANs, difference in LSMEANs between the each formulation, and corresponding 90% confidence interval (CI) will be calculated. These values will then be back-transformed to give the estimate of the geometric mean ratio (GMR) for the non-encapsulated tablets versus granules in capsule, the GMR for the encapsulated tablets versus granules in capsule, and the GMR for the non-encapsulated tablets versus encapsulated tablets, alongside with their corresponding 90% CI.

The estimates of the geometrics mean ratios with their corresponding 90% CI will be displayed in a summary plot.

Additionally, the between-participant CVs available for single formulation at given gastric pH condition may be calculated.

5.4.2.2 Sensitivity required for Primary Objective (on Primary PK endpoints)

The analysis described in Section 5.4.2.1 will be performed on the PK parameters separately to the data for each formulation in comparison to the reference formulation in separate mixed model procedure (Model 1.1a, Model 1.1b, Model1.2a, and Model 1.2b in Table 6-10).

5.4.2.3 Analyses required for Other Objective (on Primary PK endpoints)

Another objective of the study is to estimate the relative bioavailability of UCB0599 under elevated gastric pH versus normal gastric pH for each tested formulation.

- granules in capsule under elevated pH condition vs granules in capsule under normal pH condition
- non-encapsulated tablets under elevated pH condition vs non-encapsulated tablets under normal pH condition
- encapsulated tablets under elevated pH condition vs encapsulated tablets under normal pH condition

To that effect, a supplementary analysis will be performed using the PK parameters (C_{max}, AUC_{0-t}, and AUC_{inf}) where all 3 formulation data from all 6 periods (normal and elevated gastric pH data) will be combined into a single linear mixed model a random intercept term for participant within sequence and with fixed effect categorical terms for sequence, gastric status, formulation,

formulation (nested to the gastric condition), and period within substudy (ie, 3-level categorical variable) (Model 2.1 in Table 6-10).

The linear mixed model is given as following:

$$\ln(Y) = Q + S_i + G + T + T_g + P + \varepsilon, \text{ where} \quad \textbf{(2)}$$

- *ln(Y)* is the log transformed PK parameter value,
- Q is the fixed effect term for the sequence,
- S_i is the fixed effect term of the participant nested to the sequence,
- G is the fixed effect for the gastric status,
- T is the fixed effect term for the formulation,
- T_g is the fixed effect for the formulation nested to gastric status,
- P is the fixed effect term for the period,
- ε is the random error.

The MIXED procedure in SAS software will be used for this analysis. For estimation based on a linear mixed model, covariance matrix applied to the within-subject error will be estimated by restricted maximum likelihood. The Kenward-Roger approximation will be used to estimate the degree of freedom. Variance component structure will be used as covariance in this linear mixed model.

For each PK parameter and formulation, the LSMEAN for elevated gastric pH and normal gastric pH and corresponding 95%CI, difference in LSMEANs between the elevated gastric pH and normal gastric pH, and corresponding 90% CI will be calculated. These values will then be back-transformed to give the estimate of GMR for elevated gastric pH versus normal gastric pH, alongside with their corresponding 90% CI.

The ratios and corresponding 90% CIs will be obtained for the granules in capsule, non-encapsulated tablet, or encapsulated tablet under elevated gastric pH condition versus the respective formulation under normal gastric pH condition and displayed in a summary plot.

5.4.2.4 Sensitivity required for Other Objective (on Primary PK endpoints)

The analysis described in Section 5.4.2.3 will be performed on the PK parameters separately to the data for each formulation when comparing pH condition (Model 2.1a, Model 2.1b, and Model 2.1c in Table 6-10).

5.4.2.5 Analyses required for Other Objective (on Other PK endpoints)

The other PK parameters of UCB0599 and metabolites will be summarized by formulation and gastric condition using descriptive statistics as described in Section 5.3.1.

- For UCB0599: t_{max}, $t_{½}$, CL/F, and Vz/F (if possible but not limited). For t_{max}, only the median, IQR, minimum, and maximum will be reported.

