AN OPEN-LABEL, RANDOMIZED STUDY TO EVALUATE THE RELATIVE BIOAVAILABILITY OF A NEW TABLET FORMULATION OF MINZASOLMIN AND THE POTENTIAL EFFECT OF FOOD ON THE PHARMACOKINETICS OF MINZASOLMIN IN HEALTHY PARTICIPANTS

PROTOCOL UP0152 AMENDMENT 2

PHASE 1

SHORT TITLE:

A randomized, open-label Phase 1 study to assess the relative bioavailability of a new formulation of minzasolmin in healthy participants

Sponsor:

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Confidentiality Statement

Confidential

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Date**	**Type of amendment**
Amendment 2	08 Aug 2024	Not applicable
Amendment 1	16 May 2024	Not applicable
Original Protocol	25 Mar 2024	Not applicable

Amendment 2 (08 Aug 2024)

Overall Rationale for the Amendment

UP0152 Protocol Amendment 2 was completed to update the protocol based on Requests for Information received during the initial Clinical Trial Application.

Section # and name	Description of change	Brief rationale
Section 5.1 Inclusion criteria	Inclusion criterion #5a (previously #5) was revised to remove the strikethrough text: "~~Capable of giving s~~Signed informed consent."	To clarify the informed consent process.
Section 10.1.3 Informed consent process	In the third paragraph, the possibility that the ICF is signed and dated by a legal representative was removed.	To clarify the informed consent process.
Section 10.3.2 Definition of SAE	The first bullet point under "**c. Requires inpatient hospitalization or prolongation of existing hospitalization**" was revised to remove parenthetical text that admission usually involves at least an overnight stay.	To clarify that hospitalization signifies in-patient admission, regardless of length of stay.

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** +32 2 386 24 21 (Note: a country-specific exit code may need to be added)
Email	**Global:** DS_ICT@ucb.com

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LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
ASYN	alpha-synuclein
AUC	area under the plasma concentration-time curve from time zero to infinity
AUC%Extrap	area under the plasma concentration-time curve extrapolated from the time t to infinity as a percentage of total AUC
AUC_{0-t}	area under the plasma concentration-time curve from time 0 to t
BID	twice daily
BMI	body mass index
BP	blood pressure
CA	Competent Authority
CI	confidence interval
CL/F	apparent total body clearance
C_{max}	maximum observed plasma concentration
CRF	case report form
CRO	contract research organization
CV	coefficient of variation
DBP	diastolic blood pressure
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ETV	Early Termination Visit
EU	European Union
EUDAMED	European Database on Medical Devices
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GMR	geometric mean ratio

HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LLOQ	lower limit of quantification
MedDRA®	Medical Dictionary for Regulatory Activities
NCT number	ClinicalTrials.gov identifier
NDA	new drug application
PD	Parkinson's disease
PDILI	potential drug-induced liver injury
PK	pharmacokinetic(s)
PKS	Pharmacokinetics Set
POC	proof of concept
PR	pulse rate
QTc	corrected QT interval
QTcF	QT corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SFU	Safety Follow-Up

SoC	standard of care
SOP	standard operating procedure
SS	Safety Set
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
t_{max}	time of occurrence of C_{max}
ULN	upper limit of normal
Vz/F	apparent volume of distribution
WOCBP	woman of childbearing potential

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol title: An open-label, randomized study to evaluate the relative bioavailability of a new tablet formulation of minzasolmin and the potential effect of food on the pharmacokinetics of minzasolmin in healthy participants

Short title: A randomized, open-label Phase 1 study to assess the relative bioavailability of a new formulation of minzasolmin in healthy participants

Regulatory agency identifying numbers:

EudraCT Number:	Not applicable
EU CT Number:	2024-511301-31
EUDAMED Number:	Not applicable
IND Number:	Not applicable
IDE Number:	Not applicable
NCT Number:	Not applicable

Rationale:

A new tablet formulation has been developed for minzasolmin. The current study UP0152 is designed to evaluate the relative bioavailability of a new tablet formulation compared with the current clinical formulation (ie, granules in capsule) under fasting conditions. UP0152 will provide safety, tolerability, and pharmacokinetic (PK) information of minzasolmin in fed and fasting conditions after single oral doses of minzasolmin [redacted] administered once per period in healthy study participants. In addition, the study is also designed to evaluate the potential effect of a high-fat meal on the PK of minzasolmin when administered as tablet formulation.

Objectives, endpoints, and estimands:

Table 1–1: Objectives and endpoints

Objectives	Endpoints
Primary	
• To estimate the relative bioavailability of a new minzasolmin tablet formulation versus reference 'granules in capsule' formulation in healthy participants and to evaluate the effect of food with the new tablet formulation on the PK of minzasolmin.	Primary PK Endpoint(s) • AUC_{0-t}, AUC, and C_{max} in fasting (for both granules in capsule and tablet formulations) and fed (tablet formulation only) conditions for minzasolmin
Secondary	
• To evaluate the safety and tolerability of single-dose administration of minzasolmin in healthy participants using different formulations in fed condition (tablet formulation) and fasting condition (tablet and 'granules in capsule' formulations).	Secondary Safety Endpoint(s) • Occurrence of TEAEs • Occurrence of treatment-emergent SAEs • Occurrence of TEAEs leading to withdrawal from study
Other	
• To further evaluate the PK of minzasolmin and its [redacted] metabolites after single-dose administration with reference 'granules in capsule' formulation or the new tablet formulation in fasting (tablet and 'granules in capsule' formulations) or fed condition (tablet formulation).	Other PK Endpoints • For minzasolmin: – t_{max}, $t_{½}$, CL/F, and Vz/F (if possible but not limited) • For [redacted] metabolites: – AUC_{0-t}, AUC, C_{max}, and t_{max}, in fasting and fed conditions – metabolite/parent C_{max} and AUC ratio, as appropriate

AUC=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

Overall design:

This is a Phase 1, 3-treatment, 6-sequence, 3-period crossover, open-label study in healthy male and female participants designed to evaluate the relative bioavailability under fasting condition of a new tablet formulation when compared with the current granules in capsule formulation used in clinical studies (Treatment B and A, respectively). The study is also designed to evaluate effect of high fat meal on the PK of minzasolmin following administration of a single dose of the new tablet formulation in fed condition (Treatment C). The safety and tolerability of single-dose administration of minzasolmin will also be investigated.

