A 2-PART STUDY TO EVALUATE THE RELATIVE BIOAVAILABILTY 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)

PROTOCOL UP0073 AMENDMENT 1

Phase 1

SHORT TITLE:

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 in healthy participants of Japanese and Chinese origins (Part B, double-blind)

Sponsor:

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Confidential Material

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Date**	**Type of amendment**
Amendment 1	26 Oct 2023	Not applicable
Original Protocol	02 Mar 2023	Not applicable

Amendment 1 (26 Oct 2023)

Overall Rationale for the Amendment

UP0073 Protocol Amendment 1 was completed to include UCB0599 capsules (reference formulation in Part A) as a study treatment option for Part B.

Section # and name	Description of change	Brief rationale
Global	Throughout, "new" or "newly selected" was removed when referring to the formulation for Part B.	To acknowledge the addition of the capsule formulation as study treatment option for Part B.
Title page and Section 1.1 Synopsis, **Short title**	The short title for Part B was changed from "…and to assess UCB0599 with the new formulation in healthy participants of Japanese and Chinese origins (Part B, double-blind)" to "…and to assess UCB0599 in healthy participants of Japanese and Chinese origins (Part B, double blind)."	To align short title with study title.
Title page	NCT number was added.	To complete the table with regulatory agency identifying numbers.
Section 1.1 Synopsis, **Rationale** and Section 2.1 Study rationale	The sentence "This approach will assess UCB0599 exposure from film-coated tablets with or without encapsulation to support the selection of the new formulation" was changed to "This approach will assess UCB0599 exposure from film-coated tablets with or without encapsulation to inform formulation development."	To update wording following the addition of the Part A reference formulation (capsule) as study treatment option for Part B.

Section 4.2 Scientific rationale for study design	In the last paragraph, the second sentence "Thus, this approach will also allow comparison of UCB0599 systemic exposure from film-coated tablets with or without encapsulation to support the selection of the new formulation" was changed to "Thus, this approach will also allow comparison of UCB0599 systemic exposure from film-coated tablets with or without encapsulation to inform formulation development."	To update wording following the addition of the capsule formulation as study treatment option for Part B.
Section 4.3 Justification for dose	The first 2 sentences were combined to focus on the justification for dose: "In Part A, ~~PK data will be collected to support the use of a new formulation. In this part of the study,~~ the UCB0599 dose level of 180mg single dose is being selected based on the PK properties of UCB0599."	To remove unnecessary information.
Section 6.1 Treatments administered	In Tables 6-1 through 6-3 under **Packaging and labeling**, "carton" was changed to "bottle" throughout.	To correct packaging information for study medication in both study parts.
	Table 6-4 was added.	To also include UCB0599 capsules as formulation option for Part B.
Section 9.4.2.2 Part B	Throughout, "the selected new formulation" was changed to "the formulation used in Part B."	To acknowledge the addition of the capsule formulation as study treatment option for Part B.
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized.

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	**US and Canada:** +1 800 880 6949 or +1 866 890 3175
Email	**Global:** DS_ICT@ucb.com (for interventional clinical studies)

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol title: A 2-part study to evaluate the relative bioavailabilty 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)

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

Rationale:

UCB0599 is an orally available inhibitor of alpha-synuclein (ASYN) misfolding and downstream ASYN aggregation. The current study, UP0073, is designed to evaluate the relative bioavailability of 2 new formulations (180mg film-coated tablet containing CCI with or without encapsulation) versus the current clinical formulation (ie, 2x90mg granules in capsule), in the absence and presence of esomeprazole, on the pharmacokinetics (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).

UCB0599, a weak basic drug (pKa of 6.8) following oral dose administration in humans, is expected to undergo pH-dependent absorption over different segments of the gastrointestinal (GI) tract. However, it is not known whether an elevated gastric pH affects the systemic exposure of UCB0599 and its metabolites (CCI metabolite) for the current clinical formulation. For this reason, in Part A, UP0073 will evaluate 2 formulations (ie, 180mg film-coated tablet containing CCI with or without encapsulation) to assess the relative bioavailability of 180mg UCB0599 compared with the current clinical formulation (ie, granules in capsule) in healthy participants. The hypothesis for the introduction of CCI in the tablet is the ability of this excipient to reduce the microenvironmental pH of the disintegrating tablet and potentially enhance drug dissolution in the stomach, independent of gastric pH. Thus, the encapsulation is investigated since it may extend the duration of drug dissolution during low microenvironmental pH. Part A will also evaluate drug systemic exposure under both normal and elevated gastric pH conditions. The elevation of the gastric pH in healthy participants will be achieved through the administration of the proton pump inhibitor (PPI) esomeprazole. This approach will assess UCB0599 exposure from film-coated tablets with or without encapsulation to inform formulation development.

Part B of this study is an ethnobridging study evaluating the safety, tolerability, and PK of a single oral dose of UCB0599 at 3 dose levels (90mg, 180mg, and 360mg) under normal gastric pH conditions in healthy participants of Japanese and Chinese origins.

Objectives and endpoints

Part A: The relative bioavailability in reference to the current clinical formulation in the presence and absence of PPI (esomeprazole) of 2 new UCB0599 formulations and the PK of UCB0599 after a single dose in healthy participants

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 conditions 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 conditions 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

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

Part B: The safety, tolerability, and PK of UCB0599 after administration of UCB0599 at single dose in healthy participants of Japanese and Chinese origins

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	Safety endpoint • 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	Co-primary PK endpoints for UCB0599 • C_{max} • AUC_{0-t} • AUC_{inf}
Other	
• To assess additional safety and tolerability characteristics of UCB0599 in healthy participants of Japanese and Chinese origins	Other safety endpoints • Changes from Baseline in vital signs (pulse rate, BP, respiratory rate, and body temperature) • Changes from Baseline in safety laboratory data (hematology, clinical chemistry, urinalysis) • Changes from Baseline in 12-lead ECG assessment • Physical examination findings
• 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 • 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; BP=blood pressure; 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

Overall design

UP0073 is a randomized, 2-part single-dose crossover Phase 1 study. A study overview of UP0073 is provided in Figure 1-1.

The primary objective of Part A is to estimate the relative bioavailability of 2 new UCB0599 formulations (180mg film-coated tablet containing[CCI] with or without encapsulation) versus the current clinical formulation (2x90mg granules in capsule) under both normal and elevated gastric pH conditions. This portion of the study 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. The secondary objective is to evaluate the safety and tolerability of a single dose UCB0599 alone under normal and elevated gastric pH. Other objectives are to further evaluate the PK of UCB0599 and its metabolites ([CCI]) after a single-dose UCB0599 alone and co-administrated with esomeprazole. See Section 3 for more details on the objectives and endpoints of the study.

Part B of this study is an ethnobridging study evaluating the safety, tolerability, and PK of a single oral dose of UCB0599 at 3 dose levels (90mg, 180mg, and 360mg) under normal gastric pH conditions 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 Study Schema (see Section 1.2). Sequences 3 and 4 will only commence after Sequences 1 and 2 have been completed for all 5 participants; Sequences 5 and 6 will only commence after Sequences 3 and 4 have been completed for all 5 participants, allowing the Safety Monitoring Committee (SMC) review to be carried out before the start of Sequence 5.

- 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)

The primary objectives of Part B are (1) to assess the safety and tolerability; and (2) to evaluate the plasma PK of UCB0599 after administration of a single dose of UCB0599 in healthy participants of Japanese and Chinese origins. 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. The other objectives are (1) to assess additional safety and tolerability characteristics of UCB0599; and (2) to further evaluate the PK of UCB0599 and its metabolites (CCI [redacted]) after a single dose of UCB0599 in healthy participants of Japanese and Chinese origin. See Section 3 for more details on the objectives and endpoints of the study.

Number of participants

In Part A, a maximum of 42 healthy participants will be randomly assigned to study medication with the aim that at least 36 evaluable participants complete the study (6 completers in each sequence).

In Part B, a maximum of 30 healthy participants across both origins (15 of Japanese origin and 15 of Chinese origin) will be randomly assigned to the 4 treatments following a UCB0599:placebo 4:1 ratio.

Treatment groups and duration

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 conditions.
  - 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; Table 1-1).
- A 7-day Safety Follow-Up (SFU) Period

In Treatment Period 1 through Period 3 for Part A, study participants will fast overnight for at least 10 hours prior to study medication administration on Day 1, Day 6, and Day 11, according to the randomization scheme (see Table 1-1), and will continue to fast for at least 4 hours post-study medication administration; thereafter participants will be given a standard breakfast or light snack. 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 (1 hour following esomeprazole administration) and for at least 4 hours post-study medication administration (see Table 1-1); thereafter, participants will be given a standard meal (ie, lunch). In between each Treatment Period, participants will undergo a 4-day Washout Period. On other days during the Treatment Period, study participants will receive standard meals and snacks at appropriate times as indicated by the clinic center (see Table 1-3). During the whole treatment, participants will remain under close medical supervision in the clinic.

On Day 33, after all the scheduled procedures have been performed, the participant may leave the clinic provided that, in the opinion of the Investigator, there are no safety concerns. Study

participants will return to the clinic to complete the SFU assessments. Blood samples for determination of plasma UCB0599 and its CCI [redacted] metabolites will be collected over 96 hours postdose (see Schedule of Activities, Section 1.3). Of note, for substudy 2 (Treatment Periods 4 through 6), the blood sampling time points will be based upon the timing of UCB0599 administration (to occur 1 hour after PPI administration).

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

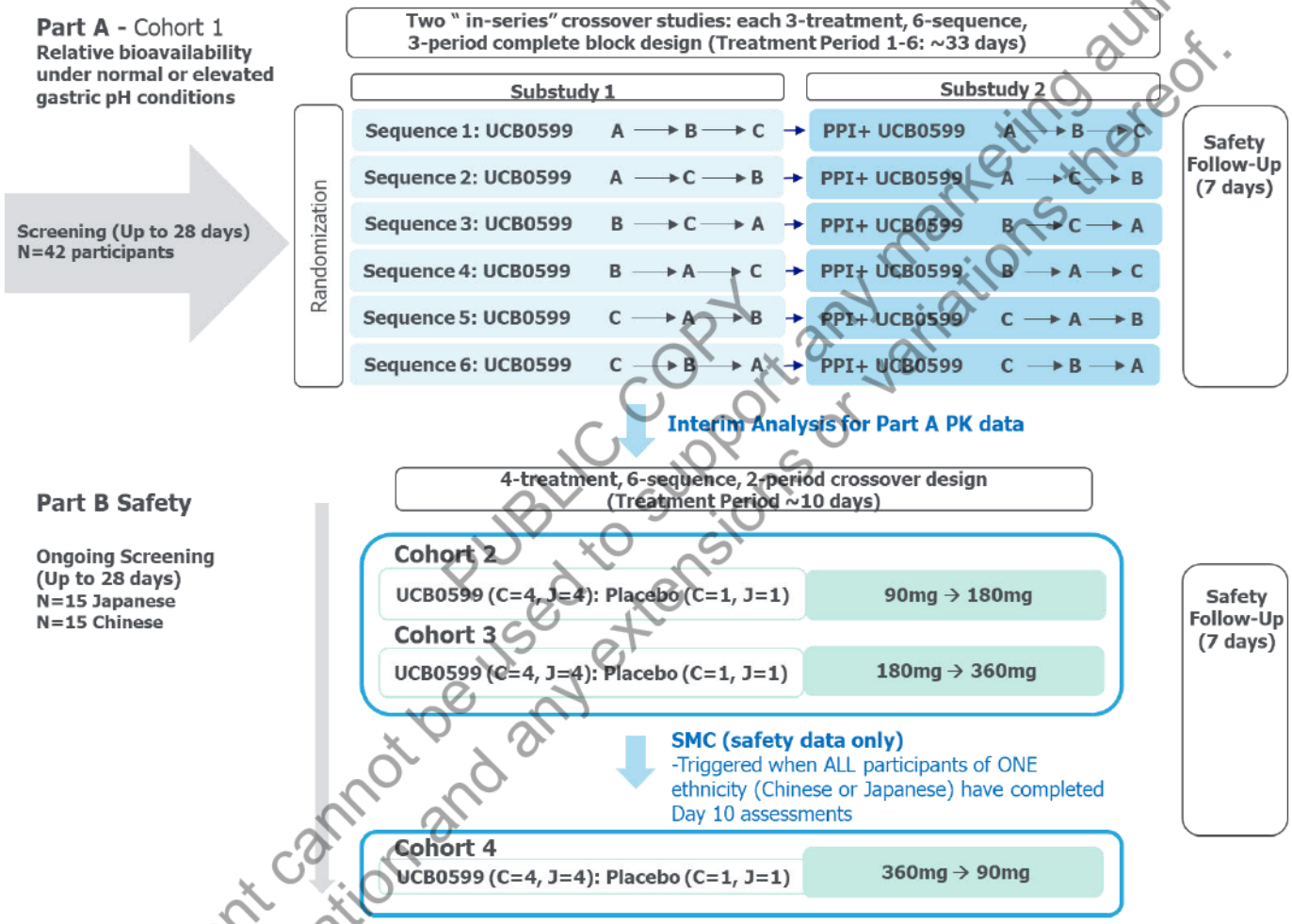
- A 28-day Screening Period (2 to 28 days before administration of study medication)
- 2 treatment periods (for a total duration of up to10 days)
  - Eligible study participants will commence the Treatment Period on Day -1. Each participant enrolled will receive a single oral dose of UCB0599 (formulation 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 1-2). 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. During the whole treatment, participants will remain under close medical supervision in the clinic.
- A SFU Period (7 days after the last study medication administration)

In Treatment Period 1 through Period 2 for Part B, study participants will fast overnight for at least 10 hours prior to study medication administration on Day 1 and Day 6, and continue to fast for at least 4 hours post-study medication administration. Thereafter participants will be given a standard breakfast or light snack (see Table 1-2 and Table 1-4).

On Day 10, after all the scheduled procedures have been performed, the study participant may leave the clinic provided that, in the opinion of the Investigator, there are no safety concerns. Study participants will return to the clinic to complete the SFU assessments. Blood samples for determination of plasma UCB0599 and its CCI [redacted] metabolites will be collected over 96 hours postdose (see Schedule of Activities, Section 1.3). Up to a maximum of 6 replacements will be targeted in case participants discontinue Part B (see Section 7).

1.2 Schema

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 CCI ; **C:** 180mg encapsulated tablet containing CCI .
Note: The PPI esomeprazole 40mg QD will be administrated on 20-consecutive days during substudy 2.

Table 1-1: Part A design: Relative bioavailability of UCB0599 under normal or elevated gastric pH conditions 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] CCI; 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 (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 1-2: Part B design: The PK of UCB0599 in healthy Japanese and Chinese participants under normal gastric pH conditions (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 (Section 5.3.1). The Washout Period will take place after each period and last for 4 days.