- For CCI [redacted] metabolites: C_{max}, t_{max}, $AUC_{0\text{-}t}$, AUC_{inf}, and each metabolite/parent C_{max} and AUC ratio (corrected for the molecular weight of the entities), as appropriate.

$$MR\_C_{max} = \frac{Cmax(metabolite)}{Cmax(parent)} * \frac{Molecular\ weight\ (parent)}{Molecular\ weight\ (metabolite)}$$

$$MR\_AUC_{inf} = \frac{AUC(metabolite)}{AUC(parent)} * \frac{Molecular\ weight\ (parent)}{Molecular\ weight\ (metabolite)}$$

where,
Molecular weight (parent) = 425.59 g/mol
CCI [redacted]

5.4.3 Part B

5.4.3.1 Analyses required for Primary Objective (on Primary PK endpoints)

Dose proportionality for C_{max}, $AUC_{0\text{-}t}$, and AUC_{inf} will be examined for each participant group (Table 5-3) via the power model

$$Y = \alpha * dose^{\beta}, \quad \textbf{(3)}$$

where α is the subject random intercept, Y is the parameter of interest, and β is the slope. The PK parameters and the dose will be logarithmically transformed prior to analysis. The power model will be estimated by regressing the log-transformed PK parameter onto the log-transformed dose.

$$\ln(Y) = \alpha + \beta * ln(dose) \quad \textbf{(4)}$$

The power model will be fitted by restricted maximum likelihood (REML) using the PROC MIXED procedure in SAS, with a fixed effect term for dose level and a random effect for participant. A lack of fit test will be performed to check the linearity assumptions for appropriateness of the power model. An unstructured covariance matrix will be specified for the participant random effect. If the model fails to converge, other covariance matrices such as VC and CS may be considered.

The results of the power model will be reported after back-transformation, including the estimated dose proportionality parameter β along with corresponding 90% CI (slope≈1 implies dose proportionality).

Graphical displays including observed values, regression line of the fitted values with the 90% CI will be provided for each log-transformed PK parameter vs. log-transformed dose.

5.4.3.2 Exploratory analysis for Primary Objective (on Primary PK endpoints)

The co-primary PK endpoint data obtained for the groups will be log-transformed. For each dose level, the transformed data will be combined into an ANOVA model with fixed effect terms for participant group. The model may be adjusted for age, height and weight. Therefore, the impact of the Baseline (Day-1) characteristics of age, height and weight will be included in the statistical

model as fixed effect and tested by 10% significant level individually. If a fixed term has a significant effect to the model for all three primary PK parameters at 10% significant level, the term will be included to the ANOVA model as fixed effect.The SAS PROC MIXED procedure will be used. Point estimates for the geometric mean ratios and corresponding 90% CIs will be obtained and compared between the Japanese participants versus the Part A participants (healthy participants on normal gastric condition on the formulation chosen for Part B), and between the Chinese participants versus the Part A using least squares means and root mean squares of error from the model with subsequent exponential transformation.

5.4.3.3 Sensitivity analysis for Primary Objective (on Primary PK endpoints)

The analysis described in Section 5.4.3.2 will be repeated on the normalized PK parameters using the same ANOVA model.

For the C_{max} normalization:

C_{max} _w= C_{max} /BW , body-weight normalization

C_{max} _d= C_{max} /Dose , dose normalization

C_{max} _wd= C_{max} /(BW*Dose) , body-weight and dose normalization

(BW=Day -1 bodyweight)

For the AUC_{inf}, and AUC_{0-t} similar normalization will be used.

5.4.3.4 Analyses required for Other Objective (on Other PK endpoints)

The other PK parameters of UCB0599 and metabolites will be summarized by group and dose level using descriptive statistics as described in Section 5.3.1..

- For UCB0599: t_{max}, CL/F, Vz/F, $t_{1/2}$, C_{max}/BW/D, AUC_{0-t}/BW/D, and AUC_{inf}/BW/D. For t_{max}, only the median, IQR, minimum, and maximum will be reported.
- For CCI [redacted] metabolites:
  - Metabolite/parent C_{max} and AUC ratio (corrected for the molecular weight of the entities), as appropriate
  - Metabolite/parent C_{max} and AUC ratio (corrected for the molecular weight of the entities) per group, as appropriate

5.5 Safety Analyses

Unless stated otherwise, all safety analyses will be performed on the SS.