Within each sequence, study participants will receive a single dose of minzasolmin ([redacted] capsules or tablets as shown in the 3 treatment conditions below) on 3 separate occasions (Day 1, Day 6, and Day 11 [Period 1, Period 2, and Period 3]):

- Treatment A: under fasting conditions [redacted] ([redacted] granules in capsules (in Period 1, Period 2, or Period 3) followed by a 4-day Washout Period
- Treatment B: under fasting conditions [redacted] tablet (in Period 1, Period 2, or Period 3) followed by a 4-day Washout Period
- Treatment C: under fed condition [redacted] tablet (in Period 1, Period 2, or Period 3) followed by a 4-day Washout Period

The order of the 3 treatment conditions received will differ between each sequence.

Number of participants:

A maximum of 18 healthy participants will be randomized in this study.

Study duration:

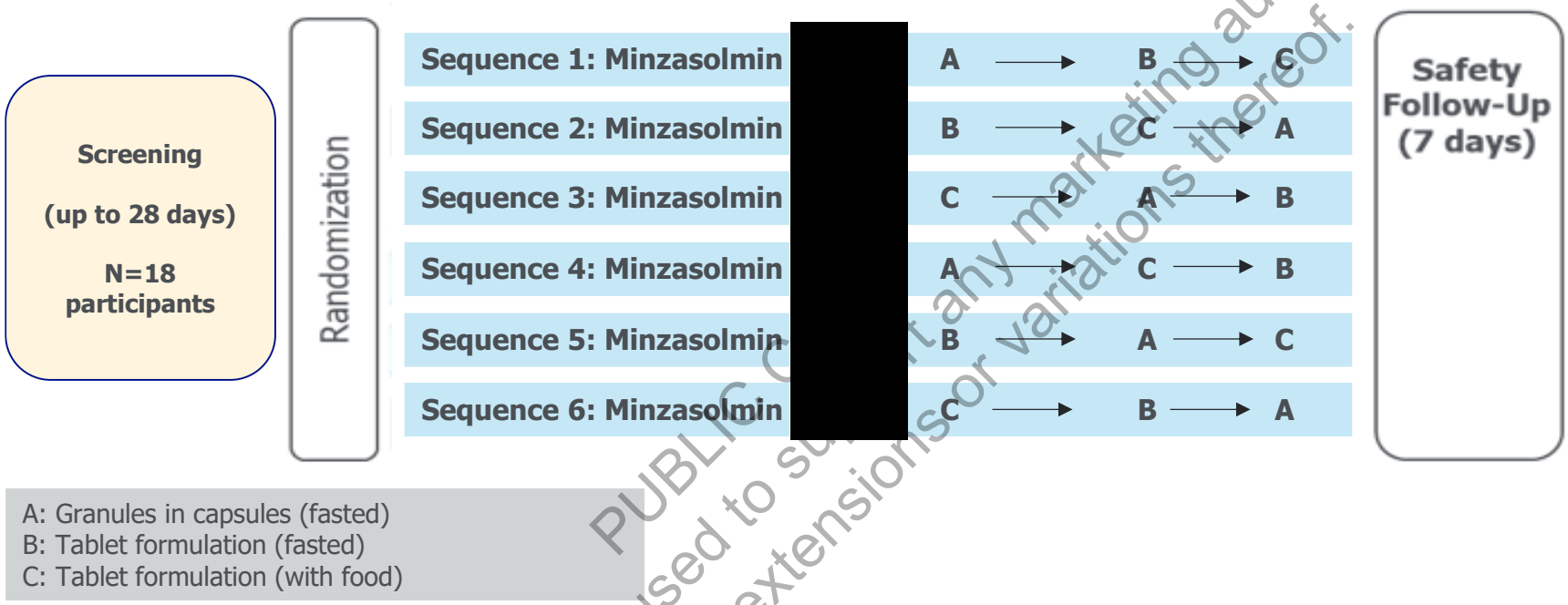
The maximum study duration will be 48 days, including the Treatment Period and the Safety Follow-Up (SFU) Period. There are 3 study periods in this study:

- Screening Period: Eligibility will be assessed during the Screening Period (up to 28 days). Treatment must be started as soon as possible for participants who have fulfilled the eligibility criteria.
- Treatment Period: Participants who have been confirmed eligible will be randomized to receive open-label single doses of minzasolmin [redacted] on Days 1, 6, and 11 with a 4-day Washout Period between doses.
- Safety Follow-Up Period: Study participants will have SFU procedures performed within 5 to 9 days after final dose. Participants who prematurely withdraw from the study will return to the clinic center for the Early Termination Visit (ETV) as soon as possible after the time of withdrawal and will have all SFU procedures performed.

Data monitoring/Other committee: No

1.2 Schema

Figure 1–1: Study schematic



ETV=Early Termination Visit; SFU=Safety Follow-Up

Note: Participants who have been confirmed eligible will be randomized to receive single doses of minzasolmin [redacted] with a 4-day Washout Period between doses.

Note: Study participants will have SFU procedures performed within 5 to 9 days after their final dose. Participants who prematurely withdraw from the study will return to the study clinic center for the ETV as soon as possible after the time of withdrawal and will have all SFU procedures performed.

1.3 Schedule of Activities

Procedure	Screening		Treatment Period A, B and C[a]							SFU[b]/ETV
			In-Clinic Period							
	D -28 to -2	D -1	D1[c]	D2-5	D6[c]	D7-10	D11[c]	D12-14	D15	D18 (±2 days)
Informed consent	X									
Verification of inclusion/exclusion criteria	X	X								
Verification of withdrawal criteria			X	X	X	X	X	X	X	
Demography (height, weight, BMI)	X									
Physical examination	X	X	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X
General medical/procedure history	X									
Blood pregnancy test (WOCBP only)	X	X								X
Laboratory assessments (hematology, clinical chemistry, urinalysis, and FSH and estradiol)[e]	X	X		X (D5)		X (D10)			X	X
SARS-CoV-2 testing (PCR)		X								

Procedure	Screening		Treatment Period A, B and C[a]							SFU[b]/ETV
			In-Clinic Period							
	D -28 to -2	D -1	D1[c]	D2-5	D6[c]	D7-10	D11[c]	D12-14	D15	D18 (±2 days)
Viral serology (HBsAg, HCV-Ab, HIV, and HBcAb)	X									
Urine cotinine, drug screen and urine alcohol test	X	X								
12-lead ECG[f]	X	X			X		X		X	X
Vital signs[g]	X	X	X		X		X		X	X
Randomization		X								
Minzasolmin administration			X		X		X			
Adverse event review	X	X	X	X	X	X	X	X	X	X
Prior- and concomitant medication review	X	X	X	X	X	X	X	X	X	X
Blood sampling for PK[h]			X	X	X	X	X	X	X	
Blood sampling for exploratory genetic biomarkers (DNA)		X								
Meals[i]		X	X	X	X	X	X	X		
Confinement		X	X	X	X	X	X	X		