1.3 Schedule of activities

Table 1-3: Part A Schedule of activities

Procedure	Screening	Treatment Period 1—6[a]												SFU[b] / ETV
		In-Clinic Period												
	D-28 to D-2	D-1	D1	D2 to D5	D6	D7 to D10	D11	D12 to D18[c]	D19	D20 to D23	D24	D25 to D28	D29	D30 to D33	Day 37 (± 2 days)
Informed consent	X														
Verification of inclusion/exclusion criteria	X	X													
Demography (height, weight, BMI)	X														
Physical examination	X	X						X[d] (D14)						X[d] (D33)	X
General medical/procedure history	X														
Pregnancy test[e] (females only)	X	X													X
Laboratory assessments (hematology, clinical chemistry, and urinalysis)[f]	X	X						X[g] (D14)						X[g] (D33)	X
SARS-CoV-2 testing (PCR)[h]		X													
Viral serology (HBsAg, HCV-Ab, and HIV)	X														
Urine cotinine, drug screen, and alcohol breath test	X	X													
12-lead ECG[i]	X	X	X												X

Table 1-3: Part A Schedule of activities

Procedure	Screening	Treatment Period 1—6[a]													SFU[b] / ETV
		In-Clinic Period													
	D-28 to D-2	D-1	D1	D2 to D5	D6	D7 to D10	D11	D12 to D18[c]	D19	D20 to D23	D24	D25 to D28	D29	D30 to D33	Day 37 (± 2 days)
Vital signs[j]	X	X	X		X		X		X		X		X		X
Randomization		X[k]													
Study medication administration[k]			X		X		X		X		X		X		
Esomeprazole administration[c]								X	X	X	X	X	X	X	
Adverse event review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sampling for PK[l]			X	X	X	X	X	X	X	X	X	X	X	X	
Genetic blood sampling			X[m]												
Meals		X[n]	X[o]	X[n]	X[o]	X[n]	X[o]	X[n]	X[o]	X[n]	X[o]	X[n]	X[o]	X[n]	
Confinement		X	X	X	X	X	X	X	X	X	X	X	X	X[p]	

AKI=acute kidney injury; BMI=body mass index; BP=blood pressure; COVID-19=Coronavirus Disease 2019; D=Day; ECG=electrocardiogram; ETV=Early Termination Visit; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IRT=interactive response technology; PCR=polymerase chain reaction; PK=pharmacokinetic(s); QD=once daily; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SFU=Safety Follow-Up

[a] Each study participant will attend 6 treatment periods and will be in the clinical center for every Treatment Period 1, 2, 3, 4, 5 and 6. In Treatment Period 4, an oral dose of 40mg esomeprazole will be administered QD for 20-consecutive days from Day 14 to Day 33. On Day 19, Day 24, and Day 29, a single oral dose of 180mg UCB0599 will be administered 1 hour after intake of esomeprazole. All 6 dosing days will be in a fasted state (Section 5.3.1). The washout of UCB0599 will take place after each period and last for 4 days.

[b] Study participants will have SFU procedures performed within 10 days after last dose. Participants who prematurely withdraw from the study will have the ETV as soon as possible after the time of withdrawal, and will have all SFU procedures performed.

[c] An oral dose of 40mg esomeprazole will be administered QD for 20-consecutive days from Day 14 to Day 33.

[d] The physical examination will only be performed on Day 14 and Day 33 during the treatment periods.

Table 1-3: Part A Schedule of activities

Procedure	Screening	Treatment Period 1—6[a]												SFU[b] / ETV
		In-Clinic Period												
	D-28 to D-2	D-1	D1	D2 to D5	D6	D7 to D10	D11	D12 to D18[c]	D19	D20 to D23	D24	D25 to D28	D29	D30 to D33	Day 37 (± 2 days)

[e] The blood pregnancy test will be done at the Screening Visit and the urine pregnancy test will be done on all other occasions.
[f] Blood hematology and chemistry laboratory tests will be obtained in the fasting state following an overnight fast of at least 10 hours. Urinalysis includes standard analysis, microscopy, and renal biomarker analysis. For the AKI biomarkers, analysis should be performed on the fresh urine sample. Spot analysis will be performed on either fresh urinalysis sample or 24 hours urine sample, as noted.
[g] Only performed on Day 14 and Day 33.
[h] A COVID-19 test will take place per site standard to allow flexibility in the event the COVID-19 response plan changes throughout the study (ie, frequency of testing).
[i] During the Screening Period, at Baseline (only if the ECG was done more than 3 days before screening [between D-28 and D-2, inclusive]), and on Day 1, the 12-lead ECG (single recordings) will be performed after a rest of at least 10 minutes predose and 2 hours after dosing. If there are abnormalities that are considered clinically significant for a particular study participant, ECG recordings will be performed in triplicate at 2- to 3-minute intervals (3 ECGs within a 5-minute timeframe) prior to the exclusion of the participant (Section 7.1.2).
[j] Systolic and diastolic blood pressure, respiration rate, pulse rate, and tympanic body temperature will be assessed. Vital signs will be performed after a rest of at least 5 minutes predose, then 30 min, and 2 hours after study medication dosing on Day 1, Day 6, Day 11, Day 19, Day 24, and Day 29. Vital signs (to be taken before blood collection for laboratory tests) will consist of 3 pulse rates and 3 blood pressure (BP) measurements (3 consecutive BP readings will be recorded at intervals of at least 1 minute).
[k] An IRT will be used for assigning eligible participants to a treatment regimen based on a predetermined production randomization and/or packaging schedule provided by UCB (or designee) (Section 6.3).
[l] The PK sampling time points will be done at predose and at 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48, 72, and 96 hours after UCB0599 administration.
[m] Genetic blood sampling will be mandatory for study participation and will be performed on Day 1 (Section 8.7).
[n] Study participants will receive standard meals and snacks at appropriate times as indicated by the clinic center, except for when they are required to fast.
[o] 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 after study medication administration; thereafter participants will be given a standard meal (ie, lunch). 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 (1 hour following esomeprazole administration) and for at least 4 hours post-study medication administration; thereafter study participants will be given a standard meal (ie, lunch). 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. For the rest of the day, study participants will receive standard meals and snacks at appropriate times as indicated by the clinic center (Section 5.3.1).
[p] Study participants will be discharged from the clinic center after the 96-hour PK sampling time point.

Table 1-4: Part B Schedule of Activities

Procedure	Screening	Treatment Period 1				Treatment Period 2			SFU[a]/ETV
		In-Clinic Period				In-Clinic Period			
	D-28 to D-2	D-1	D1	D2-4	D5	D6	D7-9	D10	D13 (±2 days)
Informed consent	X								
Verification of inclusion/exclusion criteria	X	X							
Demography (height, weight, BMI)	X								
Physical examination	X	X			X			X	X
General medical/procedure history	X	X							
Pregnancy test[b] (females only)	X	X							X
Laboratory assessments (hematology, clinical chemistry, and urinalysis)[c]	X	X			X			X	X
SARS-CoV-2 testing (PCR)[d]		X							
Viral serology (HBsAg, HCV-Ab, and HIV)	X								
Urine cotinine, drug screen, and alcohol breath test	X	X							
12-lead ECG[e]	X	X	X	X		X	X		X
Vital signs[f]	X	X	X	X	X	X	X	X	X
Randomization[g]		X							
Study medication administration[g]			X			X			
Adverse event review	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X
Blood sampling for PK[h]			X	X	X	X	X	X	

Table 1-4: Part B Schedule of Activities

Procedure	Screening	Treatment Period 1				Treatment Period 2			SFU[a]/ETV
		In-Clinic Period				In-Clinic Period			
	D-28 to D-2	D-1	D1	D2-4	D5	D6	D7-9	D10	D13 (±2 days)
Genetic blood sampling			X[i]						
Meals[j]		X	X[k]	X	X	X[k]	X	X	
Confinement		X	X	X	X	X	X	X[l]	

AE=adverse event; AKI=acute kidney injury; BMI=body weight index; COVID-19=Coronavirus Disease 2019; D=Day; ECG=electrocardiogram; ETV=Early Termination Visit; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; PCR= polymerase chain reaction; PK=pharmacokinetic(s); QD=once daily; SFU=Safety Follow Up

[a] An SFU Visit is planned after 7 days of the last study medication administration. Participants who prematurely withdraw from the study will have the ETV as soon as possible after the time of withdrawal, and will have all SFU procedures performed.

[b] The blood pregnancy test will be done at the Screening Visit and the urine pregnancy test will be done on all other occasions.

[c] Blood hematology and chemistry laboratory tests will be obtained in the fasting state following an overnight fast of at least 10 hours. Urinalysis includes standard analysis, microscopy, and renal biomarker analysis. For the AKI biomarkers, analysis should be performed on the fresh urine sample. Spot analysis will be performed on either fresh urinalysis sample or 24 hours urine sample, as noted.

[d] A COVID-19 test will take place per site standard to allow flexibility in the event the COVID-19 response plan changes throughout the study (ie, frequency of testing).

[e] 12-lead ECGs (single recordings) will be performed during the Screening Period, at Baseline (only if the ECG was done more than 3 days before screening [between D-28 and D-2, inclusive]), Day 1 (after a rest of at least 10 minutes predose and 2 hours after dosing), Day 2 (24 hours postdose), Day 6 (after a rest of at least 10 minutes predose and 2 hours after dosing), Day 7 (24 hours postdose), and the SFU Visit. If there are abnormalities that are considered clinically significant for a particular study participant, ECG recordings will be performed in triplicate at 2- to 3-minute intervals (3 ECGs within a 5-minute timeframe) prior to the exclusion of the participant (Section 7.1.2).

[f] Systolic and diastolic blood pressure, respiration rate, pulse rate, and tympanic body temperature will be assessed. Vital signs will be performed after a rest of at least 5 minutes. On Day 1 and Day 6, vital signs will be measured predose, then 30 minutes, 2 hours, and 24 hours after study medication administration.

[g] An IRT will be used for assigning eligible participants to a treatment regimen based on a predetermined production randomization and/or packaging schedule provided by UCB (or designee) (see Section 6.3). Study participants will receive 3 dose levels (90mg, 180mg, and 360mg) of UCB0599 or placebo under normal gastric pH conditions. The Washout Period will take place after each period and last for 4 days. See Section 4.1 for details on the overall study design of Part B.

[h] The PK sampling time points will be done at predose and at 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48, 72, and 96 hours after UCB0599 administration.

[i] Genetic blood sampling will be mandatory for study participation and will be performed on Day 1 (Section 8.7).

[j] Study participants will receive standard meals and snacks at appropriate times as indicated by the clinic center, except for when they are required to fast.

Table 1-4: Part B Schedule of Activities

Procedure	Screening	Treatment Period 1				Treatment Period 2			SFU[a]/ETV
		In-Clinic Period				In-Clinic Period			
	D-28 to D-2	D-1	D1	D2-4	D5	D6	D7-9	D10	D13 (±2 days)

[k] In Treatment Period 1 and Period 2, study participants will fast overnight for at least 10 hours prior to study medication administration on Day 1 and Day 6, and will continue to fast for at least 4 hours after study medication administration; thereafter study participants will be given a standard meal (ie, lunch). 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 (Section 5.3.1).

[l] Study participants will be discharged from the clinic center after the 96-hour PK sampling time point.

2 INTRODUCTION

2.1 Study rationale

UCB0599 is an orally available inhibitor of ASYN misfolding and downstream ASYN aggregation. Aggregated forms of ASYN are the hallmark fibrillar protein deposits in Parkinson's disease (PD) and other synucleinopathies, and evidence suggests that the misfolded forms of ASYN propagate through the central nervous system (CNS) during disease progression. The accumulation of ASYN forms neuronal inclusions referred to as Lewy bodies and Lewy neurites.

The current study, UP0073, is designed to evaluate the relative bioavailabilty of 2 new formulations compared with the current clinical formulation 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).

UCB0599, a weak basic drug (pKa of 6.8) following oral dose administration in humans, is expected to undergo pH-dependent absorption over different segments of the GI tract. However, it is not known whether an elevated gastric pH affects the systemic exposure of UCB0599 and its metabolites (CCI [redacted] metabolite) for the current clinical formulation. For this reason, in Part A, UP0073 will evaluate 2 formulations (ie, 180mg film-coated tablet containing CCI [redacted] with or without encapsulation) to assess the relative bioavailability of 180mg UCB0599 compared with the current clinical formulation (ie, granules in capsule) in healthy participants. The hypothesis for the introduction of CCI [redacted] in the tablet is the ability of this excipient to reduce the microenvironmental pH of the disintegrating tablet and potentially enhance drug dissolution in the stomach, independent of gastric pH. Thus, the encapsulation is investigated since it may extend the duration of drug dissolution during low microenvironmental pH. Part A will also evaluate drug systemic exposure under both normal and elevated gastric pH conditions. The elevation of the gastric pH in healthy participants will be achieved through the administration of esomeprazole. This approach will assess UCB0599 exposure from film-coated tablets with or without encapsulation to inform formulation development.

Part B of this study is an ethnobridging study evaluating the safety, tolerability, and PK of a single oral dose of UCB0599 at 3 dose levels (90mg, 180mg, and 360mg) under normal gastric pH conditions in healthy participants of Japanese and Chinese origins.

2.2 Background

Parkinson's disease is a progressive neurodegenerative disorder that presents with a spectrum of motor and nonmotor signs and symptoms. The mean age at onset is 60 years. The incidence of PD is approximately 20/100,000 persons per year; however, it is much higher in the population aged 65 years or older (>100/100,000 persons per year) (Twelves et al, 2003). The clinical diagnosis of PD relies on the presence of the cardinal motor signs: bradykinesia, rigidity, tremor, and postural instability. However, nonmotor symptoms such as loss of smell, depression, constipation, dysautonomia, and rapid eye movement sleep behavior disorder can occur several years before the onset of motor symptoms.

Early-stage PD is characterized by mild, manageable motor symptoms that may not require symptomatic treatment or that show a good response to low-dose levodopa, which represents the

standard of care (SoC) first-line symptomatic treatment. Other commonly used SoC symptomatic medications include dopamine agonists, monoamine oxidase-B inhibitors, and catechol-O-methyltransferase inhibitors.

Parkinson's disease is pathologically characterized by the loss of dopaminergic neurons in the substantia nigra, associated with ASYN pathology (neuronal cytosolic inclusions called Lewy bodies, which consist of misfolded, pathological aggregates of ASYN). Treatments that prevent misfolding and aggregation of ASYN may slow the neurodegeneration in PD, resulting in slower progression of motor symptoms, thus providing a therapeutic benefit to patients with PD.

UCB0599 is an orally available inhibitor of ASYN misfolding and downstream ASYN aggregation. In vivo and nonclinical pharmacology data suggest UCB0599 may slow neurodegeneration in PD, resulting in slower disease progression, thus providing a therapeutic benefit to patients with PD.

UCB0599 has not been approved by any health authorities worldwide as of the date of this document. UCB has conducted 5 Phase 1 clinical studies to support the development of UCB0599 that have demonstrated good PK properties and an acceptable safety and tolerability profile (UP0023, UP0030, TM0017, and UP0077) as well as a minimal food effect on the PK profile for UCB0599 (UP0078). Minzalsolmin is currently being tested in a running Phase 2a trial (PD0053) and its extension study (PD0055). Further information regarding UP0023, UP0030, TM0017, UP0077, and UP0078 is provided in the Investigator's Brochure (IB).

2.3 Benefit/risk assessment

This study will not provide any benefit to the study population, ie, healthy study participants, instead it will provide relevant pharmacological and clinical safety information to support UCB0599 new formulation development as well as to support the further development of UCB0599 in Japanese and Chinese populations. In Phase 1 development of UCB0599, 5 studies (UP0030, TM0017, UP0023, UP0077, and UP0078) demonstrated that UCB0599 has acceptable safety, PK, and tolerability profiles for further clinical development.

Drug hypersensitivity is an important identified risk for UCB0599. Cardiac effects are an important potential risk based on nonclinical data. Overall, the majority of treatment-emergent adverse events (TEAEs) seen in the Phase 1 and Phase 2 studies were mild or moderate in intensity and resolved. In UP0030, 2 events of hypersensitivity were reported. An additional 2 events of hypersensitivity occurred in study participants who received UCB0599 in UP0077. A causal relationship between the reported events of drug hypersensitivity and UCB0599 is considered plausible. There have been no reports of anaphylaxis in the UCB0599 clinical program.

Based on the results of UP0030, drug hypersensitivity and symptoms commonly associated with anaphylaxis and angioedema have been considered adverse events of special interest (AESI) and an important identified risk, based on reasonable clinical judgment. To minimize the risks for study participants, the study team at UCB and the contract research organization (CRO) will continue to systematically review safety data and UCB0599 exposure data. The site will be informed and trained appropriately about the risk of a hypersensitivity reaction (such as rash, angioedema, or anaphylaxis) and the actions that need to be taken in case of a hypersensitivity reaction. The participant will be informed by the Investigator during the consent procedure about the risk of a hypersensitivity reaction and other important potential risks for UCB0599. Risk

mitigation measures include using a standard approach of: (1) obtaining a detailed history of the hypersensitivity reaction and its evolution; (2) response with appropriate treatment, if needed; (3) a detailed physical examination and regular monitoring of vital signs; and, (4) the addition of guidance for the evaluation of suspected hypersensitivity reactions (refer to Section 8.3.6.1) and reporting of the suspected hypersensitivity reaction as an AESI.