5.5.1 Extent of Exposure

Administration of treatments will be listed by study part and sequence. Exposure data will be listed only.

5.5.2 Adverse Events

An Adverse Event is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study medication, whether considered related to the study medication.

Adverse events with start date/time prior to first treatment are defined as pre-treatment. These events will not be included in any tabulated summaries, but will be listed.

Treatment emergent AEs (TEAE) are all AEs starting on or after the date/time of first treatment and up to including 4 days after last treatment, or any unresolved event already present before administration of treatment that worsens in intensity following exposure to the treatment.

AEs with a start date after 4 days of last treatment are defined as post-treatment. These events will not be included in any tabulated summaries, but will be listed.

In case of missing or partially missing AE dates, the following rules will apply. Start and stop dates of AEs will be displayed as reported in the participant data listings (ie, no imputed values will be displayed in data listings).

The following rules will be applied for partial start dates and time:

- If only the month and year are specified and the month and year of the first treatment is not the same as the month and year of the start date, then use the 1st of the month, or the date of Screening if this is later (if the imputation results in an end date that is earlier than the start date, then use the 1st of the month). If time is missing, it will be imputed as 00:00 h
- If only the month and year are specified and the month and year of the first treatment is the same as the month and year of the start date, then use the date of the first treatment. If the imputed start date that is after the specified end date, then use the 1st of the month, or the date of Screening if this is later (if the imputation results in an end date that is earlier than the start date, then use the 1st of the month). If the imputed date is the date of treatment then time will be imputed as the start time of the treatment (ie, event will be regarded as treatment emergent)
- If only the year is specified, and the year of the first treatment is not the same as the year of the start date, then January 01 will be used. If time is missing, it will be imputed as 00:00 h
- If only the year is specified, and the year of the first treatment is the same as the year of the start date, then the date of the first treatment will be used. If this results in an imputed start date that is after the specified end date, then January 01, or the date of Screening if this is later will be used (if the imputation results in an end date that is earlier than the start date, then January 01 will be used). If the imputed date is the date of first treatment then time will be imputed as the start time of the treatment (ie, event will be regarded as treatment emergent)
- If the start date is completely unknown, then use the date of first treatment. If this results in an imputed start date that is after the specified end date, then use January 01 of the year of the end date, or the date of Screening if this is later.

The following rules will be applied for partial stop dates:

- If only the month and year are specified, then use the last day of the month
- If only the year is specified, then use December 31 of the known year
- If the stop date is completely unknown, do not impute the stop date

Missing or partially missing date and/or times will be imputed as described in Table 5-7 for the calculation of duration of each AE. AE duration is computed and reported in day and time format.

Table 5-7: Calculation Rules for Duration of AEs

Data Availability	Onset Date/Time	Outcome Date/Time	Calculation Rules
Complete data	D1/T1	D2/T2	Duration = (D2-D1)*24+(T2-T1)
End time missing	D1/T1	D2/--	End time is substituted by time 23:59h (=23.98 in decimal format). Duration=<(D2-D1)*24+(23.98-T1)
Start time missing	D1/--	D2/T2	Onset time is substituted by 00:00h. Duration=<(D2-D1)*24+T2
Start and end time missing	D1/--	D2/--	Duration=<[(D2-D1)+1]*24
Start day and time missing	--/--	D2/T2	Duration=<(D2-D0)*24+(T2-T0) For a participant in the SS, D0 and T0 are the date and time of the first administration of study medication and for screen failures, D0 is the date of the Screening Visit date and T0=00:00h.
End day and time missing	D1/T1	--/--	If the stop date is missing, duration will not be calculated.
Start and end date missing	--/--	--/--	If the stop date is missing, duration will not be calculated.