Procedure	Screening		Treatment Period A, B and C[a]							SFU[b]/ETV
			In-Clinic Period							
	D -28 to -2	D -1	D1[c]	D2-5	D6[c]	D7-10	D11[c]	D12-14	D15	D18 (±2 days)
Discharge									X	

BMI=body mass index; D=day; DBP=diastolic blood pressure; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ETV=Early Termination Visit; FSH=follicle stimulating hormone; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HCV-Ab=hepatitis C virus antibody; HIV=human immunodeficiency virus; PCR=polymerase chain reaction; PK=pharmacokinetic(s); PR=pulse rate; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SBP=systolic blood pressure; SFU=Safety Follow-Up; WOCBP=women of childbearing potential

[a] Each participant will attend 3 Treatment Periods. Participants will be in the clinical center for the whole Treatment Period A, B and C.

[b] Study participants will have SFU procedures performed within 5 to 9 days after final dose. Participants who prematurely withdraw from the study will return to the clinic center for the ETV as soon as possible after the time of withdrawal and will have all SFU procedures performed.

[c] Clinical assessments performed on Days 1, 6, and 11 need to be performed predose.

[d] Complete physical examinations will be performed during Screening, at Day -1, and at SFU/ETV. Symptom-directed physical examinations will be performed during Treatment Periods.

[e] Blood hematology and chemistry laboratory tests will be obtained in the fasting state following an overnight fast of at least 10 hours. Hepatic function tests only will also be performed 24 hours before each dosing (ie, Day 5 and Day 10). Note that FSH and estradiol will only be determined for females at the Screening Visit.

[f] 12-lead ECG will be performed in single after a rest in supine position for at least 10 minutes before recordings, but can be repeated in triplicate if clinically indicated.

[g] SBP, DBP, respiration rate, PR, and body temperature. Vital signs will be performed after a rest of at least 5 minutes.

[h] The PK sampling timepoints will be: predose and at 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48, 72, and 96h after minzasolmin administration on Day 1, Day 6, and Day 11.

[i] Study participants will receive standard meals and snacks at appropriate times indicated by the clinic center, except when they are required to fast. All participants fast overnight for at least 10 hours before minzasolmin administration. Participants in Treatment A and B continue fasting for at least 4 hours after minzasolmin administration. Thereafter they receive a standard lunch. Fed study participants (Treatment C) should start the recommended high-fat high-calorie meal 30 minutes before administration of minzasolmin. Study participants should eat this meal in 30 minutes or less; however, minzasolmin should be administered 30 minutes after start of the meal. No food should be allowed for at least 4 hours postdose. During the rest of the day, study participants receive standard meals and snacks at appropriate times indicated by the clinic center.

2 INTRODUCTION

2.1 Study rationale

A new tablet formulation is developed for minzasolmin, which is planned to be used in future studies and for commercialization purpose. The current study UP0152 is designed to evaluate the relative bioavailability of a new tablet formulation compared with the current clinical formulation (ie, granules in capsule) under fasting condition. In addition, the study is also designed to evaluate the potential effect of a high-fat meal on the pharmacokinetics (PK) of minzasolmin when administered as tablet formulation.

2.2 Background

Parkinson's disease (PD) 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 alpha-synuclein (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.

Minzasolmin is an orally available inhibitor of ASYN misfolding and downstream ASYN aggregation. Aggregated forms of ASYN are the hallmark fibrillar protein deposits in PD and other synucleinopathies, and evidence suggests that the misfolded forms of ASYN propagate through the central nervous system during disease progression. The accumulation of ASYN forms neuronal inclusions referred to as Lewy bodies and Lewy neurites. In vivo and nonclinical pharmacology data suggest minzasolmin may slow neurodegeneration in PD, resulting in slower disease progression, thus providing a therapeutic benefit to patients with PD.

Minzasolmin 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 minzasolmin. The pharmacokinetics (PK) of minzasolmin has been well characterized following administration of single and multiple doses in healthy volunteers and patients with PD (UP0030, UP0023, TM0017, UP0077, UP0078). Minzasolmin is rapidly absorbed following administration of single ([redacted] or multiple doses ([redacted]) with maximum plasma concentration were attained within 1.5 to 2 hours and had moderate to extensive tissue

distribution. The apparent terminal elimination half-life ($t_{½}$) of minzasolmin at single doses of [redacted] has been found to be approximately 11 to 13 hours. In general, the maximum observed plasma concentration (C_{max}) and area under the plasma concentration-time curve from time zero to infinity (AUC) increased in an approximately dose-proportional manner after a single dose ([redacted]) and multiple doses ([redacted]). In the dose range evaluated, minzasolmin follows linear kinetics (no change in apparent total body clearance [CL/F] and apparent volume of distribution [Vz/F] was observed), and steady state was achieved by Day 7 following multiple dose administration. The PK of minzasolmin were also comparable between healthy volunteers and patients with PD (UP0030 and UP0077). Minzasolmin had an acceptable safety and tolerability profile (UP0023, UP0030, TM0017, and UP0077).

The effect of food has been evaluated with granules in capsule in the previous study UP0078. Food intake delays gastric emptying as expected thereby increasing t_{max} (1.5 hour to 3 hour). The rate and extent of minzasolmin absorption (C_{max} and AUC, respectively) were not impacted by food. The point estimates for the geometric least squares mean ratio of fed/fasting calculated for minzasolmin C_{max} and AUC were 104.5% and 109.4%, respectively. The elimination rates were similar between the fed and fasting groups for minzasolmin and its metabolites.

Minzasolmin is currently being tested in an ongoing Phase 2a study (PD0053), its extension study (PD0055), and an ongoing Phase 1 study (UP0073). 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 a benefit to the study population, ie, healthy study participants. This study will provide relevant PK and clinical safety information to support minzasolmin new tablet formulation development.

A summary of possible risks and adverse reactions is provided in the IB based on a review of adverse event (AE) data from 98 study participants exposed to minzasolmin in completed clinical studies UP0030 (51 participants), TM0017 (4 participants), UP0077 (21 participants), and UP0078 (22 participants), and based on the review of safety data in the ongoing clinical studies UP0073 (42 participants), and PD0053 and its extension study PD0055 conducted in approximately 490 participants (from PD0053).