Considering the potential benefits, risks, and mitigation measures in place, the overall benefit-risk ratio for study participants who will be receiving single doses of UCB0599 is considered to be acceptable in the current study.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of UCB0599 may be found in the IB.

2.3.1 Coronavirus Disease-2019 benefit/risk assessment

UCB0599 is not known to exert an effect on the immune or respiratory systems, and its mechanism of action is not linked to immune or respiratory system agonism or inhibition.

To date, no increased risk of infection or respiratory problems has been identified in association with clinical UCB0599 administration. No such risks have been identified through regular review of published literature.

Although there is some evidence that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) might affect the CNS, there is no reason to assume on the basis of the mechanism of action that UCB0599 will have any substantial effect to worsen a Coronavirus Disease-2019 (COVID-19) infection or increase the risk of CNS and other complications in case a study participant acquires SARS-CoV-2.

Therefore, UCB0599 is not expected to pose an additional risk of complications or poor prognosis of COVID-19.

Considering the mechanism of action, the inclusion and exclusion criteria, and the measures to mitigate risks described in this protocol, the risk to study participants in UP0073, both in terms of exposure to SARS-CoV-2 and morbidity from COVID-19, is not expected to be significantly different from the general population. The benefit-risk profile of UCB0599 in UP0073 in the context of COVID-19 vaccination remains positive.

2.3.1.1 COVID-19 risk mitigation measures

- Current national laws and local recommendations for the prevention and control of the pandemic will be strictly adhered to.
- Participants are asked to follow the visit schedule to the extent possible. If they are unable to come to the study site, the Investigator may contact the participant directly via telephone and/or video conference calls.
- Participants will be closely monitored for and encouraged to report any signs and symptoms of COVID-19. The Investigator will consider the individual benefit/risk of the study participant upon identification of any signs and symptoms of COVID-19 infection (eg, continuation of dosing, site visits).
- COVID-19 testing by optional laboratory assessment will be conducted based on availability and other practical considerations (eg, test capacity and turnaround time) of approved tests

and at the Investigator's discretion. The Investigator will consider the individual benefit/risk of the study participant in case of a positive COVID-19 test.

- The possibility of virus transmission will be controlled as much as possible by:
  - Advising participants to adhere to local requirements for reduction of exposure to the public while ambulatory.
  - Advising participants to adhere to clinical site requirements for reduction of exposure while at the site or interacting with site staff. This advice will be included in the Informed Consent form (ICF).
- COVID-19 testing for clinical staff will be conducted if required by local guidelines.

2.3.1.2 COVID-19 benefit/risk conclusion

Considering the mechanism of action of UCB0599, the inclusion and exclusion criteria, and the measures to mitigate risks described in this protocol, the risk to study participants in UP0073, both in terms of exposure to SARS CoV-2 and morbidity from COVID-19, is not expected to be significantly different from the general population.

3 OBJECTIVES AND ENDPOINTS

Table 3-1: <u>Part A:</u> The relative bioavailability in reference to the current clinical formulation in the presence and absence of PPI (esomeprazole) of 2 new UCB0599 formulations and the PK of UCB0599 after a single dose in healthy participants

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 conditions in healthy participants	<u>PK endpoints of UCB0599</u> • 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 conditions in healthy participants	<u>Safety endpoints</u> • 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	<u>Other PK endpoints</u> • For UCB0599:

Table 3-1: Part A: The relative bioavailability in reference to the current clinical formulation in the presence and absence of PPI (esomeprazole) of 2 new UCB0599 formulations and the PK of UCB0599 after a single dose in healthy participants

Objectives	Endpoints
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	– C_{max}, AUC_{0-t}, and AUC_{inf} – t_{max}, $t_{½}$, CL/F, and Vz/F (if possible but not limited) • 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

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 3-2: Part B: The safety, tolerability, and PK of UCB0599 after administration of UCB0599 at single dose in healthy participants of Japanese and Chinese origins

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	Safety endpoint • 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	Co-primary PK endpoints for UCB0599 • C_{max} • AUC_{0-t} • AUC_{inf}
Other	
• To assess additional safety and tolerability characteristics of UCB0599 in healthy participants of Japanese and Chinese origins	Other safety endpoints • Changes from Baseline in vital signs (pulse rate, blood pressure [BP], respiratory rate, and body temperature)

Table 3-2: Part B: The safety, tolerability, and PK of UCB0599 after administration of UCB0599 at single dose in healthy participants of Japanese and Chinese origins

Objectives	Endpoints
	• Changes from Baseline in safety laboratory data (hematology, clinical chemistry, urinalysis) • Changes from Baseline in 12-lead ECG assessment • Physical examination findings
• 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 • 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

4 STUDY DESIGN

4.1 Overall 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.

4.1.1 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. Each substudy evaluates the UCB0599 relative bioavailability of the new formulations (180mg film-coated tablet containing CCI [redacted] with or without encapsulation) versus the current clinical

formulation (2x90mg granules in capsule) under both normal and elevated gastric pH conditions, respectively. See Section 3 for more details on the objectives and endpoints of the study.

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 (180 mg) of each formulation under normal gastric pH conditions.
  - 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 QD over the duration of the 3 treatment periods (Day 14 to Day 33; see Table 1-1).
- A 7-day Safety Follow-Up (SFU) Period

In Treatment Period 1 through Period 3 for Part A, study participants will fast overnight for at least 10 hours prior to study medication administration on Day 1, Day 6, and Day 11, according to the randomization scheme (see Table 1-1), and will continue to fast for at least 4 hours post-study medication administration; thereafter participants will be given a standard breakfast or light snack. 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 (1 hour following esomeprazole administration) and for at least 4 hours post-study medication administration (see Table 1-1); thereafter participants will be given a standard meal (ie, lunch). In between each Treatment Period, participants will undergo a 4-day Washout Period. On other days during the Treatment Period, study participants will receive standard meals and snacks at appropriate times as indicated by the clinic center (see Table 1-3). During the whole treatment, participants will remain under close medical supervision in the clinic.

On Day 33, after all the scheduled procedures have been performed, the participant may leave the clinic provided that, in the opinion of the Investigator, there are no safety concerns. Study participants will return to the clinic to complete the SFU assessments. Blood samples for determination of plasma UCB0599 and its CCI [redacted] metabolites will be collected over 96 hours postdose (see Schedule of Activities, Section 1.3). Of note, for substudy 2 (Treatment Periods 4 through 6), the blood sampling time points will be based upon the timing of UCB0599 administration (to occur 1 hour after PPI administration).

4.1.2 Part B

Part B of this study is an ethnobridging study evaluating the safety, tolerability, and PK of a single oral dose of UCB0599 at 3 dose levels (90mg, 180mg, and 360mg) under normal gastric pH conditions 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 Study Schema (Figure 1-1). Sequence 6 will only commence after Sequence 5 has been completed for all 4 participants. 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.

- 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)

See Section 3 for more details on the objectives and endpoints of the study.

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 1-2). 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. During the whole treatment, participants will remain under close medical supervision in the clinic.
- A SFU Period (7 days after the last study medication administration)

In Treatment Period 1 through Period 2 for Part B, study participants will fast overnight for at least 10 hours prior to study medication administration on Day 1 and Day 6, and continue to fast for at least 4 hours post-study medication administration. Thereafter participants will be given a standard breakfast or light snack (see Table 1-2 and Table 1-4).

On Day 10, after all the scheduled procedures have been performed, the study participant may leave the clinic provided that, in the opinion of the Investigator, there are no safety concerns. Study participants will return to the clinic to complete the SFU assessments. Blood samples for determination of plasma UCB0599 and its CCI [redacted] metabolites will be collected over 96 hours postdose (see Schedule of Activities, Section 1.3). Up to a maximum of 6 replacements will be targeted in case participants discontinue Part B (see Section 7).

There is 1 planned interim analysis for Part B in which safety data from Part B will be analyzed (Section 9.8). Throughout the study, data will be reviewed on an ongoing basis by an SMC.

4.2 Scientific rationale for study design

UP0073 has a 2-part design and is intended to evaluate the relative bioavailabilty of 2 new UCB0599 formulations (180mg film-coated tablet containing CCI with or without encapsulation) versus the current clinical formulation (ie, 2x90mg granules in capsule); to evaluate 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).

Previously published studies and nonclinical research demonstrate that significant ethnic differences can exist in the metabolism of some drugs, which are caused by cytochrome P450 (CYP) polymorphism. Cytochrome 2D6, 2C19, and 2C9 polymorphisms account for the most frequent variations in the Phase 1 metabolism of drugs. For example, approximately 5 to 14% of Caucasians and 0 to 1% of Asians lack CYP2D6 activity and are known as poor metabolizers. However, there is insufficient evidence to show that there are some ethnic differences for CYP3A4 polymorphism. Based on preclinical drug metabolism studies, no differences in exposure are expected in healthy participants of Japanese and Chinese origins compared with Caucasian participants.

Part B of this study will be conducted to generate continued clinical development of UCB0599 doses up to 360mg/day. The rationale for testing the proposed dose levels of UCB0599 (90mg, 180mg, and 360mg/day single dose) in this healthy population is based on data from previously conducted studies (UP0030, UP0077, and UP0078) as well as PK information for multiple dose exposures of 180mg/day for up to 21 days in elderly healthy volunteers (defined as ≥55 and ≤75 years of age) (see Section 4.3 for more details). The PK analysis of UCB0599 revealed that exposure increased close to proportionally with increased doses between 45mg and 450mg (single doses tested). Furthermore, multiple dose exposures (AUC_{tau}) were predictable from single dose exposures, indicating linear PK behavior. Therefore, the evaluation of UCB0599 180mg single dose to assess relative bioavailability should provide adequate guidance for the development of a new formulation for further clinical development in Phase 2 and 3 studies.

Approximately 25% of PD patients receive acid reducing agents as concomitant medications to manage acid reflux through the elevation of the gastric pH (Lai et al, 2020). UCB0599 is a weak basic drug (pKa of 6.8) following oral dose administration in humans, and is expected to undergo pH-dependent absorption over different segments of the GI tract, with more absorption in the intestine (pH range 6 to 8) compared with the upper segments of the GI tract (pH range is 2 to 6). However, it is not known whether an elevated gastric pH affects the systemic exposure of UCB0599 and its metabolites (CCI metabolite) for the current clinical formulation. For this reason, in Part A, UP0073 will evaluate 2 formulations (ie, film-coated tablet containing CCI with or without encapsulation) to assess the relative bioavailability of 180mg UCB0599 compared with the current clinical formulation (ie, granules in capsule) in healthy participants. The addition of CCI excipient to the new tablet is expected to create a "microenvironment" in the tablet which should allow UCB0599 to dissolve uniformly in the stomach independent of gastric pH (Badawy and Hussain, 2007).

The use and inclusion of CCI is supported by results from biorelevant dissolution testing (Taniguchi et al, 2014). Data indicate that the encapsulation of the tablet may result in an improved robustness in vitro in some biopredictive in-vitro experiments. This in vitro observation may be explained by the fact that the presence of the capsule results in an intimate contact between the active pharmaceutical ingredient (API) and acidifier CCI, thereby resulting in higher concentrations of CCI close to the surface of the API (Badawy and Hussain, 2007).

As the current study will evaluate healthy participants, elevation of the gastric pH will be achieved through the administration of a PPI (esomeprazole), in which drug systemic exposure will be compared in the absence or presence of PPI. Thus, this approach will also allow comparison of UCB0599 systemic exposure from film-coated tablets with or without encapsulation to inform formulation development. The current complete block study design in Part A will evaluate each study participant under both elevated and normal gastric pH conditions.

4.2.1 Patient input into design

Not applicable.

4.3 Justification for dose

In Part A, the UCB0599 dose level of 180mg single dose is being selected based on the PK properties of UCB0599. Upon oral intake of doses 90mg to 450mg, both C_{max} and AUC increase approximately linearly with dose, indicating dose proportionality. In addition, clinical data show that AUC at steady state over the dose interval is similar to AUC_{inf} after single dose, suggesting linear behavior of UCB0599 in the clinically tested dose range of 180mg/day to 360mg/day; hence UCB0599 180mg single dose administration is projected to provide exposure information that can be used to bridge between the current clinical formulation and a new formulation.

In Part B, UP0073 will be conducted to generate supportive safety, tolerability, and PK data in healthy participants of Japanese and Chinese origins for the continued clinical development of UCB0599 doses up to 360mg/day. The rationale for testing the proposed dose levels of UCB0599 (90mg, 180mg, and 360mg/day single dose) in this healthy population is based on data from previously conducted studies (UP0030, UP0077, and UP0078). UP0030 tested 90mg twice per day for 21 days in elderly healthy participants to assess the safety, tolerability, and PK information for multiple dose exposures. This study showed that UCB0599 exposures increased linearly (both C_{max} and AUC) across the tested dose range (90mg to 450mg, single dose). UP0077 provided the safety, tolerability, and PK of UCB0599 for multiple doses of 180mg/day and 360mg/day in PD patients. The collective data from UP0030 and UP0077 further showed that exposure after multiple dosing is predictable from single-dose data and that dose-exposure relationship is similar between (elderly) healthy participants and PD patients. These 2 dose levels (180mg/day and 360mg/day, achieved by twice daily dosing) were selected for the proof-of-concept study PD0053 to obtain initial evidence of UCB0599 efficacy in slowing PD disease progression. The therapeutic dose of UCB0599 is likely to be ≤360mg/day. Hence, 360mg was chosen as the maximum single dose in Part B of this study; 2 dose levels below 360mg have been selected (90mg and 180mg) and are set in a common ratio of 2 to adequately evaluate the PK characteristics and dose proportionality of UCB0599. Therefore, these 3 dose levels (90mg, 180mg, and 360mg) are believed to be appropriate doses for this portion of the study, and steady state PK will be projected based on single dose data.

Further information regarding UP0030, UP0077, and UP0078 is provided in the most recent IB.

4.4 End of study definition

A participant is considered to have completed the study if he/she has completed all periods of the study including the SFU Visit (within 10 days after the last dose for Part A or 7 days after the last dose for Part B).

The end of the study is defined as the date of the last scheduled procedure for the last study participant in the study (see Section 1.3 for details on Schedule of Activities).

5 STUDY POPULATION

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

5.1 Inclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 18 to 55 years of age inclusive at the time of signing the ICF.

Type of participant and disease characteristics

2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.

   Note: study participants must have clinical laboratory test results within the local reference ranges or values that are considered as not clinically relevant by the Investigator and approved by the Medical Monitor. Laboratory parameters outside the reference ranges may be retested once and if the retest is within the reference range or considered as clinically not relevant, the study participants will be allowed in the study (Section 5.4).

3. Part A only: all healthy study participants except for those participants who are eligible for Part B of the study.

4. For participants of Japanese origin (Part B): study participant is of Japanese descent as evidenced by appearance and verbal confirmation of familial heritage (a participant has all 4 Japanese grandparents born in Japan).

   For participants of Chinese origin (Part B): study participant is of Chinese descent as evidenced by appearance and verbal confirmation of familial heritage (a participant has all 4 Chinese grandparents born in China).

Weight

5. Body weight within 45 to 100kg (female) and 50 to 100kg (male) and body mass index (BMI) within the range 18 to 30 kg/m^2 (inclusive at screening).