The duration of each AE will be calculated as follows and will be presented in dd:hh:mm format where dd represent days, hh: hours, and mm: minutes:

Duration of AE = End date/time of AE – Start date/time of AE **(5)**

Adverse events will be assigned to Treatment Periods, based on the onset date/time of the AE. Assignment to Treatment Periods will be done after missing dates have been imputed as described above. AE will be assigned to a treatment based on the treatment received in the Treatment Periods as given in Table 5-8.

Table 5-8: AE Treatment Period Assignment

Study Part	Period	Start	End
Part A	Treatment Period 1	Start date is on or after administration of treatment in Treatment Period 1	Prior to administration of treatment in Treatment Period 2
	Treatment Period 2	Start date is on or after administration of treatment in Treatment Period 2	Prior to administration of treatment in Treatment Period 3
	Treatment Period 3	Start date is on or after administration of treatment in Treatment Period 3	Prior to administration of treatment in Treatment Period 4
	Treatment Period 4	Start date is on or after administration of treatment in Treatment Period 4	Prior to administration of treatment in Treatment Period 5
	Treatment Period 5	Start date is on or after administration of treatment in Treatment Period 5	Prior to administration of treatment in Treatment Period 6
	Treatment Period 6	Start date is on or after administration of treatment in Treatment Period 6	
Part B	Treatment Period 1	Start date is on or after administration of treatment in Treatment Period 1	Prior to administration of treatment in Treatment Period 2
	Treatment Period 2	Start date is on or after administration of treatment in Treatment Period 2	

The following summaries will be provided for Part A by formulation and for Part B by dose level and group:

- Incidence of TEAEs – Overview
- Incidence of TEAEs
- Incidence of Serious AEs
- Incidence of TEAEs leading to discontinuation
- Incidence of TEAEs by maximum intensity
- Incidence of TEAEs by relationship to study medication

AEs will be presented as “number of participant (percentage of participant) [number of events]”. In this style of output, “[number of events]” will include all cases of an AE including repeat occurrences in individual participant, while “number of participant ” will count each participant only once.

AEs will be presented by system organ class (SOC), high level term (HLT) and preferred term (PT) in a frequency table, giving the number of events, the number of participants, and the percentage of participants who experienced the event. Participants with multiple AEs are only counted once within each PT, each HLT and within each SOC.

Summaries by maximum severity will count each participant at most once within each MedDRA level based on the maximum severity/event intensity within that MedDRA level.

In summaries including intensity, the following intensity categories will be summarized: 'Mild', 'Moderate', 'Severe'. Participants who experience the same event multiple times will be included in the most severe category for tabulations by maximum intensity. Events with missing intensity will be considered as 'Severe' events for summary purposes but recorded as missing in the listings.

All summaries will be sorted alphabetically by SOC. Within SOC, it will be sorted by decreasing frequency of PT.

A by-participant listing will be presented for Part A by formulation and for Part B by dose level and group for all AEs for the SS. This will include reported term, SOC, PT, the onset date/time and outcome date/time of the event (including relative days), stop date and time (or ongoing, if applicable; relative days), the AE duration, severity, relationship, action taken, and outcome. In addition, the listing will flag TEAEs, SAEs, and AE of special interest. A glossary of AE terms including reported term, SOC and PT will also be presented.

5.5.3 Additional Safety Assessments

5.5.3.1 Clinical laboratory evaluations

The protocol-required laboratory parameters collected within UP0073 are given in Table 5-9. All non-protocol-required laboratory parameters will not be presented in any tabulated summaries, but will be listed.

Table 5-9: Protocol-required Laboratory Assessments

Laboratory Assessment	Parameters
Hematology	Platelet count
	Red blood cell count
	Hemoglobin
	Hematocrit
	Red blood cell indices – Mean corpuscular volume, Mean corpuscular hemoglobin, % reticulocytes.
	White blood cell count with differentials – Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils
Clinical Chemistry	Blood urea nitrogen
	Potassium
	Aspartate Aminotransferase/Serum Glutamic-Oxaloacetic Transaminase
	Total and direct bilirubin
	Creatinine