Overall, the majority of treatment-emergent adverse events (TEAEs) observed in clinical studies with minzasolmin to date 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 minzasolmin in UP0077. A causal relationship between the reported events of hypersensitivity and minzasolmin is considered plausible. Hypersensitivity reactions are considered an important identified risk for minzasolmin and are further described in the IB.

There have been no reports of anaphylaxis in the minzasolmin clinical program.

Of all the adverse drug reactions reported in completed minzasolmin clinical studies, based on the frequency of occurrence, all are considered common (≥1% and <10%).

In the ongoing Phase 2 study (where participants are receiving daily doses of Study Drug for 18 months), of the 496 participants, 8 reports of aspartate aminotransferase (AST) and/or alanine transaminase (ALT) elevations >3x upper limit of normal (ULN) (of which 2 were >10xULN)

have been received. In the majority of reports, the transaminase elevations were noted 2 to 3 months after the first dose of study medication. None of the reports had an increase in bilirubin or international normalized ratio (INR) and none met Hy's law criteria. Transaminase values decreased spontaneously without study drug discontinuation in 3 participants or after discontinuation of the drug in 5 participants.

As a consequence, monthly routine liver function tests should now be conducted during the first 6 months of treatment for study participants who receive multiple doses of Study Drug. The protocol contains relevant safety monitoring activities for hepatic effects as well as instructions for the management of patients with hepatic enzyme elevations.

To minimize the risks for study participants, the study team at UCB and the contracted contract research organization (CRO) will continue to closely monitor study participants, systematically review safety data and minzasolmin exposure data.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of minzasolmin may be found in the IB.

3 OBJECTIVES AND ENDPOINTS

Table 3–1: Objectives and endpoints

Objectives	Endpoints
Primary	
• To estimate the relative bioavailability of a new minzasolmin tablet formulation versus reference 'granules in capsule' formulation in healthy participants and to evaluate the effect of food with the new tablet formulation on the PK of minzasolmin.	Primary PK Endpoint(s) • AUC_{0-t}, AUC, and C_{max} in fasting (for both granules in capsule and tablet formulation) and fed (tablet formulation only) conditions for minzasolmin
Secondary	
• To evaluate the safety and tolerability of single-dose administration of minzasolmin in healthy participants using different formulations in fed condition (tablet formulation) and fasting condition (tablet and 'granules in capsule' formulation).	Secondary Safety Endpoint(s) • Occurrence of TEAEs • Occurrence of treatment-emergent SAEs • Occurrence of TEAEs leading to withdrawal from study
Other	
• To further evaluate the PK of minzasolmin and its [redacted] metabolites after single-dose administration with reference 'granules in capsule' formulation or the new tablet formulation in fasting (tablet and 'granules in capsule' formulation) or fed condition (tablet formulation).	Other PK Endpoints • For minzasolmin: – t_{max}, $t_{½}$, CL/F, and Vz/F (if possible but not limited) • For [redacted] metabolites: – AUC_{0-t}, AUC, C_{max} and t_{max}, in fasting and fed conditions – metabolite/parent C_{max} and AUC ratio, as appropriate

AUC=area under the plasma concentration-time curve from 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); $t_{½}$=apparent terminal elimination half-life; SAE=serious adverse event; 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

UP0152 is an open-label, randomized, 3-treatment, 6-sequence, 3-period crossover study in healthy male and female participants designed to evaluate relative bioavailability under fasting condition of a new tablet formulation when compared with the current granules in capsule formulation used in clinical studies (Treatment B and A, respectively). The study is also designed to evaluate effect of high fat meal on the PK of minzasolmin following administration of a single dose of the new tablet formulation in fed condition (Treatment C). Eighteen participants will be randomized in the study to ensure a minimum of 2 completers in each of the 6 sequences. The study consists of a Screening Period of up to 28 days, a baseline health status assessment (on Day -1) and 3 Treatment Periods with washout periods between the treatments. 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. Participants will return to the clinic to complete the SFU Visit assessments 7 days (±2 days) after the final dose (Table 4–1).

Table 4–1: Relative bioavailability of minzasolmin under fasting and fed condition (3-treatment, 6-sequence, 3-period crossover design)

Sequence	Period 1	Washout	Period 2	Washout	Period 3	Washout	Discharge	SFU
Day	**D1**	**D2-5**	**D6**	**D7-10**	**D11**	**D12-15**	**D15**	**D18 (±2 days)**
1 (ABC)	A		B		C			
2 (BCA)	B		C		A			
3 (CAB)	C		A		B			
4 (ACB)	A		C		B			
5 (BAC)	B		A		C			
6 (CBA)	C		B		A			

D=day; SFU=Safety Follow-Up
Note: A: Granules in capsule (fasting); B: Tablet formulation (fasting); C: Tablet formulation (fed).

4.2 Scientific rationale for study design

A new tablet formulation is developed for minzasolmin, which is planned to be used in future studies and for commercialization purpose. The current study UP0152 is designed to evaluate the relative bioavailability of a new tablet formulation compared with the current clinical formulation (ie, granules in capsule) under fasting condition. In addition, the study is also designed to evaluate the potential effect of a high-fat meal on the PK of minzasolmin when administered as tablet formulation. A crossover study design was selected as it provides more robust comparison between different formulations and fed conditions as each participant will receive all study treatments. Six sequences were implemented in order to balance the allocation of treatments across study periods.

The half-life of minzasolmin and its 2 metabolites ([redacted]) are 11, 10 and 16 hours, respectively (see the IB for further details). Considering 5 half-lives for elimination of the drug, the 4 days washout is considered adequate for the study. In study UP0073, a similar design and washout period was used, and carryover (<5% of C_{max}) was observed in only few participants. The t_{max} for minzasolmin and the [redacted] metabolites were 1.5, 2.0, and 2.0 hours, respectively (see the IB for further details).

UP0152 will provide safety, tolerability, and PK information of minzasolmin formulations in fed condition (tablet formulation) and fasting condition (tablet and 'granules in capsule' formulation) after single oral doses of minzasolmin [redacted] administered once per period in healthy study participants.

4.2.1 Patient input into design

Not applicable.