Sex

6. Healthy male and female study participants

- A male participant must agree to use contraception as detailed in Appendix 4 of this protocol during the treatment period and for at least 1 week after the last dose of study medication, and refrain from donating sperm during this period (Section 10.4)
- A female participant is eligible to participate if she is not pregnant (see Appendix 4, Section 10.4), not breastfeeding, and at least one of the following conditions applies:
  - Not a woman of childbearing potential (WOCBP) as defined in Appendix 4
    OR
    A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 during the treatment period and for at least 1 week after the last dose of study medication.

Informed consent

7. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1) which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2 Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

1. Participant has any medical or psychiatric condition that, in the opinion of the Investigator, could jeopardize or would compromise the study participant's ability to participate in this study.
2. Participant has a history or presence of/significant history of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrinological, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study intervention; or interfering with the interpretation of data.
3. Participant has had lymphoma, leukemia, or any malignancy within the past 5 years, except for basal cell carcinomas that have been resected, squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.
4. Participant has had breast cancer within the past 10 years.
5. Participant has a history of alcohol or drug abuse within the last 1 year from Screening, as defined according to the Diagnostic and Statistical Manual of Mental Disorders.
6. Participant has a known hypersensitivity to any components of the study medication or comparative drugs as stated in this protocol.
7. Participant has a consumption of more than 600mg of caffeine/day at screening and throughout the study (1 cup of coffee contains approximately 100mg of caffeine, 1 cup of tea approximately 30mg, and 1 glass of cola approximately 20mg).

8. Participant has consumed any grapefruit, grapefruit juice, grapefruit-containing products, or star fruit within 14 days prior to administration of study medication or is not willing to refrain from consuming these products for the duration of the study.
9. Participant is excluded if any of the following COVID-19 criteria apply:

- Participant has a positive test result for SARS-CoV-2 using reverse transcription-polymerase chain reaction (RT-PCR) on admission.
- Participant has clinical signs and symptoms consistent with COVID-19 (eg, fever, dry cough, dyspnea, sore throat, fatigue) or confirmed infection by appropriate laboratory test within the previous 14 days prior to screening or on admission or a history of in-patient hospitalization secondary to COVID-19.
- Participant is currently in quarantine (has been in contact with a SARS-CoV-2 positive patient in the last 14 days).
- Participant has had a severe course of COVID-19 (eg, requiring extracorporeal membrane oxygenation, mechanical ventilation or hospitalization).

10. Participant has, in the opinion of the Investigator, a known relevant allergy (not including mild seasonal hay fever and/or conjunctivitis or low-grade food intolerances), a preexisting history of a relevant allergic condition, or a predisposition for an allergic reaction (eg, total immunoglobulin E [IgE] value above normal range at screening).

Prior/concomitant therapy

11. Participant has received or intends to use any prescription or nonprescription medicines, including enzyme inhibitors or inducers, any gastric pH modifying agents, over the counter remedies, herbal and dietary supplements (including St. John's Wort) up to 2 weeks (4 weeks for enzyme inducers) or 5 half-lives of the respective drug (whichever is longer) before the first administration of study medication and during the clinical part of the study, unless required to treat an AE. Drugs with known CYP3A4 interaction (strong inducers and inhibitors) are prohibited. This does not include oral contraceptives exceeding 30µg ethinyl estradiol or postmenopausal hormone replacement therapy or implants, patches, or intrauterine devices (IUDs)/intrauterine hormone-releasing system (IUSs) delivering progesterone (for female study participants).

Prior/concurrent clinical study experience

12. Participant has previously participated in this study or participant has previously been assigned to treatment in a study of the medication under investigation in this study.
13. Participant has participated in another study of a study medication (and/or an investigational device) within the previous 30 days or 5 half-lives, whichever is greatest, or is currently participating in another study of an study medication (and/or an investigational device).

Diagnostic assessments

14. Participant has a medical history or current diagnosis of renal impairment and/or screening laboratory results show:

- An estimated glomerular filtration rate (eGFR) <80mL/min/1.73m^2 (using the Chronic Kidney Disease Epidemiology Collaboration formula)
- An albumin/creatinine ratio ≥30mg/mmol
- Participant has a urinary tract infection but could be rescreened once the infection has been resolved
- Clinically significant electrolyte abnormalities

15. Participant has any clinically relevant abnormal findings in physical examination, laboratory tests, or vital signs, which, in the opinion of the Investigator, may place the participant at risk because of participation in the study.
16. Presence of hepatitis B surface antigen (HBsAg) at screening or within 3 months prior to dosing.
17. Positive hepatitis C antibody test (HCVAb) result at screening or within 3 months prior to starting study intervention. NOTE: Participants with positive HCVAb due to prior resolved disease can be enrolled if a confirmatory negative hepatitis C ribonucleic acid (RNA) test is obtained.
18. Positive hepatitis C RNA test result at screening or within 3 months prior to first dose of study medication. NOTE: Test is optional and participants with negative HCVAb test are not required to also undergo hepatitis C RNA testing.
19. Positive immunodeficiency virus antibody test (HIV1Ab and HIV2Ab) at screening.
20. Participant has alanine transaminase (ALT), aspartate transaminase (AST) or alkaline phosphatase (ALP) are greater than the upper limit of normal (ULN) at Screening.

    For randomized participants with a baseline result >ULN for ALT, AST, ALP, or total bilirubin, a baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the electronic case report form (eCRF).

    If study participant has >ULN ALT, AST, or ALP that does not meet the exclusion limit at screening, repeat the tests, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the participant must be discussed with the Medical Monitor.

    Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. This includes rescreening.
21. Participant has bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if fractionated and direct bilirubin <35%).
22. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

23. Participant has any clinically relevant electrocardiogram (ECG) finding at the Screening Visit or at Baseline, or a family history of sudden death due to long QT syndrome which, in the opinion of the Investigator, would put the participant at increased risk of QT prolongation during the study (See Section 7.1.2 for QTcF withdrawal criteria). In addition, any study participant with any of the following findings will be excluded at Screening: QT interval correlated for heart rate using Fridericia's formula >450 msec for males and 470msec for females; other conduction abnormalities (defined as PR>=220 ms), irregular rhythm other than sinus arrhythmia or occasional, rare supraventricular, and rare ventricular ectopic beats.

Other exclusions

24. For women of childbearing potential, study participant is pregnant, planning on becoming pregnant during the study, or is breastfeeding.
25. Participants who may have a history of confirmed gastric ulceration.

5.3 Lifestyle restrictions

5.3.1 Meals and dietary restrictions

Study participants receive standard meals and snacks at appropriate times indicated by the clinic center, except when they are required to fast.

- Fasting and water restrictions: Participants will fast (ie, no food or fluids except water) for at least 10 hours prior to study medication dosing and will continue to fast for at least 4 hours after study medication dosing. 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. There is no water restriction for esomeprazole dosed 1 hour prior to UCB0599 administration in Periods 4 through 6 (Part A). At all other times, participants may drink water ad libitum. UCB0599 will be administered with approximately 240mL of water and esomeprazole with approximately 250ml of water.
- No grapefruit, grapefruit juice, grapefruit-containing products, or star fruit is to be consumed within 14 days before the start of study treatment until after the final dose. Participants who are not willing to refrain from consuming these products for the duration of the study will be excluded (Section 5.2). These fruits are not allowed during the Treatment Period and throughout the study due to an ingredient that is an inhibitor sensitive substrate of CYP3A. If a deviation occurs, it must be noted in the database.
- No cruciferous vegetables (eg, brussel sprouts, broccoli, cabbage, cauliflower) may be ingested for 7 days prior to first dosing until after study completion. If a deviation occurs, it must be noted in the database.

5.3.2 Caffeine, alcohol, and tobacco

- Participants will abstain from ingesting more than 600mg of caffeine/day at screening and throughout the study (1 cup of coffee contains approximately 100mg of caffeine, 1 cup of tea approximately 30mg, and 1 glass of cola approximately 20mg) (see Section 5.2 and Section 5.3.1).

- Participants will abstain from alcohol for 48 hours before the first dosing until after the SFU Visit or Early Termination Visit (ETV) evaluation.
- Use of tobacco products will not be allowed from screening until after study completion.
- Use of cannabis will not be permitted for 4 weeks before screening until after study completion.

5.3.3 Activity

Strenuous activity (eg, weight training, aerobics, football) is to be restricted from screening until the SFU Visit or ETV evaluation. Participants may participate in light recreational activities during the study.

5.4 Screen failures

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

Study participants who do not meet the criteria for participation in this study (screen failures) may be rescreened once at the discretion of the Investigator.

Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. This includes rescreening.

6 STUDY TREATMENTS

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

6.1 Treatments administered

The treatments for Part A are described in Table 6-1 and the possible treatment options for Part B are described in Table 6-2 (UCB0599 film-coated tablet), Table 6-3 (UCB0599 encapsulated tablet), and Table 6-4 (UCB0599 capsule). For Part B only, the preferred formulation will depend on the formulation that will be selected at the end of Part A.

Table 6-1: Study treatment for Part A

Treatment name	UCB0599 180mg/day capsules	UCB0599 180mg/day tablets	UCB0599 180mg/day encapsulated tablets	Co-administration of PPI
Intervention name	UCB0599	UCB0599	UCB0599	Esomeprazole
Type	Drug	Drug	Drug	Drug
Dose formulation	Granules in oral capsules (reference formulation)	Oral film-coated tablets with CCI	Oral encapsulated tablets with CCI	Oral capsules
Unit dose strength(s)	90mg	180mg	180mg	40mg capsules (Nexium® delayed-release capsule)
Dosage level(s)	180mg/day SD (2x90mg capsules)	180mg/day SD (1 tablet)	180mg/day SD (1 encapsulated tablet)	40mg QD (1 capsule)
Route of administration	Oral	Oral	Oral	Oral
Use	Experimental	Experimental	Experimental	Experimental
IMP and NIMP/AxMP	IMP	IMP	IMP	NIMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Sourced locally by the clinical site
Packaging and labeling	The study medication is manufactured, packaged, and labeled according to GMP guidelines and in accordance with all applicable laws or regulations. Each study medication bottle will be labeled according to individual country requirements. Details of the packaging and labeling will	The study medication is manufactured, packaged, and labeled according to GMP guidelines and in accordance with all applicable laws or regulations. Each study medication bottle will be labeled according to individual country requirements. Details of the	The study medication is manufactured, packaged, and labeled according to GMP guidelines and in accordance with all applicable laws or regulations. Each study medication bottle will be labeled according to individual country requirements. Details of the	NA

Table 6-1: Study treatment for Part A

	be provided in the study medication Handling Manual.	packaging and labeling will be provided in the study medication Handling Manual.	packaging and labeling will be provided in the study medication Handling Manual.	
Current/ former name	UCB0599	UCB0599	UCB0599	NA

AxMP=auxiliary medicinal product; GMP=Good Manufacturing Practices; IMP=investigational medicinal product; NA=not applicable; NIMP=non-investigational medicinal product; PPI=proton pump inhibitor; QD=once daily; SD=single dose

Table 6-2: Study treatment for Part B option: UCB0599 film-coated tablet used as new formulation

Treatment name	UCB0599 90mg tablets	UCB0599 matching placebo 90mg tablets	UCB0599 180mg tablets	UCB0599 matching placebo 180mg tablets	UCB0599 360mg tablets	UCB0599 matching placebo 360mg tablets
Intervention name	UCB0599	Placebo	UCB0599	Placebo	UCB0599	Placebo
Type	Drug	Placebo	Drug	Placebo	Drug	Placebo
Dose formulation	Oral film-coated tablets with CCI	Matching placebo tablets	Oral film-coated tablets with CCI	Matching placebo tablets	Oral film-coated tablets with CCI	Matching placebo tablets
Unit dose strength(s)	90mg	0mg	180mg	0mg	180mg	0mg
Dosage level(s)	90mg/day SD (1 tablet)	0mg/day SD (1 matching placebo tablet)	180mg/day SD (1 tablet)	0mg/day SD (1 matching placebo tablet)	360mg/day SD (2x180mg tablets)	0mg/day SD (2 matching placebo tablets)
Route of administration	Oral	Oral	Oral	Oral	Oral	Oral
Use	Experimental	Experimental	Experimental	Experimental	Experimental	Experimental
IMP and NIMP/AxMP	IMP	IMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor

Table 6-2: Study treatment for Part B option: UCB0599 film-coated tablet used as new formulation

Packaging and labeling	The study medication is manufactured, packaged, and labeled according to GMP guidelines and in accordance with all applicable laws or regulations. Each study medication bottle will be labeled according to individual country requirements. Details of the packaging and labeling will be provided in the study medication Handling Manual.	The study medication is manufactured, packaged, and labeled according to GMP guidelines and in accordance with all applicable laws or regulations. Each study medication bottle will be labeled according to individual country requirements. Details of the packaging and labeling will be provided in the study medication Handling Manual.	The study medication is manufactured, packaged, and labeled according to GMP guidelines and in accordance with all applicable laws or regulations. Each study medication bottle will be labeled according to individual country requirements. Details of the packaging and labeling will be provided in the study medication Handling Manual.	The study medication is manufactured, packaged, and labeled according to GMP guidelines and in accordance with all applicable laws or regulations. Each study medication bottle will be labeled according to individual country requirements. Details of the packaging and labeling will be provided in the study medication Handling Manual.	The study medication is manufactured, packaged, and labeled according to GMP guidelines and in accordance with all applicable laws or regulations. Each study medication bottle will be labeled according to individual country requirements. Details of the packaging and labeling will be provided in the study medication Handling Manual.	The study medication is manufactured, packaged, and labeled according to GMP guidelines and in accordance with all applicable laws or regulations. Each study medication bottle will be labeled according to individual country requirements. Details of the packaging and labeling will be provided in the study medication Handling Manual.
Current/ former name	UCB0599	NA	UCB0599	NA	UCB0599	NA

AxMP=auxiliary medicinal product; GMP=Good Manufacturing Practices; IMP=investigational medicinal product; NA=not applicable; NIMP=non-investigational medicinal product; SD=single dose

Table 6-3: Study treatment for Part B option: UCB0599 encapsulated tablet used as new formulation

Treatment name	UCB0599 90mg encapsulated tablets	UCB0599 matching placebo 90mg encapsulated tablets	UCB0599 180mg encapsulated tablets	UCB0599 matching placebo 180mg encapsulated tablets	UCB0599 360mg encapsulated tablets	UCB0599 matching placebo 360mg encapsulated tablets
Intervention name	UCB0599	Placebo	UCB0599	Placebo	UCB0599	Placebo
Type	Drug	Placebo	Drug	Placebo	Drug	Placebo
Dose formulation	Oral encapsulated tablets with CCI	Matching placebo encapsulated tablets	Oral encapsulated tablets with CCI	Matching placebo encapsulated tablets	Oral encapsulated tablets with CCI	Matching placebo encapsulated tablets
Unit dose strength(s)	90mg	0mg	180mg	0mg	180mg	0mg
Dosage level(s)	90mg/day SD (1 encapsulated tablet)	0mg/day SD (1 matching placebo encapsulated tablet)	180mg/day SD (1 encapsulated tablet)	0mg/day SD (1 matching placebo encapsulated tablet)	360mg/day SD (2x180mg encapsulated tablets)	0mg/day SD (2 matching placebo encapsulated tablets)
Route of administration	Oral	Oral	Oral	Oral	Oral	Oral
Use	Experimental	Experimental	Experimental	Experimental	Experimental	Experimental
IMP and NIMP/AxMP	IMP	IMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor

Table 6-3: Study treatment for Part B option: UCB0599 encapsulated tablet used as new formulation