Table 5-9: Protocol-required Laboratory Assessments

Laboratory Assessment	Parameters
	Sodium
	Alanine Aminotransferase/Serum Glutamic-Pyruvic Transaminase
	Total Protein
	Glucose (fasted)
	Calcium
	Alkaline Phosphatase
Routine Urea	Specific gravity
	pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick
	Microscopic examination (if blood or protein is abnormal)
	Renal biomarker analysis
Other screening tests	Follicle-stimulating hormone (FSH) and estradiol (as needed in women of non-childbearing potential only)
	Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, methadone, and benzodiazepines)
	Serum and urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)
	Serology (HIV antibody, HBsAg and hepatitis C virus antibody)

5.5.3.1.1 Laboratory values over time

Laboratory variables and changes from Baseline will be summarized using descriptive statistics for Part A by time point, and sequence, and for Part B by time point, and sequence. A by-participant listing will be provided for the SS.

Measurements that are below the limit of quantification (BLQ) or above the limit of quantification (ALQ) will be presented as BLQ or ALQ in the listings. For the purpose of calculating change from Baseline or for descriptive statistics, BLQ values will be imputed with half of the lower limit of quantification (LLoQ) and ALQ values will be imputed to the upper quantification limit.

5.5.3.2 Vital Signs

Supine vital signs measured within UP0073 include:

- Pulse rate
- Systolic blood pressure

- Diastolic blood pressure
- Respiratory rate
- Tympanic body temperature

Vital signs will be measured in triplicate. The mean values will be calculated and recorded on the CRF.

Reference ranges for each vital sign will be recorded on the CRF. Clinically significant abnormalities will be flagged in the listings.

5.5.3.2.1 Vital Sign Values Over Time

The vital sign variables and changes from Baseline will be summarized using descriptive statistics for Part A by time point, gastric condition ,and formulation, and for Part B by time point, dose level, and participant group. A listing will be provided for the SS.

5.5.3.3 Electrocardiograms

The following ECG parameters will be obtained:

- Heart rate (beats/min),
- PR-interval (msec [milliseconds]),
- QRS-duration (mesc),
- QT-interval (mesc),
- QTcF (QT corrected for heart rate using Fridericia's formula) (mesc),
- Investigator’s conclusion on ECG profile.

5.5.3.3.1 Electrocardiogram Values Over Time

The electrocardiogram results and changes from Baseline will be summarized using descriptive statistics for Part A by time point, gastric condition, and formulation, and for Part B by time point, dose level, and participant group. A by-participant listing will be provided for the SS.

The following cut-points in QTcF based on the mean of the triplicate data will be summarized categorically (number and percentage of participants).

For observed data:

- <450 msec
- ≥450 to <480 msec
- ≥480 to <500 msec
- ≥500 msec

For change from Baseline in QTcF:

- <30 msec
- ≥30 to <60 msec
- ≥60 msec "

5.5.3.4 Physical examination

A by-participant listing will be provided for physical examinations for the SS.

5.6 Subgroup analyses

Not Applicable.

5.7 Interim Analyses

There is 1 planned interim analysis. After completion of Part A, an interim analysis will be performed on key PK endpoints for all data, to support the decision on selection of the Part B formulation. Selected outputs flagged in the tables, listing, figure shells will be produced for the interim analysis.

5.8 Safety Monitoring Committee (SMC)

An SMC is planned for between Cohort 3 and Cohort 4 in Part B of the study to assess the safety data accumulated. This is set to take place once all participants of one ethnic group have completed Day 10 assessments. A detailed description of the composition and conduct of the SMC will be provided in a separate SMC Charter.

6 SUPPORTING DOCUMENTATION

6.1 Appendix 1 Non-key analysis specifications

6.1.1 Baseline characteristics and demographics

The body mass index (BMI) value collected in the eCRF will not be used for this summary. The BMI will be
recalculated using the following formula and reported to 1 decimal place:

$$BMI(kg/m^2) = \frac{body\ weight\ at\ screening\ (kg)}{[height\ at\ screening\ (m)]^2} \quad \textbf{(6)}$$

6.1.2 Protocol deviations

Important protocol deviations (IPDs) are deviations from the protocol that potentially could have a meaningful impact on study conduct, safety, or PK outcomes for an individual study participant. Furthermore, study participants will be excluded from the Safety Set only when there is documented evidence that they received no treatment. The criteria for identifying IPDs and the classification of IPDs will be defined within the Protocol Deviation Assessment Plan. IPDs will be reviewed as part of the Data Cleaning Meeting and Data Evaluation Meeting (DEM). Any important deviation will be identified and documented before unblinding to confirm exclusion from analysis sets.