4.3 Justification for dose

The rationale for testing the proposed dose level of minzasolmin [redacted] in healthy participants is based on the data from previously conducted studies (UP0030, UP0077, and UP0078) and doses currently being explored in the Phase 2 proof of concept (POC) study PD0053 and the Phase 1 study UP0073. UP0030 showed that minzasolmin exposures increase linearly (both AUC and C_{max}) across the tested dose range ([redacted], single dose). UP0030 also evaluated [redacted] twice daily (BID) for 21 days in elderly healthy study participants to assess the safety/tolerability, and PK following multiple doses. UP0077 provided the safety, tolerability, and PK information of minzasolmin for multiple-dose administration of [redacted] and [redacted] in study participants with PD for 28 days. The collective data from UP0030 and UP0077 further showed that exposure after multiple dosing is predictable from single-dose data and that the dose-exposure relationship is similar between healthy study participants and study participants with PD.

In addition, doses of [redacted] BID and [redacted] BID are being evaluated in the POC study PD0053 in participants with PD. In the study, [redacted] BID is the highest expected therapeutic dose being evaluated. Considering linear kinetics and dose proportionality between [redacted] doses of minzasolmin, the highest dose evaluated in the Phase 2 study is proposed for the current study. This dose also provides the opportunity to compare exposure of minzasolmin across previously conducted Phase 1 studies (UP0030, UP0077, UP0078, and UP0073).

The selection of minzasolmin [redacted] to evaluate the food effect is in line with the Guidance for Industry "Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations" (Food and Drug Administration, Guidance for Industry, 2022) where it is recommended using the highest dose to be marketed for this assessment.

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 5 to 9 days after final dose).

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 informed consent form (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.

Weight

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

Sex and contraceptive/barrier requirements

4. Male and female.

   - 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 final dose of study intervention, and refrain from donating sperm during this period.
   - A female participant is eligible to participate if she is not pregnant (see Appendix 4 [Section 10.4]), not breastfeeding (including pumping breastmilk to feed a child), and at least 1 of the following conditions applies:
     - Not a woman of childbearing potential (WOCBP) as defined in Appendix 4 (Section 10.4).

       OR
     - A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 (Section 10.4) during the Treatment Period and for at least 1 week after the final dose of study intervention.

Informed consent

5a. Signed informed consent as described in Appendix 1 (Section 10.1.3) 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 any history of cancer in the past 10 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 a history of chronic alcohol abuse (more than 24g [males] or 12g [females] per day; 12g pure alcohol are contained in approximately 300mL of beer (5%), 1 small glass [125 mL] of wine [12%], or 1 measure [40mL] of spirits [37.5%]) or drug abuse within the last 1 year from Screening, as defined according to the Diagnostic and Statistical Manual of Mental Disorders.
5. Participant has a history of smoking within 3 months before Screening.
6. Participant has a known hypersensitivity to any components of the study intervention or comparative drugs as stated in this protocol.
7. 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 value above normal range at screening).
8. Study participant has a consumption of more than 600mg of caffeine/day at study entry 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).
9. Study participant has consumed cruciferous vegetables (eg, Brussel sprouts, broccoli, cabbage, cauliflower) within 7 days before administration of minzasolmin or is not willing to refrain from consuming these products for the duration of the study.
10. Study participant has consumed any grapefruit, grapefruit juice, grapefruit-containing products, or star fruit within 14 days before administration of minzasolmin or is not willing to refrain from consuming these products for the duration of the study.
11. Participant has a positive test result for severe acute respiratory syndrome coronavirus 2using reverse transcription polymerase chain reaction.

Prior/Concomitant therapy

12. Study 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 minzasolmin. This does not include paracetamol/acetaminophen, ibuprofen, or oral contraceptives not exceeding 30µg ethinyl estradiol or postmenopausal hormonal replacement therapy (HRT) or implants, patches, or intrauterine devices/intrauterine hormone-releasing systems (IUDs/IUSs) delivering progesterone (for female study participants) (see Section 6.9.1).

Prior/Concurrent clinical study experience

13. Participant has previously participated in this study or participant has previously been assigned to intervention in a study of the medication under investigation in this study.
14. Participant has participated in another study of an investigational medicinal product (IMP) (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 IMP (and/or an investigational device).

Diagnostic assessments

15a. Participant has any clinically relevant abnormal findings in physical examination or laboratory tests or a value outside the normal range for vital signs (systolic blood pressure 90-139mmHg, diastolic blood pressure 50-89mmHg, or pulse rate 50-90bpm), which, in the opinion of the investigator, may place the participant at risk because of participation in the study.

16a. Participant has ALT, AST, or alkaline phosphatase (ALP) >1.0x ULN.

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

17. Participant has total bilirubin >1.0xULN. Bilirubin >ULN and ≤1.5xULN is acceptable if fractioned and direct bilirubin <35%, and if a baseline diagnosis of Gilbert's syndrome is understood and recorded in ClinBase.
18. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
19. 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 Protocol Section 7.1.2).

    In addition, any study participant with any of the following findings will be excluded at Screening:

    - QT interval corrected for heart rate using Fridericia's formula >450 msec for males and >470msec for females
    - other conduction abnormalities (defined as PR interval ≥220ms)
    - irregular rhythm other than sinus arrhythmia or occasional, rare supraventricular, and rare ventricular ectopic beats
20. Study participant has a medical history or current diagnosis of renal impairment and/or Screening laboratory results show:

- An estimated glomerular filtration rate <90 mL/min/1.73m^2 (using the Chronic Kidney Disease Epidemiology Collaboration formula)
- An albumin/creatinine ratio ≥30mg/mmol
- Urinary tract infection; in this case a study participant can be rescreened once the infection has been resolved
- Clinically significant electrolyte abnormalities

21. Presence of hepatitis B surface antigen (HBsAg) [or hepatitis B core antibody (HBcAb) immunoglobulin M], indicative of active hepatitis B, at Screening or within 3 months before first dose of study intervention.
22. Positive hepatitis C antibody test result at Screening or within 3 months before starting study intervention. NOTE: Participants with positive hepatitis C antibody test results due to prior resolved disease can be enrolled only if a confirmatory negative hepatitis C ribonucleic acid test is obtained.
23. Positive human immunodeficiency virus (HIV) antibody test.

Other exclusion criteria

24. Participants who have a history of confirmed gastric ulceration.
25. Vulnerable study participants (eg, participants kept in detention, protected adults under guardianship or trusteeship, and soldiers or participants committed to an institution by governmental or juridical order), employees of the sponsor or the CRO with direct involvement in the proposed study or other studies under the direction of the investigator or the CRO, as well as family members of the employees or the investigator.
26. Participant has donated blood or experienced blood loss >350mL within the last 1 month before the first IMP administration.