Packaging and labeling	The study medication is manufactured, packaged, and labeled according to GMP guidelines and in accordance with all applicable laws or regulations. Each study medication bottle will be labeled according to individual country requirements. Details of the packaging and labeling will be provided in the study medication Handling Manual.	The study medication is manufactured, packaged, and labeled according to GMP guidelines and in accordance with all applicable laws or regulations. Each study medication bottle will be labeled according to individual country requirements. Details of the packaging and labeling will be provided in the study medication Handling Manual.	The study medication is manufactured, packaged, and labeled according to GMP guidelines and in accordance with all applicable laws or regulations. Each study medication bottle will be labeled according to individual country requirements. Details of the packaging and labeling will be provided in the study medication Handling Manual.	The study medication is manufactured, packaged, and labeled according to GMP guidelines and in accordance with all applicable laws or regulations. Each study medication bottle will be labeled according to individual country requirements. Details of the packaging and labeling will be provided in the study medication Handling Manual.	The study medication is manufactured, packaged, and labeled according to GMP guidelines and in accordance with all applicable laws or regulations. Each study medication bottle will be labeled according to individual country requirements. Details of the packaging and labeling will be provided in the study medication Handling Manual.	The study medication is manufactured, packaged, and labeled according to GMP guidelines and in accordance with all applicable laws or regulations. Each study medication bottle will be labeled according to individual country requirements. Details of the packaging and labeling will be provided in the study medication Handling Manual.
Current/ Former name	UCB0599	NA	UCB0599	NA	UCB0599	NA

AxMP=auxiliary medicinal product; GMP=Good Manufacturing Practices; IMP=investigational medicinal product; NA=not applicable; NIMP=non-investigational medicinal product; SD=single dose

Table 6-4: Study treatment for Part B option: UCB0599 capsules (Part A reference formulation)

Treatment name	UCB0599 90mg capsules	UCB0599 matching placebo 90mg capsules	UCB0599 180mg capsules	UCB0599 matching placebo 180mg capsules	UCB0599 360mg capsules	UCB0599 matching placebo 360mg capsules
Intervention name	UCB0599	Placebo	UCB0599	Placebo	UCB0599	Placebo
Type	Drug	Placebo	Drug	Placebo	Drug	Placebo
Dose formulation	Granules in oral capsules	Matching placebo capsules	Granules in oral capsules	Matching placebo capsules	Granules in oral capsules	Matching placebo capsules
Unit dose strength(s)	90mg	0mg	90mg	0mg	90mg	0mg
Dosage level(s)	90mg/day SD (1 capsule)	0mg/day SD (1 matching placebo capsules)	180mg/day SD (2 capsules)	0mg/day SD (2 matching placebo capsules)	360mg/day SD (4 capsules)	0mg/day SD (4 matching placebo capsules)
Route of administration	Oral	Oral	Oral	Oral	Oral	Oral
Use	Experimental	Experimental	Experimental	Experimental	Experimental	Experimental
IMP and NIMP/AxMP	IMP	IMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor

Table 6-4: Study treatment for Part B option: UCB0599 capsules (Part A reference formulation)

Packaging and labeling	The study medication is manufactured, packaged, and labeled according to GMP guidelines and in accordance with all applicable laws or regulations. Each study medication bottle will be labeled according to individual country requirements. Details of the packaging and labeling will be provided in the study medication Handling Manual.	The study medication is manufactured, packaged, and labeled according to GMP guidelines and in accordance with all applicable laws or regulations. Each study medication bottle will be labeled according to individual country requirements. Details of the packaging and labeling will be provided in the study medication Handling Manual.	The study medication is manufactured, packaged, and labeled according to GMP guidelines and in accordance with all applicable laws or regulations. Each study medication bottle will be labeled according to individual country requirements. Details of the packaging and labeling will be provided in the study medication Handling Manual.	The study medication is manufactured, packaged, and labeled according to GMP guidelines and in accordance with all applicable laws or regulations. Each study medication bottle will be labeled according to individual country requirements. Details of the packaging and labeling will be provided in the study medication Handling Manual.	The study medication is manufactured, packaged, and labeled according to GMP guidelines and in accordance with all applicable laws or regulations. Each study medication bottle will be labeled according to individual country requirements. Details of the packaging and labeling will be provided in the study medication Handling Manual.	The study medication is manufactured, packaged, and labeled according to GMP guidelines and in accordance with all applicable laws or regulations. Each study medication bottle will be labeled according to individual country requirements. Details of the packaging and labeling will be provided in the study medication Handling Manual.
Current/ Former name	UCB0599	NA	UCB0599	NA	UCB0599	NA

AxMP=auxiliary medicinal product; GMP=Good Manufacturing Practices; IMP=investigational medicinal product; NA=not applicable; NIMP=non-investigational medicinal product; SD=single dose

6.2 Preparation, handling, storage, and accountability requirements

The Investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study medication received, and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive the study medication and only authorized site staff may supply or administer the study medication. All study medication must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study medication accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

In case an out-of-range temperature is noted, it must be immediately reported as per instructions contained in the study medication Handling Manual.

The Investigator (or designee) will instruct the participant to store the study medication following the instructions on the label.

Further guidance and information for the final disposition of unused study medication are provided in the study medication Handling Manual.

6.2.1 Drug accountability

A Drug Accountability form will be used to record study medication dispensing and return information on a by-participant basis and will serve as source documentation during the course of the study. Details of any study medication lost, damaged (due to breakage or wastage), not used, partially used, disposed of at the study site, or returned to the Sponsor or designee must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

The Investigator (or designee) is responsible for retaining all used, unused, and partially used containers of study medication until returned or destroyed.

The Investigator may assign some of the Investigator's duties for drug accountability at the study site to an appropriate pharmacist/designee.

The Investigator must ensure that the study medication is used only in accordance with the protocol.

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers/partially used), unused, damaged, and/or expired study medication must be reconciled and either destroyed at the site according to local laws, regulations, and UCB standard operating procedures (SOPs) or returned to UCB (or designee). Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

6.3 Measures to minimize bias: randomization and blinding

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. This portion of the study is planned to enroll up to 42 study participants, in which 7 participants will

be randomized (approximately 6 completers) to each sequence. Randomization numbers will be assigned at the site in an unblinded fashion and will be entered into the eCRF.

In Part B, 15 study participants of each ethnic origin will be randomized to the 4 treatments following a UCB0599:placebo 4:1 ratio (see Section 4.1 for study design details). Participants will be blinded to the treatment (ie, UCB0599 or placebo), but not to the dosage within a sequence. As study participants are being screened for Part B, participants will be randomized to blocks of 2 sequences at a time: Sequences 1 and 2 (Cohort 2), followed by Sequences 3 and 4 (Cohort 3), and finally Sequences 5 and 6 (Cohort 4) after the SMC review.

An interactive response technology (IRT) will be used for assigning eligible participants (in Part A and Part B) to a treatment regimen (as applicable) based on a predetermined production randomization and/or packaging schedule provided by UCB (or designee). The randomization schedule will be produced by the IRT vendor. The IRT will generate individual assignments for kits of the study medication, as appropriate, according to the visit schedule.

To enroll a study participant (Visit 1), the Investigator or designee will contact the IRT and provide brief details about the participant to be enrolled. Each participant will receive a 5-digit number assigned at screening that serves as the participant identifier throughout the study. The participant number will be required in all communication between the Investigator or designee and the IRT regarding a particular participant. Participant numbers and kit numbers will be tracked via the IRT.

To randomize a participant, the Investigator or designee will contact the IRT and provide brief details about the participant to be randomized. The IRT will automatically inform the investigator or designee of the participant's randomization number. The IRT will allocate kit numbers to the participant based on the participant number during the course of the study. The randomization number must be incorporated into the eCRF.

All participant treatment details will be allocated and maintained by the IRT. The following individuals will have received the randomization code at the start of the UP0073 study:

- Designated CRO bioanalytical staff analyzing samples
- Sponsor clinical study supply staff
- IRT provider

The following individuals may have access to the randomization code as indicated:

- Sponsor patient safety staff as needed for reporting SAEs to regulatory authorities

6.3.1 Procedures for maintaining and breaking the treatment blind

6.3.1.1 Maintenance of study treatment blind

All participant treatment details will be allocated and maintained by IRT system.

6.3.1.2 Breaking the treatment blind in an emergency situation

In the event of an emergency, it will be possible to determine to which treatment arm and dose the participant has been allocated by contacting the IRT. The site will be provided with details of

how to contact the system for code breaking at the start of the study. The Medical Monitor or equivalent should be consulted prior to unblinding, whenever possible.

The Clinical Project Manager will be informed immediately via the IRT when a code is broken, but will remain blinded to specific treatment information. Any unblinding of the study medication performed by the investigator must be recorded in the source documents and on the Study Termination eCRF page.

6.4 Treatment compliance

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

Drug accountability must be recorded on the Drug Accountability form.

6.5 Concomitant medication(s)/treatment(s)

6.5.1 Permitted concomitant treatments (medications and therapies)

The following concomitant medications are permitted during the study:

- Paracetamol/acetaminophen for the treatment of mild symptoms (eg, headache or other pain), given at most every 6 hours to 8 hours, not exceeding 2g per day, and with a total of no more than 5g over 7 days.
- Ibuprofen, not exceeding 1.2g per day.
- Nasal corticosteroids for seasonal rhinitis and topical corticosteroids for controlled dermatological conditions.
- Oral contraceptives not exceeding 30µg ethinyl estradiol or postmenopausal hormonal replacement therapy (HRT) or implants, patches, or IUDs/IUSs delivering progesterone (for female study participants).

For all study participants: if a concomitant medication is required during the Washout Period and if there is no impact on the study participant's safety and the impact on quality of further study data is deemed to be minimal, the study participant can remain in the study after Sponsor approval. If the concomitant medication use does not violate these criteria and no drug allergy has been reported, the study participant will be permitted to continue in the study.

6.5.1.1 Permitted Coronavirus Disease-2019 vaccination

During the study, COVID-19 vaccinations are allowed as long as they are not administered in the 10 days prior to or in the 7 days after administration of the final dose of the study medication.

6.5.2 Prohibited concomitant treatments (medications and therapies)

The following concomitant medications are prohibited during the study:

- Medicines known to strongly interact with CYP3A4 (both inducers [including St. John's Wort] and inhibitors).
- Medicines known to strongly affect gastric pH (excluding esomeprazole as used per protocol in Part A).

6.5.3 Rescue medication

No rescue medication will be provided as part of this study.

6.6 Dose modification

There is no dose modification allowed in UP0073.

6.7 Criteria for study hold or dosing stoppage (Part A and Part B)

Study medication will be stopped if the study participant develops a medical condition (or laboratory abnormality or ECG change) that, in the opinion of the Investigator, compromises the study participant's ability to participate or compromises the study participant's safety.

In all cases, the study participant should be followed until the condition has resolved as agreed by the Investigator and the UCB Study Physician.

See the Schedule of Activities (Section 1.3) for data to be collected at the time of treatment discontinuation and follow up and for any further evaluations that need to be completed.

Detailed procedures for reporting SAEs and other safety events which may meet study hold criteria are provided in Appendix 8 (Section 10.8).

6.8 Treatment after the end of the study

There are no plans for study participant continued care after the end of the study, since study participants are healthy volunteers.

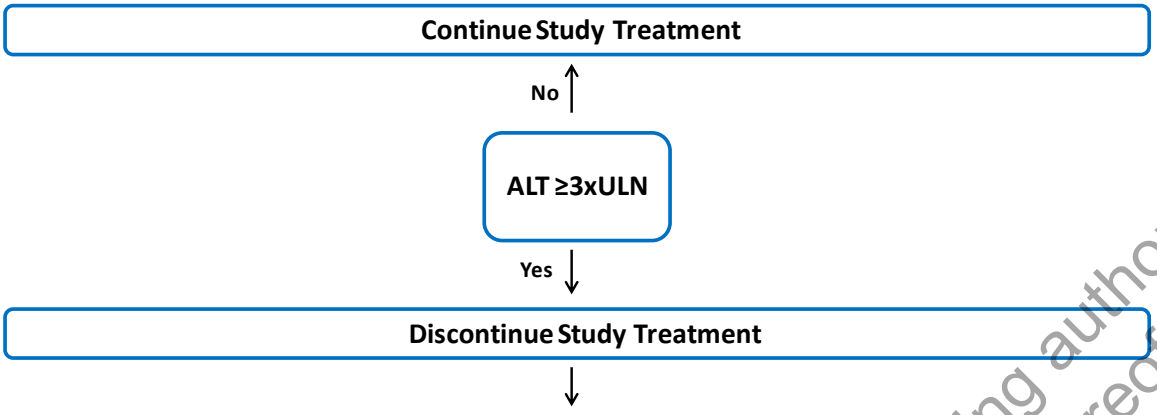
7 DISCONTINUATION OF STUDY MEDICATION AND STUDY PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of study medication

7.1.1 Liver chemistry stopping criteria

Discontinuation of study medication for abnormal liver function should be considered by the Investigator when a participant meets one of the conditions outlined in Figure 7-1 or if the Investigator believes that it is in best interest of the participant. Study medication will be discontinued immediately and permanently for a healthy participant if liver chemistry stopping criteria are met.

Figure 7-1: Phase I Liver Chemistry Stopping Algorithm



ALT=alanine transaminase; ULN=upper limit of normal

Specific assessments and follow up actions for potential drug-induced liver injury (PDILI) are provided in Appendix 6 (Section 10.6).

7.1.2 QTc stopping criteria

A study participant who meets either bulleted criterion based on a single 12-lead ECG reading will be withdrawn from study treatment. If there are abnormalities that are considered clinically significant for a particular study participant, ECG recordings will be performed in triplicate at 2- to 3-minute intervals (3 ECGs within a 5-minute timeframe) prior to the exclusion of the participant.

- QT corrected for heart rate using Fridericia's formula (QTcF) >500ms OR Uncorrected QT >600ms
- Change from Baseline of QTcF >60ms

For study participants with underlying bundle branch block, follow the discontinuation criteria listed below:

Baseline QTc with bundle branch block	Discontinuation QTc threshold with bundle branch block
<450ms	>500ms
450 to 480ms	≥530ms

If a clinically significant finding is identified (including, but not limited to, changes from Baseline in QTcF after enrollment), the Investigator or qualified designee will determine if the study participant can continue the study medication and if any change in study participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

See the Schedule of Activities (Section 1.3) for data to be collected at the time of treatment discontinuation and follow up and for any further evaluations that need to be completed.

7.1.3 Renal toxicity stopping criteria

Participants must be discontinued from the study medication if renal toxicity considered possibly related to the study treatment occurs.

Laboratory tests suggestive of renal toxicity which should trigger further assessment may include:

- Increase in serum creatinine ≥0.3mg/dL from Baseline **OR**
- Increase in serum creatinine to ≥1.5 times from Baseline **OR**
- New persistent albuminuria or clinically significant increase in preexisting albuminuria.

Any clinically significant findings in laboratory results for renal function will be monitored until resolution or stabilization.

7.1.4 Hypersensitivity reaction stopping criteria

Study participants will be informed that if they develop any symptoms suggestive of an hypersensitivity reaction (eg, rash, angioedema, or anaphylaxis), they should contact the Investigator immediately. The Investigator should assess the presenting symptoms to determine if this is possibly a hypersensitivity reaction.

If the event is not considered to be a hypersensitivity reaction, the Investigator should document this and the participant may continue dosing. If the event is possibly a hypersensitivity reaction, the Investigator will withhold dosing and arrange additional investigations. Study participants may be referred to a dermatologist for additional investigation. The event should be reported to UCB as an AESI.

- Two or more study participants have an hypersensitivity reaction that, based on reasonable medical judgement, could lead to significant toxicities that would be unacceptable for this study population **OR**
- Two or more study participants have a study medication-related severe hypersensitivity reaction (Grade 3 according to the Common Terminology Criteria for Adverse Events [CTCAE] classification) **OR**
- One or more study participants have a study medication-related hypersensitivity reaction of Grade 4 or 5 according to the CTCAE classification.

If any of the above events occur during the study, the following should take place:

  - Further administration of the study medication will be suspended for all study participants.
  - The SMC will meet as soon as possible and will provide recommendations regarding individual study participants, individual groups, the study overall, the suspension or continuation of dosing, the stopping or continuation of the study or the modification of the protocol.