Protocol deviations will be classified as follows:

- AE SAE
- Disallowed medications
- Inclusion/Exclusion criteria
- Informed Consent

- Study treatment
- Other
- Procedures/tests
- Procedures/tests/lab
- Visit schedule
- Withdrawal criteria
- Time window deviation

The IPDs will be tabulated using the SS by study parts and sequence, and will present the deviation type.

6.1.3 Medical history

Medical history and ongoing medical conditions will be listed and summarized for the RS by study parts, treatment sequence, and for all participants by MedDRA SOC and PT. The reported term will be included in the listing. The summary will include the number and percentage of study participants and will be sorted alphabetically by SOC and by descending incidence of PT within each SOC, based on the 'All Participants' column.

6.1.4 Prior/concomitant medications

Medications with a start date prior to the first treatment will be considered as prior medications. Medications with a start date prior to, at or after the first treatment will be considered as concomitant medications if the duration overlaps at least 1 day with the any treatment period. Medications with a missing start date whose stop date is either unknown or after the date of the first treatment will be considered as concomitant.

Concomitant medications will be listed and summarized for the RS by study parts and treatment sequence, and will include WHODD (World Health Organization Drug Dictionary) Anatomical Main Group [Level 1 term text], Pharmacological Subgroup [Level 3 term text] and PT. The reported term will be included in the listing. Prior medications and concomitant medications will be summarized separately within the same table, ie, paged by prior and concomitant medications. Prior medications which continued into the study period are also classified as concomitant and are included in both summaries.

In the case of missing dates, the classification of medications as prior or concomitant will be performed after imputation of dates as described below. Imputations of missing dates will be performed prior to calculation of relative days.

The following rules are applied to impute partial start dates for medications:

- If only the month and year are specified and the month and year of first treatment is not the same as the month and year of the start date, then use the 1st of the month.
- If only the month and year are specified and the month and year of first treatment is the same as the month and year of the start date, then use the date/time of first treatment.
- If only the year is specified, and the year of first treatment is not the same as the year of the start date, then use January 1 of the year of the start date.

- If only the year is specified, and the year of first treatment is the same as the year of the start date, then use the date/time of first treatment.
- If the start date is completely unknown, then use the date/time of first IMP dose.

The following rules will be applied for partial stop dates and will be imputed for the calculation of duration of each medication:

- If only the month and year are specified, then use the last day of the month.
- If only the year is specified, then use December 31 of that year.
- If the stop date is completely unknown, do not impute the stop date.

Medications permitted to be continued during the study are limited to those listed in Section 6.5.1 of the protocol. No rescue medications are permitted.

All tabulations will be sorted alphabetically by Level 1 term, alphabetical Level 3 term within Level 1 and decreasing frequency of PT in the 'All Participants' column.

6.1.5 Data derivation rules

Not applicable.

6.1.6 AEs of Special Interest

AE of special interest are:

- Hy's Law: Potential Hy's Law is defined as ≥3xULN, ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality (ie, without waiting for any additional etiologic investigations to have been concluded).
- Hypersensitivity reactions (such as rash, angioedema, or anaphylaxis).

A listing will be produced of Potential Hy's Law for the SS for Part A by treatment and for Part B by dose level and ethnic group.

A listing will be produced for Hypersensitivity reactions for the SS for Part A by formulation and for Part B by dose level and participant group using the following search strategy: Standardized MedDRA Queries (SMQ)='Hypersensitivity' (Broad) AND SMQ=Anaphylactic reaction (Broad).

6.1.7 Potentially Clinically Significant Criteria for Safety Endpoints

Not applicable.

6.1.8 Compliance

For all study participants, study medication will be administered at the study unit.