5.3 Lifestyle restrictions

5.3.1 Meals and dietary restrictions

- Study participants receive standard meals and snacks at appropriate times indicated by 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 before Screening and dosing. Participants in Treatment Period A and B continue fasting for at least 4 hours after dosing. Thereafter they receive a standard lunch. Fed study participants (Treatment C) should start the recommended high-fat high-calorie meal within 30 minutes before dosing. Study participants should eat this meal in 30 minutes or less; however, minzasolmin should be administered 30 minutes after start of the meal. No food should be allowed for at least 4 hours postdose. During the rest of the day, study participants receive standard meals and snacks at appropriate times indicated by the clinic center. Please refer to the dosing instructions in Table 6–1.
- Intake of xanthine (eg, caffeine) containing food or beverages must be discontinued 48 hours before first dosing. Consumption of such foods and beverages (ie, coffee, tea, soda,

chocolate) is not permitted at any time while the participants are confined. 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 before first dosing until study completion. If a deviation occurs, it must be noted in the database.
- No grapefruit-containing products and star fruit are to be consumed for 14 days before first dosing until 7 days following the final dose. If a deviation occurs, it must be noted in the database.

5.3.2 Caffeine, alcohol, and tobacco

The following restrictions related to caffeine, alcohol, tobacco are applicable for this study:

- No alcohol for 48 hours before first dosing until after end of study evaluation
- No cannabis use for 4 weeks before screening until after study completion
- No cigarettes/use of nicotine products from screening until after study completion

5.3.3 Activity

The following restriction related to activity is applicable for this study:

- No strenuous physical exercise (eg, weight training, aerobics, football) within 48 hours before admission until study completion

5.3.4 Other restrictions

Not applicable.

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 intervention. 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 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).

Individuals who do not meet the criteria for participation in this study (screen failure) 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 INTERVENTIONS/INVESTIGATIONAL DEVICE AND CONCOMITANT THERAPY

Study interventions are all prespecified, investigational and noninvestigational medicinal products, medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

6.1 Study interventions administered

Table 6–1: Study interventions administered

Arm name	Minzasolmin [redacted] capsules under fasting conditions	Minzasolmin [redacted] tablet under fasting conditions	Minzasolmin [redacted] tablet under fed conditions
Intervention name	A	B	C
Type	Drug	Drug	Drug
Dose formulation	Granules in oral capsules	Oral film-coated tablets	Oral film-coated tablets
Unit dose strength(s)	[redacted]		
Dosage level(s)	[redacted] SD: 2 capsules of [redacted]	[redacted] SD: 1 tablet of [redacted]	[redacted] SD: 1 tablet of [redacted]
Dosing instructions	During Treatment A, a single [redacted] dose of minzasolmin will be administered under fasting conditions, according to the randomization scheme. Participants will have an overnight fast of at least 10h before dosing. Minzasolmin should be administered with 240mL (8 fluid ounces) of water. No food should be allowed for at least 4h postdose. Water can be allowed as desired except for 1h before and 1h after drug administration. Study participants should receive standardized meals scheduled at the same time in each period of the study.	During Treatment B, a single [redacted] dose of minzasolmin will be administered under fasting conditions, according to the randomization scheme. Participants will have an overnight fast of at least 10h before dosing. Minzasolmin should be administered with 240mL (8 fluid ounces) of water. No food should be allowed for at least 4h postdose. Water can be allowed as desired except for 1h before and 1h after drug administration. Study participants should receive standardized meals scheduled at the same time in each period of the study.	During Treatment C, a single [redacted] dose of minzasolmin will be administered under fed (standard high-fat, high-calorie meal) conditions, according to the randomization scheme. Participants will have an overnight fast of at least 10h before dosing. Participants should start the recommended meal within 30 minutes before administration of minzasolmin. Study participants should eat this meal in 30 minutes or less; however, minzasolmin should be administered 30 minutes after start of the meal. Minzasolmin should be administered with 240mL (8 fluid ounces) of water. No food should be allowed for at least 4h postdose. Water can be allowed as desired except for 1h before and 1h after drug administration. Study participants should receive standardized

Table 6–1: Study interventions administered

			meals scheduled at the same time in each period of the study.
Route of administration	Oral	Oral	Oral
Use	Experimental	Experimental	Experimental
IMP and NIMP/AxMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and labeling	Minzasolmin capsules are manufactured, packaged, and labeled according to GMP guidelines and applicable laws or regulations.	Minzasolmin tablets are manufactured, packaged, and labeled according to GMP guidelines and applicable laws or regulations.	Minzasolmin tablets are manufactured, packaged, and labeled according to GMP guidelines and applicable laws or regulations.
Comment		Tablet formulation without fumaric acid	Tablet formulation without fumaric acid
Current/Former name	UCB0599	UCB0599	UCB0599

AxMP=auxiliary medicinal product; GMP=Good Manufacturing Practice; IMP=investigational medicinal product; NIMP=non-investigational medicinal product; SD=single dose

6.2 Preparation, handling, storage, and accountability

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

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention. All study interventions 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), or authorized site staff is responsible for study intervention 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 IMP Handling Manual.

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

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

6.2.1 Drug accountability

Dispensing of study intervention will be documented in ClinBase to record study intervention dispensing on a by-participant basis and will serve as source documentation during the course of the study. Details of any study intervention lost, damaged (due to breakage or wastage), not used, partially used, or disposed of at the study site 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 intervention until destroyed.

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

The investigator must ensure that the study intervention 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 intervention must be reconciled and destroyed at the site according to local laws, regulations, and UCB standard operating procedures (SOPs). Study intervention intended for the study cannot be used for any other purpose than that described in this protocol.

6.3 Assignment to study intervention

Randomization numbers will be assigned at the site in an unblinded fashion and will be entered into ClinBase.

6.4 Blinding

This is an open-label study. Blinding will not be performed.

6.5 Study intervention compliance

For all study participants, minzasolmin will be administered at the study site.

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.6 Dose modification

There is no dose modification allowed in UP0152.

6.7 Continued access to study intervention after the end of the study

There will be no access to study intervention after the end of the study.

6.8 Treatment of overdose

For all study participants, minzasolmin will be administered at the study site. No treatment for overdose is recommended by UCB and treatment for overdose should be at the discretion of the principal investigator.

6.9 Concomitant medication(s)/treatment(s)

6.9.1 Permitted concomitant therapy (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
- Oral contraceptives not exceeding 30µg ethinyl estradiol or postmenopausal HRT or implants, patches, or IUDs/IUSs delivering progesterone (for female study participants)

6.9.2 Prohibited concomitant therapy (medications and therapies)

Concomitant medications are not allowed with the exceptions listed in Section 6.9.1.