Detailed procedures for reporting SAEs and other safety events which may meet study hold criteria are provided in Appendix 8 (Section 10.7).

7.1.5 General stopping criteria for the study - Part B only

UCB will halt further dosing if any of the following criteria are met during the course of the study and following case review to confirm causality and seriousness and/or severity of reported events.

During the study, planned dosing and procedures must be discontinued or suspended for all remaining study participants who are yet to be dosed in the study and appropriate follow-up procedures established for (but not limited to) any of the following reasons:One study participant has an SAE considered related to the study medication as judged by the Investigator.Two or more study participants in a single cohort have a severe AE, similar clinically significant abnormal laboratory results or other clinically significant safety findings that would be unacceptable for this study population.If one of the stopping criteria for dosing and single dose escalation has been met, the SMC will meet as soon as possible to make a recommendation on discontinuation, pausing, or suspension of study medication dosing or on the stopping or continuation of the study. Consideration will be given to severity and relatedness of events. Further details on the role and process of ensuring close safety monitoring through the SMC are provided in the respective charters.See the Schedule of Activities (Section 1.3) for data to be collected at the time of treatment discontinuation and follow up.Temporary discontinuation

The Investigator or SMC may consider temporary discontinuation of dosing of study participants on a case-by-case basis (for Part B only).

7.1.6 Rechallenge

The Investigator after agreement with the SMC may consider rechallenge of study participants on a case-by-case basis (for Part B only).

7.2 Participant discontinuation/withdrawal from the study

Participants are free to withdraw from the study at any time, without prejudice to their continued care.

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

See the Schedule of Activities (Section 1.3)for data to be collected at the time of study discontinuation and follow up and for any further evaluations that need to be completed.

Participants should be withdrawn from the study if any of the following events occur:

1. Participant develops a clinically relevant medical condition (physical or psychiatric) that, in the opinion of the Investigator, jeopardizes or compromises the study participant's ability to participate in the study or makes it unsafe to continue.
2. Participant is noncompliant with the study procedures or medications in the opinion of the Investigator.

3. Participant's laboratory tests suggest evidence of renal toxicity.
4. Participant takes prohibited concomitant medications as defined in this protocol.
5. Participant withdraws his/her consent.
6. There is confirmation of a pregnancy during the study, as evidenced by a positive serum pregnancy test.
7. Participant has an anaphylactic reaction after their first administration.
8. The Sponsor or a regulatory agency requests withdrawal of the participant.

Investigators should attempt to obtain information on study participants in the case of withdrawal.

Investigators should contact the UCB Medical Monitor, whenever possible, to discuss the withdrawal of a study participant in advance. See Appendix 1 (Section 10.1 for details on study discontinuation).

Participants who withdraw in Part A will not be replaced, and participants who withdraw in Part B will be replaced up to a maximum of 6 study participants.

7.3 Lost to follow up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (at least 1 phone call and 1 written message to the participant), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the participant, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal.

Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow up documented in the eCRF.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Activities (Section 1.3 for Part A [Table 1-3] and Part B [Table 1-4]).

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study medication.

Adherence to the study design requirements, including those specified in the Schedule of Activities (Section 1.3), is essential and required for study conduct.

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

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities (Section 1.3).

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy assessments

Not applicable.

8.2 Safety assessments

Planned time points for all safety assessments are provided in the Schedule of Activities (Section 1.3 for Part A [Table 1-3] and Part B [Table 1-4]).

8.2.1 Physical examination

Physical examinations will be performed at the scheduled time points presented in Section 1.3 for Part A (Table 1-3) and Part B (Table 1-4).

A complete physical examination will include, at a minimum, general appearance; ear, nose, and throat; eyes, hair, and skin; and assessments of the cardiovascular, respiratory, gastrointestinal, neurological (including sensation, muscle strength, reflexes, balance and mental state), musculoskeletal, and hepatic systems.

Height and weight will be measured and recorded at the Screening Visit, and the study participant's BMI will be calculated. Height will be measured with the study participant not wearing shoes, and the outcome will be rounded to the nearest 1cm. Body weight will be measured with the study participant wearing light clothing and without wearing shoes; the outcome will be rounded to the nearest 0.1kg. The BMI will be calculated (weight [kg]/[height (m^2)]) and will be reported to 1 decimal place.

A symptom-directed physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). A physical examination of the skin will include, at a minimum, a visual check of the skin, and may be conducted by a nurse or physician.

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

Clinically relevant findings or worsening of previous findings will be recorded as AEs.

8.2.2 Vital signs

Vital signs, including pulse rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate, and tympanic body temperature will be measured with a completely automated device after 5 minutes of rest in a supine position (in a quiet setting without distractions such as a television or cell phones). Pulse rate, SBP, and DBP will be measured with a completely automated device. Manual techniques will be used only if an automated device is not available. Any clinically significant abnormality in the view of the Investigator will be recorded as an AE.

Vital signs (to be taken before blood collection for laboratory tests) will be measured in triplicate. The mean values will be calculated and recorded on the eCRF. The vital signs will consist of 3 pulse rates and 3 blood pressure (BP) measurements (3 consecutive BP readings will be recorded at intervals of at least 1 minute).

Vital signs will be performed at the scheduled time points presented in Section 1.3 for Part A (Table 1-3) and Part B (Table 1-4).

8.2.3 Electrocardiograms

Single 12-lead ECG recordings will be obtained as outlined in the Schedule of Activities in Section 1.3 for Part A (Table 1-3) and Part B (Table 1-4) using an ECG machine that automatically calculates the pulse rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 7.1.2 for QTcF withdrawal criteria and any additional QTc readings that may be necessary.

The study participant should be resting in the supine position for at least 10 minutes before the start of the recordings.

The Investigator should review all ECG recordings and, if there are abnormalities that are considered clinically significant for a particular study participant, then the Investigator should initiate a review by a specialist of all ECG data pertaining to that study participant. The following ECG parameters will be recorded in the eCRF: heart rate, PR-interval, QRS-duration, QT-interval, QTcF, and Investigator's conclusion on ECG profile.

8.2.4 Clinical safety laboratory assessments

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Section 1.3 for Part A [Table 1-3] and Part B [Table 1-4]) for the timing and frequency.

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

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the final dose of study medication should be repeated until the values return to normal or Baseline or are no longer considered clinically significant by the Investigator or UCB Study Physician.

If such values do not return to normal/Baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the UCB Study Physician notified.

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the Schedule of Activities (Section 1.3).

If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.2.5 Suicidal risk monitoring

Suicidal risk moditoring is not applicable for this single-dose study.

8.3 AEs and SAEs

The definitions of an AE or SAE can be found in Appendix 3 (Section 10.3).

Adverse events will be reported by the participant (or, when appropriate, by a caregiver or surrogate).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study medication or study procedures, or that caused the participant to discontinue UCB0599 (see Section 7).

Note that in this case the national recommendation for reporting AEs related to COVID-19 vaccines should be followed.

For results disclosure on public registries (eg, ClinicalTrials.gov), TEAEs and treatment emergent SAEs will be published.

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs and SAEs will be collected from the signing of the ICF until the SFU Visit at the time points specified in the Schedule of Activities (Section 1.3 for Part A [Table 1-3] and Part B [Table 1-4]).

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the ICF), including any pretreatment and posttreatment periods required by the protocol, must be reported in the eCRF even if no study medication was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs that recurred or worsened after the initial visit.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

The Investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the Investigator is certain that they are in no way associated with the study medication), up to 30 days from the end of the study for each participant, and to also inform participants of the need to inform the Investigator of any SAE within this period. Serious AEs that the Investigator thinks may be associated with the study medication must be reported to UCB regardless of the time between the event and the end of the study.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.3.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and nonserious AESIs (as defined in Section 8.3.6), will be followed until resolution, stabilization, the Investigator determines that it is no longer clinically significant, the event is otherwise explained, or the participant is lost to follow up (as defined in Section 7.3). Further information on follow up procedures is given in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

Prompt notification by the Investigator to the UCB Study Physician of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of study participants and the safety of an study medication under clinical investigation are met.

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

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the UCB0599 IB and will notify the Institutional Review Board (IRB)/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of all pregnancies in female participants and, if consented, female partners of male participants will be collected after the start of study medication and until at least 12 months after the delivery date.

If a pregnancy is reported, the Investigator must immediately inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).

The participant should be withdrawn from the study as soon as pregnancy is known (by positive pregnancy test [ie, a positive urine test confirmed with a blood test]), and the following should be completed:

- The participant should return for an ETV.

- The participant should immediately stop the intake of the study medication as instructed at the ETV.
- An SFU Visit should be scheduled approximately 10 days after the participant has discontinued her study medication.

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

8.3.6 AESIs

An AESI is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound.

For UCB0599, the following events require immediate reporting (within 24 hours regardless of seriousness) to UCB:

- Hy's Law
  - Potential Hy's Law, 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). Follow up information should be reported if an alternative etiology is identified during investigation and monitoring of the participant.
- Hypersensitivity reactions (such as rash, angioedema, or anaphylaxis)

8.3.6.1 Hypersensitivity reaction monitoring and management

If a study participant experiences a hypersensitivity reaction (such as rash, angioedema, or anaphylaxis), he or she will contact the clinical site immediately (24 hours a day) or seek urgent medical advice in accordance with instructions from the Investigator.

The advice will be based on the clinical presentation and may be to present to the clinical site or seek medical attention in the community.

The study participant should be rapidly and thoroughly assessed in line with the actions below.

Hypersensitivity reactions will be AESIs and require expedited reporting to UCB, regardless of seriousness, expectedness, or relatedness in line with Section 8.3.6. This will allow for rapid evaluation.

In case of a suspected hypersensitivity reaction or any clinical indication of an unexpected immune response, the points described in Sections 8.3.6.1.1 through Section 8.3.6.1.6 should be observed.

Consideration for restarting study medication is provided in Section 7.1.4.

Procedures for the management of UCB0599 are provided in Appendix 3 (Section 10.3).

8.3.6.1.1 Medical history

Detailed history of the hypersensitivity reaction (eg, rash, angioedema, or anaphylaxis) with onset time of symptoms and signs, location of symptoms and signs, first appearance, its

evolution (eg, where the rash appeared and to where it spread), any other symptoms (eg, pruritus, swelling, breathlessness), especially if showing a systemic involvement (anaphylaxis), will be recorded. The criteria for anaphylaxis are described in Section 8.3.6.1.1.1.

The clinical progression of the hypersensitivity reactions symptoms should be recorded and any change in symptoms or severity should also be recorded together with the timing.

All AEs reported concurrently should be included within the review.

It will also be important to investigate any recent intake of new medications, herbs, supplements, or the recent use of any topical substances.

8.3.6.1.1.1 Anaphylaxis

Sampson et al. listed criteria for the diagnosis of anaphylaxis. This was developed at the Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium (Sampson et al, 2006).

Acute onset=minutes to a few hours.

Criteria for diagnosis-1 or more of the following:

- Acute onset of an illness with symptom complex 1 (see below)
- Acute onset of symptom complex 2 (see below) after exposure to a likely allergen
- Acute onset of a reduced SBP after exposure to a known allergen for the participant

Symptom complex 1: both of the following:

- At least 1 of the following:
  - Skin involvement (generalized hives, pruritis, flushing)
  - Mucous membrane involvement (swollen lips, swollen tongue, swollen uvula)
- At least 1 of the following:
  - Respiratory compromise (dyspnea, wheezing, bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
  - Reduced SBP, collapse, syncope, incontinence or other symptom of end-organ dysfunction

Symptom complex 2: Two or more of the following:

- Skin or mucous membranes (as above)
- Respiratory compromise (as above)
- Reduced BP (as above)
- Persistent GI tract symptoms (cramping, abdominal pain, vomiting)

Reduced SBP is indicated by 1 of the following:

- BP <70% of Baseline SBP

Limitations:

Treudler et al. found that the criteria may not perform as well as others for the recognition of severe, immediate reactions (Treudler et al, 2008).

8.3.6.1.2 Complete physical examination

Evaluation of a possible hypersensitivity reaction includes a complete physical examination of the entire body as soon as feasible after reporting by the study participant. The complete physical examination includes a detailed description of the signs such as rash or angioedema, the location of the signs, and an examination for other possible signs, such as:

- Blanched or flushed skin
- Mucous membrane erosions or ulceration
- Maculae
- Papulae
- Blisters
- Confluent erythema
- Angioedema: face, lips, and/or tongue swelling, also back of hands or feet
- Wheeze, stridor, dyspnea
- Palpable purpura
- Lymphadenopathy

An examination of the entire skin surface, not just local to the site of reaction, is required.

Furthermore, a complete physical examination will also include:

- Vital signs (high fever, dyspnea, or hypotension)
  - Vital signs (pulse rate, SBP, diastolic BP, respiratory rate, body temperature, and oxygen saturation) will be taken when the AE of hypersensitivity is reported and at regular intervals (approximately 20 to 30 minutes) for a minimum of 2 hours. The frequency thereafter will be based on clinical judgement. If there is worsening of clinical status, the Investigator will apply the appropriate treatment and safety procedures (eg, call emergency) and contact the UCB study physician.
- Photography of rash and other symptoms at the first opportunity and with reasonable time sequence to document resolution. If timely site visit is not possible the participant may be requested to take photos to ensure photos of active symptoms. If participant is requested to provide photos the Investigator should advise the participant in data protection requirements (eg, avoidance of identifying features such as characteristic tattoos, parts of the face). The Investigator will ensure that identifiable characteristics are removed/hidden before sharing the pictures with the Sponsor.
- Re-examination should the symptoms significantly worsen
- Occurrence of other recent or current symptoms, even if they appear not related

8.3.6.1.3 Additional investigations

Investigators should arrange for the following investigations; further investigations may be requested after consultation with the Medical Monitor:

- Additional blood sampling for extended etiological characterization of the hypersensitivity reaction including:
  - Basophil Activation Test
  - Lymphocyte Transformation Test assays
  - Tryptase
  - Immunoglobulin E
- Rapid referral to experts (ie, dermatologist, allergist, or immunologist)

Additionally, a skin biopsy may be considered following review by expert.

8.3.6.1.4 Treatment

Investigators will administer the appropriate treatment as deemed necessary in cases of hypersensitivity. This includes the use of antihistamines for urticaria and the appropriate management in case of potentially life-threatening events such as anaphylaxis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis.

8.3.6.1.5 Blood sampling

Blood samples should be taken as soon as possible for safety and/or for further identification of the underlying mechanism of the reaction (hematology: eosinophilia; chemistry: check renal function including electrolytes, liver function tests, immunology, and IgE). Specific laboratory parameters (eg, cytokines, tryptase, complement, high-sensitivity C-reactive protein) will be collected at Day -1, and will be stored and used only in case of a hypersensitivity event (see Section 1.3).

The timing of the blood collection and other details for each test will be specified in the laboratory manual, and the full set of clinical laboratory tests are provided in Appendix 2 (Section 10.2).

8.3.6.1.6 Rapid referral to experts

Expert consulting (eg, dermatologist/allergist/immunologist) is required for expert opinion (diagnosis), diagnostic testing (eg, prick test for other potential allergens), further treatment, and follow up. Same day referral is required, especially if there is presentation of systemic symptoms and/or signs.

8.3.6.2 Renal function safety monitoring and management

If a participant develops clinically significant renal dysfunction, repeat laboratory testing should be undertaken as soon as possible and other appropriate investigations may be arranged. An increase in serum creatinine of >25% from the previous value will trigger repeat testing within 48 hours. The Medical Monitor should be notified, and consideration should be given to more frequent monitoring.

Clinically significant renal dysfunction will trigger an SMC review.

Participants must be discontinued from study medication (but not necessarily from the study) if laboratory tests suggest evidence of renal toxicity (see Section 7.1.3 for renal toxicity stopping criteria and Section 7.2 for participant discontinuation/withdrawal from the study). Any clinically significant findings in laboratory results for renal function will be monitored until resolution or stabilization.