Drug accountability must be recorded on the Drug Accountability form.

As dosing is performed in-house by the investigator or member of staff, no specific assessment or compliance is warranted. Any dosing deviation will be addressed in the DEM and described in the CSR.

6.2 Appendix 2: Standard Reporting Procedures

6.2.1 PK Concentrations

When reporting individual data in listings the following rules will apply:

- Missing data will be reported as NV (no value).
- Concentrations below the limit of quantification will be reported as BLQ.
- Concentrations will be listed to the same number of significant figures supplied by the bioanalytical laboratory.

When reporting individual data in figures the following rules will apply:

- BLQ values prior to C_{max} will be set to 0 for purposes of plotting the figure (to capture lag-time).
- Actual sampling times will be used.

When summarizing the data in tables the following rules will apply:

- To calculate descriptive statistics, BLQ values will be set to half the LLOQ (lower limit of quantification) value and missing values will be excluded.
- When the total number of BLQ and missing values exceeds one third of the total then only minimum and maximum will be reported for this time point. Other descriptive statistics will be reported as missing ("-"). The minimum will be reported as "BLQ".
- When the summary statistic includes one or more replaced BLQ values then a footnote will be included to say, "contains one or more BLQ value replaced by half the LLOQ value".
- A minimum of 3 values are required to calculate summary statistics. If only 2 values are available, then these will be presented as the minimum and maximum with other descriptive statistics reported as missing ("-").
- If no participants have data, only n=0 will be presented. The other descriptive statistics will be left blank.
- Descriptive statistics for plasma concentration data will be reported to the same level of precision as the individual data for the minimum and maximum, and to 1 additional decimal place or 1 additional significant figure– depending on the reporting format of the original data with a maximum of 3 significant digits, ie, 35.12 will be 35.1, 0.0004649 will be 0.000465 - for the arithmetic mean, sd, median, IQR, geometric mean, geometric cv, the 95% CI for the geometric mean, minimum and maximum.
- The 95% CI should be left blank if the sd (or equivalently, the geometric cv) is 0
- The geometric cv will be calculated using the following formula where sd is the standard deviation from the log-transformed data:

$$Geometric\ cv\ (\%) = \sqrt{(\exp(SD^2) - 1)} \times 100 \quad \textbf{(7)}$$

- Geometric cv will be reported as a percentage to 1 decimal place

When summarizing the data in figures the following rules will apply:

- The data plotted in the figure will match the data presented in the summary table, with the exception of missing values prior to C_{max} which should be set to 0 in the figure (to capture lag-time).
- Geometric mean should be plotted (as opposed to arithmetic mean) due to the log-normal distribution of concentrations. Variability should be plotted as detransformed sd computed on ln-transformed data.
- Nominal sampling times will be used.
- Both linear and semi-logarithmic scales will be presented.

6.2.2 PK Parameters

When reporting individual data in listings the following rules will apply:

- Individual PK parameters will be reported to 3 significant figures.
- If a parameter cannot be calculated, it will be reported as NE (not estimable ie, if input data is missing which prevents calculation) or NC (not calculable ie, if the data were available but the calculation was considered unreliable).

When summarizing the data in tables the following rules will apply:

- The derived PK parameters will be considered as source data and this data without rounding will be used for calculation of summary statistics of PK parameters.

8. Descriptive statistics will be reported to 4 significant figures for the mean (arithmetic and geometric), median, sd, and IQR to 3 significant figures to the others including the 90% CI for the geometric mean.

- Geometric cv will be reported as a percentage to 1 decimal place.
- If at least two thirds of the participants have a PK parameter reported then descriptive statistics will be calculated, otherwise only minimum and maximum will be reported for this PK parameter and all other descriptive statistics will be reported as NE (ie, not estimable).
- A minimum of 3 values are required to calculate summary statistics. If only 2 values are available, then these should be presented as the minimum and maximum with other descriptive statistics reported as missing ("-")
- For t_{max} only the median, minimum, and maximum will be reported.