6.9.3 Rescue medication

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

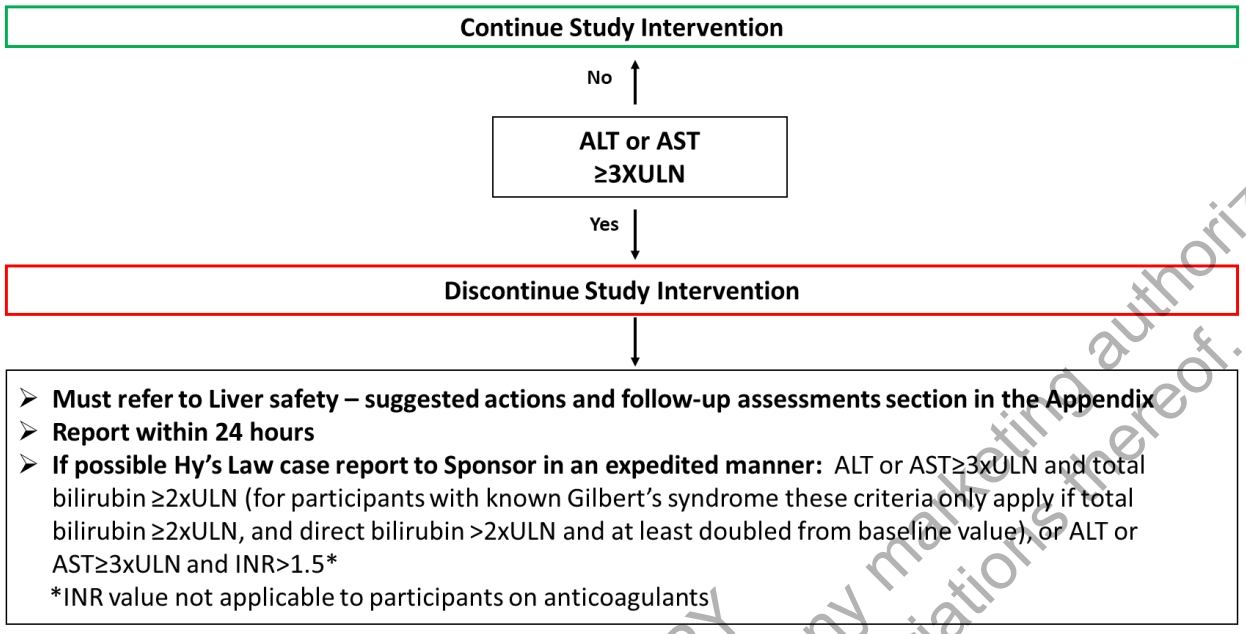
7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of study intervention

7.1.1 Liver chemistry stopping criteria

Study intervention will be discontinued immediately and permanently for a participant if liver chemistry stopping criteria are met.

Figure 7–1: Phase 1 liver chemistry stopping algorithm



ALT=alanine aminotransferase; AST=aspartate aminotransferase; INR=international normalized ratio; 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 Corrected QT interval stopping criteria

A participant who meets either bulleted criterion based on single 12-lead ECG readings will be withdrawn from the study. 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) before the exclusion of the participant.

- QTcF >500ms OR Uncorrected QT >600ms
- Change from Baseline (Day -1, before first treatment, Day 6, and Day 11) of QTcF >60ms

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 participant can continue on the study intervention and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically significant finding should be reported as an AE.

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

7.1.3 Temporary discontinuation

Study participants may be temporarily discontinued from study intervention (but not necessarily from the study) if there is a positive pregnancy test. Refer to Section 8.4.5 for additional procedures related to pregnancy in a study participant.

7.1.4 Hypersensitivity reaction stopping criteria

Study participants will be informed that if they develop any symptoms suggestive of a 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 via the SAE reporting form.

7.1.5 Study stopping criteria

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:

- A pattern of AEs, considered as related to the study drug, occurs that in the opinion of the investigator and/or UCB Study Physician contraindicates the further dosing of additional study participants.
- If the sponsor or its designee judges it necessary for medical, safety, regulatory, or any other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP).

Where it is possible to do so without threatening the safety of study participants, such discontinuation/suspension should be discussed with the UCB Study Physician before its implementation.

7.2 Participant discontinuation/withdrawal from the study

A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).

A participant may withdraw at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

At the time of discontinuing from the study, if possible, an ETV should be conducted, as shown in the Schedule of Activities (Section 1.3). See Schedule of Activities for data to be collected at the time of study discontinuation and follow up and for any further evaluations that need to be completed.

The participant will permanently discontinue from the study intervention and the study at that time.

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, the participant 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 must 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 withdraws his/her consent.
3. The sponsor or a regulatory agency requests withdrawal of the participant.
4. Participant has a confirmed positive serum pregnancy test.

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

1. Participant is noncompliant with the study procedures or medications in the opinion of the investigator.
2. Participant takes prohibited concomitant medications as defined in this protocol.

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

Investigators should contact the study physician, whenever possible, to discuss the withdrawal of a study participant in advance.

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, 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 ClinBase 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 ClinBase.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Activities (Section 1.3).

Protocol waivers or exemptions are not allowed.

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.

In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution, and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.

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 Administrative and general/baseline procedures

Participant's informed consent (see Section 10.1.3) and general medical/procedure history will be obtained at the Screening Visit. Baseline procedures including urine cotinine test, drug screen, urine alcohol test, and verification of inclusion/exclusion criteria will be performed at the Screening Visit and on Day -1. Prior and concomitant medication will be reviewed at all visits throughout the study.

8.2 Efficacy assessments

Not applicable.

8.3 Safety assessments

Planned time points for all safety assessments are provided in the Schedule of Activities (Section 1.3).

8.3.1 Physical examination

Physical examinations will be performed at the scheduled time points presented in Section 1.3.

A complete physical examination will include, at a minimum, general appearance; ears, 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 be performed in case of emerging symptoms. 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 should pay special attention to clinical signs related to previous serious illnesses.

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

8.3.2 Vital signs

Vital signs, including heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate, and aural temperature will be measured after 5 minutes of rest in a supine position (in a quiet setting without distractions such as a television or cell phones). Heart 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 consist of 3 heart rate and 3 blood pressure (BP) measurements (3 consecutive BP readings will be recorded at intervals of at least 1 minute). The average of the 3 BP readings will be recorded in ClinBase.