The SMC charter will include further details regarding the assessment of renal function.

8.4 Safety signal detection

Selected data from this study will be reviewed periodically to detect as early as possible any safety concern(s) related to the study medication so that Investigators, clinical study participants, regulatory authorities, and IRBs/IECs will be informed appropriately and as early as possible.

The study physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the Patient Safety representative.

As appropriate for the stage of development and accumulated experience with the study medication, medically qualified personnel at UCB may identify additional safety measures (eg, AEs, vital signs, laboratory or ECG results) for which data will be periodically reviewed during the course of the study.

8.5 Treatment of overdose

For this study, any administration of UCB0599 totaling greater than 360mg within approximately a 24-hour time period will be considered an overdose.

Overdose events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess study medication itself is an AE or SAE (eg, suicide attempt).

UCB does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator or treating physician should:

- Stop dosing and contact the Medical Monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until UCB0599 can no longer be detected systemically (approximately 5 days).
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

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

8.6 Pharmacokinetics

Pharmacokinetic sampling will be mandatory for study participation in Part A and Part B. Samples will be collected predose and at several time points after study medication administration. These samples are a required component of the protocol as specified in the Schedule of Activities (Section 1.3 for Part A [Table 1-3] and Part B [Table 1-4]).

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files, but will not constitute a protocol amendment. The IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

Additional samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor. Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24 hour clock time) of each sample will be recorded.

See Section 5.3 for guidelines on lifestyle restrictions including details on meals and dietary restrictions.

8.6.1 Part A

Plasma samples (approximately 2mL whole blood collection) will be used to evaluate the primary PK parameters (Table 3-1), in which the relative bioavailability of 2 new UCB0599 formulations will be assessed compared with a reference 'granules in capsule' formulation in the presence and absence of esomeprazole in healthy participants. Estimated PK parameters may be used for the exposure-response assessment of safety and tolerability observations of each formulation and across formulations in the absence/presence of esomeprazole (Table 3-1).

Collection of samples for other PK parameters will be done as part of the study objectives and will evaluate the PK of UCB0599 for each tested formulation in the presence and absence of esomeprazole; and the PK of UCB0599 and its metabolites CCI [redacted] after a single dose of UCB0599 alone and co-administrated with esomeprazole (Table 3-1). Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual for this study. All collected samples may be used for research purposes focusing on method development and assay development. Collection of these samples will enable evaluation of relevant pharmacological information to support UCB0599 new formulation development.

8.6.2 Use of residual plasma samples (Part A only)

Any residual and/or surplus PK plasma samples remaining after the protocol-defined interim analysis has been performed may be used for additional exploratory analysis related to the purpose of this study. This may include, but is not limited to, biomarker assay development/optimization, protein binding, exploratory metabolite profiling/quantification, or other bioanalytical purposes (eg, cross check between different sites and/or stability assessment). Given the exploratory nature of the work, the analytical method used for those assessments will not be validated. As such, the results from this exploratory analysis will not be included in the Clinical Study Report.

Residual and/or surplus PK plasma samples will not be used for any genetic biomarker research.

8.6.3 Part B

Plasma samples (approximately 2mL whole blood collection) will be collected to evaluate the plasma concentrations of UCB0599, as well as to further assess other PK endpoints of UCB0599 and its metabolites CCI [redacted], as specified in the Schedule of Activities (Section 1.3), after administration of a single oral dose of the formulation selected from Part A in

healthy participants of Japanese and Chinese origins. See Section 3 (Table 3-2) for details on primary and other PK endpoints.

Estimated PK parameters may be used for the exposure-response assessment of safety and tolerability observations.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.7 Biomarkers

Genetic blood sampling will be mandatory for study participation. Collection of deoxyribonucleic acid (DNA) blood samples will occur as specified in the Schedule of Activities (Section 1.3) and may be used for exploratory research to further the understanding of how genetic variation may influence the metabolism, distribution, and elimination of UCB0599. No other analysis will be performed on the participant's DNA. Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual for this study.

Additional information is presented in Appendix 5 (Section 10.5).

8.8 Medical resource utilization and health economics

Not applicable.

9 STATISTICAL CONSIDERATIONS

A description of statistical methods follows and will be described in more detail in the Statistical Analysis Plan (SAP).

9.1 Definition of analysis sets

The following analysis sets will be used:

- All Study Participants (ASP): All study participants who signed the ICF for Part A or Part B, separately.
- The Randomized Sets A (RS A) and B (RS B): All study participants who are randomized to Part A or to Part B, respectively. Of note, this set will only be produced if it differs from the Safety Set (SS).
- The Safety Sets (SS; referred to as SS A and SS B for Part A and Part B, respectively): All study participants who are randomized and receive full or partial study medication according to the treatment that the participants actually received. The SS will be used for summaries of demographics, medical history, prior and concomitant medications, study medication exposure, and general safety outcomes such as AEs, laboratory parameters, vital signs, and ECGs.
- The Pharmacokinetic Set (PKS; referred to as PKS A and PKS B for Part A and Part B, respectively): This is a subset of the SS and consists of those study participants 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.

9.2 General statistical considerations

All analyses will be performed using SAS® version 9.4 or later (SAS Institute, Cary, NC, US).

The appropriate noncompartmental PK parameters will be calculated from the UCB0599 plasma concentration-time data using Phoenix® WinNonlin® Version 8.0 or higher. Actual sample times will be used in the calculations of the PK parameters.

For calculation of the plasma PK parameters of UCB0599 and metabolites, the actual sampling time points will be used in order to evaluate the PK parameters.

9.3 Planned efficacy outcome analyses

There will be no efficacy endpoint in this study.

9.4 Planned PK outcome analyses

9.4.1 PK parameters to be measured

The following PK parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin® (Version 8.3.4), as applicable: C_{max}, t_{max}, AUC_{last}, AUC_{inf}, AUC%Extrap, $t_{1/2}$, Lambda_z (λ_z), CL/F (UCB0599 only), Vz/F (UCB0599), MRC_{max}, and $MRAUC_{inf}$ from the plasma concentration-time data.

Table 9-1: 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).
$t_{1/2}$	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

The linear trapezoidal rule will be used for AUC calculation. Regression analysis of the terminal plasma elimination phase for the determination of $t_{1/2}$ will include at least 3 data points after C_{max}. If the Rsq_adj value of the regression analysis of the terminal phase is less than 0.75, no value is to be reported for AUC_{inf}, $t_{1/2}$, CL/F, and Vz/F.

9.4.2 Analysis of the primary PK endpoint

9.4.2.1 Part A

The plasma concentration-time profiles and PK parameters of UCB0599 will be summarized by dose level and group using descriptive statistics (number of available observations, arithmetic mean, standard deviation, geometric mean, coefficient of variation of geometric mean, median, minimum, and maximum). Values below the lower limit of quantification (LLOQ) will be reported with a clear sign indicating that they were below the LLOQ. Descriptive statistics of concentrations will be calculated if at least two-thirds of the individual data points are quantifiable (≥LLOQ).

The primary objective of Part A is to estimate the relative biovailability of 2 new UCB0599 formulations (film-coated tablet containing CCI with or without encapsulation) versus the current reference formulation (granules in capsule) under normal or elevated pH gastric conditions in healthy participants. The Part A primary PK endpoints are C_{max}, AUC_{0-t}, and AUC_{inf} for UCB0599 administered without and with esomeprazole. Descriptive statistics will be executed for all PK parameters estimated.

Individual concentration-time profiles will be displayed graphically on a linear-linear scale and semilogarithmic scale. Overall geometric mean plasma concentrations-time curves and corresponding 95% CIs will be displayed by formulation and condition (elevated and normal gastic pH).

The PK parameters (C_{max}, AUC_{0-t}, and AUC_{inf}) will be used to estimate the following:

- Primary objective: the relative bioavailability of 2 new UCB0599 formulations versus reference 'granules in capsule' formulation under elevated gastric pH and under normal conditions

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

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) and the data under elevated gastric pH condition (second 3-period crossover design substudy).

Following log-transformation, the primary PK parameters (C_{max}, AUC_{0-t}, and AUC_{inf}) will each be evaluated according to a linear mixed effect model with a random intercept term for participant and fixed effect categorical terms for treatment, sequence, and period to account for the crossover nature of the design for Part A.

The PK analyses will be performed on the PK data from Part A.

For each set of data, the estimate of the ratio of geometric mean for the UCB0599 film-coated tablet versus capsule (reference formulation) and for the UCB0599 encapsulated tablet versus capsule (reference formulation) treatments will be calculated along with its corresponding 90% confidence interval (CI) in order to assess the UCB0599 relative bioavailability.

Sensitivity analyses to the model above may be performed on the PK parameters, such as linear mixed effect models applied separately to the data for each new formulation versus reference formulation.

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. To that effect, a supplementary analysis will be performed using the PK parameters (C_{max}, AUC_{0-t}, and AUC_{inf}) where data from all 6 periods (normal and elevated gastric pH data) will be combined into a

single linear mixed effect model with a random intercept for participant and fixed effect categorical terms for treatment, gastric status, treatment by gastric status interaction, sequence, and period within substudy (ie, 3-level categorical variable). As before, ratios and corresponding 90% CIs will be obtained for the UCB0599 capsule, non-encapsulated tablet, or encapsulated tablet under elevated gastric pH condition versus the respective formulation under normal gastric pH condition.

9.4.2.2 Part B

The primary objective of Part B is 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.

The PK parameters (C_{max}, AUC_{0-t}, and AUC_{inf}) will be used to estimate the following:

- PK parameters for the 3 groups (Part A healthy participants, Japanese participants, and Chinese participants)
- Dose proportionality for each group, including graphical presentation

Individual concentration-time profiles will be displayed graphically on a linear-linear scale and semilogarithmic scale.

Overall geometric mean plasma concentration-time curves and corresponding 95% CIs will be displayed by group.

No formal comparison will be made.

The PK analyses will be performed on the PK data from Part B.

The plasma concentration-time profiles and PK parameters of UCB0599 will be summarized by dose level and group using descriptive statistics (number of available observations, arithmetic mean, standard deviation, geometric mean, coefficient of variation of geometric mean, median, minimum, and maximum). Values below the LLOQ will be reported with a clear sign indicating that they were below the LLOQ. Descriptive statistics of concentrations will be calculated if at least two-thirds of the individual data points are quantifiable (≥LLOQ).

Descriptive statistics will be executed for all PK parameters estimated by ethnicity and dose. For t_{max}, only the median, minimum, and maximum will be reported.

The PK descriptive statistics from Part A healthy participants who receive 180mg dose of the formulation used in Part B will be presented alongside.

Dose proportionality for C_{max}, AUC_{0-t}, and AUC_{inf} will be examined for each ethnic group and for Part A healthy participants who receive a 180mg dose of the formulation used in Part B and graphically reported. Dose proportionality could be achieved by dose normalization and log-transforming C_{max} and AUC data, in which a linear regression C_{max} versus dose and AUC versus dose will be used to assess if the slope of the regression line deviates statistically significantly from zero. If the slope is not different from zero, then it can be concluded that the PK is proportional to dose.

The co-primary PK endpoint data obtained for the UCB0599 formulation used in Part B at the 180mg dose under normal gastric pH condition for the three ethnicities (ie, N=36 participants from Part A, N=8 participants of Japanese origin, and N=8 participants of Chinese origin) will be log-transformed. As an exploratory analysis, transformed data will be combined into an Analysis

of Variance (ANOVA) model with fixed effect terms for cohort, assuming the data for each ethnicity come from a single parallel arm design. 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, and between the Chinese participants versus the Part A participants using least squares means and root mean squares of error from the model with subsequent exponential transformation.

9.4.3 Other PK endpoint analyses

9.4.3.1 Part A

The other PK parameters of UCB0599 and metabolites will be summarized by formulation and condition of gastric pH (elevated and normal) using descriptive statistics as described in Section 9.4.2.1.

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

9.4.3.2 Part B

The other PK parameters of UCB0599 and metabolites will be summarized by ethnicity and dose using descriptive statistics as described in Section 9.4.2.2.

- Other PK parameters of UCB0599: t_{max}, CL/F, Vz/F, $t_{1/2}$, C_{max}/BW/D, $AUC_{0\text{-}t}$/BW/D, and AUC_{inf}/BW/D. For t_{max}, only the median, minimum, and maximum will be reported.
- Other PK parameters of CCI [redacted] metabolites: C_{max}, t_{max}, $AUC_{0\text{-}t}$, and AUC_{inf}, and each metabolite/parent AUC ratio, as appropriate.

9.5 Planned safety and other analyses

9.5.1 Safety analyses

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

All AEs will be coded using the most recent Medical Dictionary for Regulatory Activities (MedDRA®) and characterized as pretreatment and treatment emergent according to the intake of the study medication.

The occurrence and incidence of TEAEs will be summarized by MedDRA system organ class (SOC), HLT, and preferred term (PT), and by treatment and ethnic group (for Part B only). The occurrence and incidence of TEAEs will also be summarized by maximum event intensity and by relationship to the study medication. Adverse events will be categorized by severity (mild/moderate/severe). All AEs will be listed and will include actions taken for each AE, the time of onset of the AE after dosing, and the duration of each AE. Adverse events leading to discontinuation and SAEs will also be summarized by treatment group and ethnic group. Laboratory variables and changes from Baseline will be summarized by time point and will be presented by treatment and ethnic group. For categorized values according to the reference range, shift tables from Baseline (Day -1, or Day 1 prior to first treatment) to each post-Baseline

time point will be presented for selected variables to be defined in the SAP. Values outside the reference range will be flagged in the listings.

Vital sign variables (SBP and DBP, pulse rate, respiration rate, and body temperature) and changes from Baseline (Day -1, or Day 1 prior to first treatment) will be summarized by time point and will be presented by treatment and ethnic group.

Single 12-lead ECGs will be recorded at each time point as noted in the study Schedule of Activities (Section 1.3). Descriptive statistics will be presented for ECG values and changes from Baseline (Day -1, or Day 1 prior to first treatment) over time.

See Section 9.8 for details on planned interim analyses and data monitoring.

9.6 Handling of protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct, or on the PK and key safety for an individual study participant. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and all important deviations will be identified and documented to confirm exclusion from analysis sets. All important deviations will be identified and documented to confirm exclusion from the analysis sets.

9.7 Handling of dropouts or missing data

In general, there will be no imputation of missing data. Handling of missing or partial dates and/or times for safety assessments will be described in the SAP.

9.8 Planned interim analysis and data monitoring

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.

An SMC will be established before the start of the study (as described in Section 10.1.6). During Part B, data will be examined after Cohort 3, in order to proceed to the next dose level in the Japanese and Chinese participants. Throughout the study, safety and tolerability data will be reviewed on an ongoing basis by the SMC as described in Section 4.1. A detailed description of the composition and conduct of the SMC will be provided in a separate SMC Charter.

9.9 Determination of sample size

9.9.1 Part A

To assess the relative bioavailability of 2 new formulations (film-coated tablet or encapsulated tablet) to the reference formulation (capsule) under conditions 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 (CV) 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").

9.9.2 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 a formulation of choice.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, International Council for Harmonisation (ICH)-GCP (ICH E6[R2]), and in accordance with the ethical principles that have their origin in the Declaration of Helsinki (1996).

The Investigator/UCB will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the Investigator/UCB will forward copies of the protocol, ICF, IB, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other participant related documents to be used for the study to the IRB/IEC for its review and approval.

Before initiating a study, the Investigator will have written and dated full approval from the responsible IRB/IEC for the protocol.

The Investigator will also promptly report to the IRB/IEC all changes in the study, all unanticipated problems involving risks to participants or others, and any protocol deviations, to eliminate immediate hazards to participants.

The Investigator will not make any changes in the study or study conduct without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to the participants. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the Investigator to obtain an expedited review by the IRB/IEC as allowed.