6.3 Appendix 3: Analysis Models

Table 6-10: Part A Analysis Models

Model Name	Formu-lation	Substudy	ANOVA	Estimation
Model 1.1	A; B; C	Substudy 1	• Random effect for participant within sequence • Fixed effect categorical terms for o Formulation (3 levels) o Sequence (6 levels) o Period (3 levels)	Completed three times: • 90% CI for GMR estimate B vs. A • 90% CI for GMR estimate C vs. A • 90% CI for GMR estimate B vs. C
Model 1.1a	A; B	Substudy 1	• Random effect for participant within sequence • Fixed effect categorical terms for o Formulation (2 levels) o Sequence (6 levels) o Period (3 levels)	90% CI for GMR estimate B vs. A
Model 1.1b	A; C			90% CI for GMR estimate C vs. A
Model 1.1c	B; C			90% CI for GMR estimate B vs. C
Model 1.2	A; B; C	Substudy 2	• Random effect for participant within sequence • Fixed effect categorical terms for o Formulation (3 levels) o Sequence (6 levels) o Period (3 levels)	Completed three times: • 90% CI for GMR estimate B vs. A • 90% CI for GMR estimate C vs. A • 90% CI for GMR estimate B vs. C
Model 1.2a	A; B	Substudy 2	• Random effect for participant within sequence • Fixed effect categorical terms for o Formulation (2 levels) o Sequence (6 levels) o Period (3 levels)	90% CI for GMR estimate B vs. A
Model 1.2b	A; C			90% CI for GMR estimate C vs. A
Model 1.2c	B; C			90% CI for GMR estimate B vs. C

Table 6-10: Part A Analysis Models

Model Name	Formu-lation	Substudy	ANOVA	Estimation
Model 2	A; B; C	Substudy 1 Substudy 2	• Random effect for participant within sequence • Fixed effect categorical terms for o Formulation (3 levels) o Gastric condition (2 levels) o Formulation x Gastric condition o Sequence (6 levels) o Period within substudy (3 levels)	Completed three times: • 90% CI for GMR estimate elevated vs. normal pH for A • 90% CI for GMR estimate elevated vs. normal pH for B • 90% CI for GMR estimate elevated vs. normal pH for C
Model 2a	A	Substudy 1 Substudy 2	• Random effect for participant within sequence • Fixed effect categorical terms for o Gastric condition (2 levels) o Sequence (6 levels) o Period within substudy (3 levels)	90% CI for GMR estimate elevated vs. normal pH for A
Model 2b	B			90% CI for GMR estimate elevated vs. normal pH for B
Model 2c	C			90% CI for GMR estimate elevated vs. normal pH for C

GMR=geometric mean ratio.

Note: A: 180mg (90mg x 2 granules in capsule) current clinical formulation (reference formulation); B: 180mg non-encapsulated tablet containing CCI [redacted]; C: 180mg encapsulated tablet containing CCI [redacted]

Note: substudy 1: data under normal gastric pH condition (first 3-period crossover design substudy); substudy 2: data under elevated gastric pH condition (second 3-period crossover design substudy).

6.4 Appendix 4: Changes to Protocol-Planned Analyses

Not applicable.

6.5 Clinical Trials Registry (CTR)

The following tables outlined in previous SAP sections fulfil the criteria for transparency reporting for clinicaltrials.gov and EudraCT:

- DS_T_03 Disposition and Discontinuation Reasons [ASPS].
- DM_T_01 Demographics (all age categories are mandatory) [SS].
- AE_T_01 Incidence of TEAEs – Overview (mandatory, including both All Deaths and TEAE leading to Deaths)] [SS].
- AE_T_06 Incidence of Non-Serious TEAEs Above Reporting Threshold of X% of Participants [SS].
- For small studies in populations where these events are not expected then the study team may utilize the lines from AE_T_01. The zeros in the relevant lines are sufficient for the CTR reporting. However, if an event is observed then the relevant table must be produced by CTR reporting.
- DS_T_04 Discontinuation due to AEs [SS]
- AE_T_04b Incidence of serious TEAEs by Relationship [SS]
- AE_T_04b Incidence of fatal TEAEs by Relationship [SS]

7 REFERENCES

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