As part of the IRB/IEC requirements for continuing review of approved studies, the Investigator will be responsible for submitting periodic progress reports to the IRB/IEC (based on IRB/IEC requirements), at intervals appropriate to the degree of participant risk involved, but no less than once per year. The Investigator should provide a final report to the IRB/IEC following study completion.

UCB (or its representative) will communicate safety information to the appropriate regulatory authorities and all active investigators in accordance with applicable regulatory requirements. The appropriate IRB/IEC will also be informed by the Investigator or the Sponsor, as specified by the applicable regulatory requirements in each concerned country. Where applicable, Investigators are to provide the Sponsor (or its representative) with evidence of such IRB/IEC notification.

10.1.2 Financial disclosure

Insurance coverage will be handled according to local requirements.

Finance and insurance are addressed in the Investigator and/or CRO agreements, as applicable.

10.1.3 Informed consent process

Participant's informed consent must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the participant in both oral and written form by the Investigator (or designee). Each participant will have the opportunity to discuss the study and its alternatives with the Investigator.

Prior to participation in the study, an IRB/IEC approved, written ICF should be signed and personally dated by the participant, or his/her legal representative, and by the person who conducted the informed consent discussion (Investigator or designee). The participant or his/her legal representative must receive a copy of the signed and dated ICF. As part of the consent process, each participant must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.

If the ICF is amended during the study, the Investigator (or the Sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended ICF by the IRB/IEC and use of the amended form.

All studies conducted at centers in the United States must include the use of a Health Insurance Portability and Accountability Act authorization form.

The participant may withdraw his/her consent to participate in the study at any time. A participant is considered as enrolled in the study when he/she has signed the ICF. An eCRF must not be started, nor may any study specific procedure be performed for a given participant, without having obtained his/her written consent to participate in the study.

10.1.4 Recruitment strategy

The participants will be recruited from the volunteer database of the study center, as well as by advertisement.

10.1.5 Data protection

UCB staff (or designee) will affirm and uphold the participant's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the participant number assigned at screening.

The Investigator agrees that representatives of UCB, its designee, representatives of the relevant IRB/IEC, or representatives of regulatory authorities will be allowed to review that portion of the participant's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a participant's study participation, and autopsy reports for deaths occurring during the study).

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.6 Committees structure

An SMC will review the safety/tolerability data in this study as described in Section 4.1.

Ad hoc SMC meetings can be held for other reasons if determined appropriate by the Sponsor. At a minimum, the SMC must include the following study participants: Investigator(s), Sponsor Study Physician, Sponsor Patient Safety representative, Quantitative Clinical Pharmacologist, and Sponsor Biostatistician.

10.1.7 Dissemination of clinical study data

All Phase 1-4 clinical studies in participants will be registered on ClinicalTrials.gov with results posted after completion of the study.

A plain language summary of the results of all Phase 1-4 clinical studies will be developed and shared on UCB's website.

UCB is committed to submitting all Phase 2-4 clinical study results, irrespective of outcome, for publication in a credible, peer-reviewed journal. While there are some exceptions owing to intellectual property considerations in early clinical development, our policy is also to submit Phase 1 study results for publication in a peer-reviewed journal wherever possible.

Due to the small sample size in this study, individual patient-level data cannot be adequately anonymized as there is a reasonable likelihood that individual participants could be re-identified. For this reason, data from this study cannot be shared.

10.1.8 Data quality assurance

All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must prepare and maintain adequate and accurate documentation (source data) of all observations and other data pertinent to the clinical study for each participants that supports the information entered in the eCRF. Frequent communication between the clinical unit and the Sponsor is essential to ensure that the safety of the study is monitored adequately. The Investigators will make all appropriate safety assessments on an ongoing basis.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, legible, contemporaneous, original, complete, verifiable, and attributable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the

currently approved protocol and any other study agreements, ICH-GCP, and all applicable regulatory requirements.

All essential documents must be retained by the Investigator for the minimum retention period mandatory under the applicable local laws and regulations. The Investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The Investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the Sponsor's trial master file.

Quality tolerance limits will be established for the study using parameters related to patient safety reporting and reliability of study results. The parameters will be monitored throughout the study to identify systematic issues. Parameters used, parameter values, important deviations from the quality tolerance limits, and actions taken will be summarized in the clinical study report.

10.1.8.1 eCRF completion

The Investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRFs and in all required reports.

Any change or correction to the eCRF after saving must be accompanied by a reason for the change.

Corrections made after the Investigator's review and approval (by means of a password/electronic signature) will be reapproved by the Investigator.

The Investigator should maintain a list of personnel authorized to enter data into the eCRF.

Detailed instructions will be provided in the eCRF Completion Guidelines.

10.1.8.2 Application

Not applicable.

10.1.9 Source documents

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes).

Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x rays, laboratory results, printouts, pharmacy records, care records, ECG, or other printouts, completed scales, Quality-of-Life questionnaires, or video, for example. Source documents should be kept in a secure, limited access area.

Source documents that are computer generated and stored electronically must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated by the Investigator and become a permanent part of the participant's source documents. The Investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

10.1.10 Study and site start and closure

The start of recruitment

The start of recruitment is the first participant's first visit and is also the start date of the clinical study.

Study/site termination

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

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

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

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study medication development
- Required adaptation of the maximum insurance sum is not possible (ie, the risk/benefit estimation changes, leading to insufficient insurance coverage while the maximum insurance sum is not adapted)
- The positive evaluation or approval is withdrawn by the IEC or local health authority

The criteria for study holds due to AEs are provided in Section 8.3 and Appendix 3 (Section 10.3).

10.1.11 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical laboratory tests

- All clinical laboratory tests will be processed at the local laboratory, with only the PK samples analyzed by a central laboratory. The tests detailed in the table below will be performed:
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Protocol-required safety laboratory assessments

Laboratory Assessments	Parameters			
Hematology[a]	Platelet count Red blood cell count Hemoglobin Hematocrit	Red blood cell indices: Mean corpuscular volume Mean corpuscular hemoglobin % Reticulocytes	White blood cell count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[a b]	Blood urea nitrogen	Potassium	Aspartate Aminotransferase / Serum Glutamic-Oxaloacetic Transaminase	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase / Serum Glutamic-Pyruvic Transaminase	Total Protein
	Glucose (fasted)	Calcium	Alkaline phosphatase	
Routine Urinalysis[c]	• 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)[d] • Serology (HIV antibody, HBsAg, and hepatitis C virus antibody All study-required laboratory assessments will be performed by a central laboratory. The results of each test must be entered into the eCRF.			

Laboratory Assessments	Parameters

[a] Blood hematology and chemistry laboratory tests will be obtained in the fasting state following an overnight fast of at least 10 hours.
[b] Details of liver chemistry stopping criteria and required actions and follow up assessments after liver stopping or monitoring event are given in Section 7.1.1 and Appendix 6 (Section 10.6). All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, may indicate severe liver injury (possible Hy's Law) and must be reported as a SAE (excluding studies of hepatic impairment or cirrhosis).
[c] Urinalysis includes standard analysis, microscopy, and renal biomarker analysis. For the AKI biomarkers, analysis should be performed on the fresh urine sample. Spot analysis will be performed on either fresh urinalysis sample or 24h urine sample, as noted.
[d] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse events – Definitions and procedures for recording, evaluating, follow up, and reporting

Definition of AE

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

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

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

Definition of SAE

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

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

Recording and follow up of AE and/or SAE

AE and SAE recording
• When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information in the eCRF. • It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to UCB in lieu of completion of the UCB/AE/SAE eCRF page. • There may be instances when copies of medical records for certain cases are requested by UCB. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to UCB. • The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of intensity
The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. • An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of a SAE, NOT when it is rated as severe (eg, a severe AE may be either serious or not serious, depending on whether these criteria are also met). The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) should be used as a supportive standardization instrument to evaluate AEs and SAEs but the final intensity grading by the Investigator must be mild, moderate, or severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study medication and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study medication administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which a SAE has occurred and the Investigator has minimal information to include in the initial report to UCB. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** UCB**.**
- The Investigator may change his/her opinion of causality in light of follow up information and send a SAE follow up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by UCB to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- An AE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the participant is lost to follow up. This follow up requirement applies to AEs, SAEs, and AEs of special interest.
- If a participant dies during participation in the study or during a recognized follow up period, the Investigator will provide UCB with a copy of any post mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of SAEs

SAE reporting to UCB via an electronic data collection tool
• The primary mechanism for reporting a SAE to UCB will be the electronic data collection tool. • If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section). • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to UCB by telephone. • Contacts for SAE reporting can be found in SERIOUS ADVERSE EVENT REPORTING.

SAE reporting to UCB via paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to UCB. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in SERIOUS ADVERSE EVENT REPORTING.

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

Definitions

Woman of childbearing potential (WOCBP)

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

Women in the following categories **are not considered WOCBP**:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception guidance

Male participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in the table below when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

In addition, male participants must refrain from donating sperm for the duration of the study and for 3 months after the last dose of study medication.

Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame and for 1 week after the last dose of study medication.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below.

Highly effective contraceptive methods[a]

Highly effective contraceptive methods that are user dependent[b] Failure rate of <1% per year when used consistently and correctly.
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[c] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly effective methods that are user independent[c]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
NOTES: a) In case of newly started contraception pills/IUDs, PI should consider the correct timing of starting/applying such methods in relation to the menstrual cycle and the manufacturing instruction as to when these newly started methods would become effective. b) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. c) Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilized during the treatment period and for at least 1 week after the last dose of study treatment.

Pregnancy testing

- A WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test at the Screening Visit.
- Additional urine pregnancy testing should be performed on Day -1 and at the SFU Visit after the last dose of study medication (and as required on all other occations).
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- A positive urine test should be confirmed by a blood test with a sensitivity of 25 mIU/mL.

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study treatment. If the participant is later found to be on placebo, then pregnancy data collection can stop.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 1 working day of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow up will be at least 12 months after the delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- Any female participant who becomes pregnant while participating in the study will discontinue study medication or be withdrawn from the study.
- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 1 working day of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, the follow up will be at least 12 months after the delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be a SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study medication by the Investigator will be reported to the Sponsor as described in Section 8.3.5. While the Investigator is not obligated to actively seek this information in former participants, he or she may learn of a SAE through spontaneous reporting.

10.5 Appendix 5: Genetics

Use and analysis of DNA

- Normal inter-individual and inter-ethnic genetic variation may impact a participant's response to study medication due to how it may affect the way the body handles the drug (ie, drug absorption, distribution, metabolism, and excretion). In addition, genetic differences may also play a role in determining response to the drug, where response is defined broadly to include safety and tolerability.
- DNA samples will only be used for research related to exposure and response to UCB0599. They may also be used to develop tests/assays including diagnostic tests related to UCB0599. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to UCB0599 or study medications of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the Clinical Study Report or in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on UCB0599 continues but no longer than 20 years or other period as per local requirements.

10.6 Appendix 6: Liver safety – suggested actions and follow up assessments

Participants with PDILI must be assessed to determine if study medication must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

Investigators should attempt to obtain information on participants in the case of study medication discontinuation to complete the final evaluation.

Participants with PDILI should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for study medication discontinuation and/or participant withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for discontinuation of study medication.

A specific monitoring plan must be agreed between the UCB study physician and the Investigator for participants who have ALT >5 ULN. The monitoring plan should include any necessary follow up assessments (until resolution of the abnormal laboratory values).

Phase 1 liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology (see Section 7.1.1 and Table 10-1).

Table 10-1: Phase 1 Liver Chemistry Stopping Criteria and Follow up Assessments Table

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥3xULN If ALT ≥3xULN **AND** bilirubin ≥2xULN (>35% direct bilirubin) or INR >1.5, report as a SAE[a b] See additional actions and follow up assessments below
Required Actions and Follow up Assessments	
Actions	**Follow up Assessments**
• **Immediately** discontinue study intervention • Report the event to the Sponsor **within 24 hours** • Complete the liver event eCRF, and complete an SAE data collection tool if the event also met the criteria for an SAE[b] • Perform liver function follow up assessments • Monitor the participant until liver function test abnormalities resolve, stabilize, or return to baseline (see **MONITORING**)	• Viral hepatitis serology[c] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain blood sample for PK analysis at predose and at 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48, 72, and 96 hours after the most recent dose of UCB0599[d] • CPK and LDH • Fractionate bilirubin, if total bilirubin ≥ 2xULN

Table 10-1: Phase 1 Liver Chemistry Stopping Criteria and Follow up Assessments Table

• Consider the need for a toxicology screening. **MONITORING:** **If ALT ≥3xULN AND bilirubin ≥2xULN or INR >1.5** • Repeat liver function tests (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver function follow up assessments within **24 hours.** • Monitor participant twice weekly until liver function test abnormalities resolve, stabilize, or return to baseline. • A specialist or hepatology consultation is recommended. **If ALT ≥3xULN AND bilirubin <2xULN and INR ≤1.5:** • Repeat liver function tests (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver function follow up assessments within **24 to 72 hours** • Monitor participants weekly until liver function abnormalities resolve, stabilize, or return to baseline	• Complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE CRF • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications CRF • Record alcohol use on the liver event alcohol intake CRF **If ALT ≥3xULN AND bilirubin ≥2xULN or INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]) **NOTE: Not required in China**. • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete liver imaging and/or liver biopsy CRFs

AE=adverse event; ALT= alanine aminotransferase; AST=aspartate transaminase; CPK=serum creatine phosphokinase; CRF=case report form; HPLC=high performance liquid chromatography; IgG= immunoglobulin G; INR=international normalized ratio; LHD=lactate dehydrogenase; PK=pharmacokinetic(s); SAE=serious adverse event; ULN=upper limit of normal

[a] Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention if ALT ≥3xULN **and** bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.

[b] All events of ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN **and** INR >1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**. The INR measurement is not required and the stated threshold value will not apply to participants receiving anticoagulants.

Table 10-1: Phase 1 Liver Chemistry Stopping Criteria and Follow up Assessments Table

[c] Includes: Hepatitis A immunoglobulin M (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.

[d] PK sample may not be required for participants known to be receiving placebo or non-comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Study Reference Manual.

10.7 Appendix 7: Medical device AEs, ADEs, SAEs, and device deficiencies: Definition and procedures for recording, evaluating, follow up, and reporting

Not applicable.

10.8 Appendix 8: Rapid alert procedures

Not applicable.

10.9 Appendix 9: Country-specific requirements

Not applicable.

10.10 Appendix 10: Abbreviations and trademarks

AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	Analysis of Variance
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
ASYN	alpha synuclein
BMI	body mass index
BP	blood pressure
CI	confidence interval
CNS	central nervous system
COVID-19	Coronavirus Disease 2019
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DBP	diastolic blood pressure
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
ETV	Early Termination Visit
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HIV	immunodeficiency virus
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent form
ICH	International Council for Harmonisation

IEC	Independent Ethics Committee
IgE	immunoglobulin E
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine devices
IUS	intrauterine hormone-releasing system
LLOQ	lower limit of quantification
MedDRA®	Medical Dictionary for Regulatory Activities
PD	Parkinson's Disease
PDILI	potential drug-induced liver injury
PK	pharmacokinetic(s)
PKS	Pharmacokinetic Set
PKS A	Pharmacokinetic Set A
PKS B	Pharmacokinetic Set B
PPI	proton pump inhibitor
QD	once daily
QTcF	QT corrected for heart rate using Fridericia's formula
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SFU	Safety Follow-Up
SMC	Safety Monitoring Committee
SoC	standard of care
SOP	standard operating procedure
SS	Safety Set
TEAE	treatment-emergent adverse events
TOST	two 1-sided ratio of means tests
ULN	upper limit of normal
WOCBP	woman of childbearing potential

10.11 Appendix 11: Protocol amendment history

Not applicable.

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SPONSOR DECLARATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol, according to Clinical Trial Regulation EU 536/2014, and according to current Good Clinical Practice.

Approval Signatures

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