8.3.3 Electrocardiograms

A single 12-lead ECG will be obtained as outlined in the Schedule of Activities (Section 1.3) - but can be repeated in triplicate if clinically indicated - using an ECG machine that automatically calculates the heart 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 ClinBase: heart rate, PR-interval, QRS-duration, QT-interval, QTcF, and investigator's conclusion on ECG profile.

8.3.4 Clinical safety laboratory tests

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and refer to the Schedule of Activities (Section 1.3) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be filed with the source documents.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7 days after SFU/ETV should be repeated until the values return to normal or Baseline (Day -1, or Day 1 before first treatment) or are no longer considered clinically significant by the investigator or UCB Study Physician.

If clinically significant values do not return to normal/Baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

All protocol-required laboratory tests, as defined in Appendix 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 tests performed at the institution's local laboratory require a change in participant management or are considered clinically

significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded.

8.3.5 Pregnancy testing

Refer to Appendix 4 (Section 10.4) for pregnancy testing guidelines.

8.4 AEs, SAEs, and other safety reporting

The definitions of AEs and SAEs can be found in Appendix 3 (Section 10.3).

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 intervention, or that caused the study participant to discontinue minzasolmin (see Section 10.3). This includes events reported by the participant.

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

8.4.1 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 or ETV (if applicable) at the time points specified in the Schedule of Activities (Section 1.3) and must be reported in the ClinBase even if no study intervention was taken but specific study procedures were conducted. This includes all AEs not present before the initial visit and all AEs that recurred or worsened after the initial visit.

All SAEs will be recorded and reported to the UCB Study Physician or designee immediately and under no circumstance should this exceed 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.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

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).

8.4.2 Method of detecting AEs and SAEs

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

8.4.3 Follow up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each study participant at subsequent visits/contacts. All AEs, and SAEs, will be followed until resolution, stabilization, the investigator determines that it is no longer clinically significant, the event is

otherwise explained, or the study 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).

8.4.4 Regulatory reporting requirements for SAEs

Prompt notification of an SAE by the investigator to the sponsor is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

Further to the reporting of an SAE from the investigator to the sponsor, an expectedness assessment will be made per the IB, as reference safety information for this study, and relevant sponsor's SOPs, and appropriate reporting of suspected unexpected serious adverse reactions (SUSARs) will be carried out to health authorities as per International Council for Harmonisation (ICH) and local regulatory requirements. Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

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

8.4.5 Pregnancy

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

If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the pregnancy, and should follow the procedures outlined in Appendix 4 (Section 10.4).

While pregnancy itself is not considered to be an AE, any pregnancy will need to be reported. In some circumstances, a pregnancy report is considered as an SAE: miscarriage, elective abortion when medically indicated (eg, when pregnancy is endangering life or health of woman or when fetus will be born with severe abnormalities), unintended pregnancy after hormonal contraceptive failure (if the hormonal contraceptive was correctly used), ectopic pregnancy, fetal demise, or any congenital anomaly/birth defect of the baby.

The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate, and the information will be forwarded to the sponsor.

Any poststudy pregnancy-related SAE in either the mother or the neonate considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in

former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention and return for an ETV as described in the Schedule of Activities (Section 1.3).

If the study participant decides to completely withdraw from the study, an SFU visit should be scheduled 5 to 9 days after the final dose of study intervention.

The investigator must inform the participant of any known potential risks the study intervention may have to the mother and/or the developing fetus/infant as well as any available treatment alternatives.

The investigator should discuss with the participant the possibility of continuing study participation by attending the scheduled visits for assessments as their condition allows but without the participant continuing study intervention. Protocol-specified blood sample collection will be adapted as indicated in the Schedule of Activities (Section 1.3) considering the study participant's condition during the study. The tests or assessments that are considered contraindicated during the pregnancy should not be performed. Caution is required with respect to concomitant medication if not contraindicated in pregnancy. As indicated, investigators are advised to discuss the case with the sponsor study physician to gain feedback on protocol-defined actions.

8.4.6 Adverse events of special interest

An adverse event of special interest (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 or associated medical device.For minzasolmin, the following events require immediate reporting (within 24 hours regardless of seriousness) to UCB:

- Possible Hy's Law (as per Section 7.1.1)
  - 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)

8.4.6.1 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 8.4.6. This will allow for rapid evaluation.

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

8.4.6.1.1 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 8.4.6.1.1.1.

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.

8.4.6.1.1.1 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 include 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 is indicated by 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 is indicated by 2 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).

8.4.6.1.2 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, DBP, 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.

8.4.6.1.3 Additional investigations

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

- 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.

8.4.6.1.4 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.

8.4.6.1.5 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 immunoglobulin E).

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).

8.4.6.1.6 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 or signs, or both.

8.5 Safety signal detection

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

As appropriate for the stage of development and accumulated experience with the study intervention, 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.

8.6 Pharmacokinetics

Pharmacokinetic sampling will be mandatory for study participation.

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).

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.

Plasma samples (approximately 2mL whole blood collection) will be used to measure minzasolmin and its metabolite plasma concentration and derive the primary PK parameters (Table 3–1). The derived PK parameters will be used to evaluate the relative bioavailability of the new minzasolmin tablet formulation versus reference granules in capsule formulation in healthy participants and to evaluate the effect of food with the new tablet formulation on the PK of minzasolmin.

Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual for this study. Collection of these samples will enable evaluation of relevant pharmacological information to support minzasolmin formulation development and food affects.

8.6.1 Use of residual plasma samples

Any residual and/or surplus PK plasma samples remaining after the protocol-defined 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.

8.7 Biomarkers

Blood sampling for exploratory genetic biomarkers 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 Immunogenicity assessments

Immunogenicity assessments including the assessment of antibodies to minzasolmin are not applicable in this study.

8.9 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). The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1 Analysis sets

9.1.1 Study Participant Set

All study participants who signed the ICF.

9.1.2 Randomized Set

The Randomized Set consists of all study participants who are randomized, regardless of whether the participant received investigational intervention. Of note, this set will only be produced if it differs from the Safety Set (SS).

9.1.3 Safety Set

The SS consists of all study participants who randomized and received full or partial study medication according to the treatment that the participants actually received. Participants who have data documenting they did not administer investigational intervention, even if received, are excluded from the SS.

9.1.4 Pharmacokinetics Set

The Pharmacokinetics Set (PKS) consists of all study participants in the SS who have at least 1 observable PK concentration data point and who have no important protocol deviations affecting the PK during the study.

9.2 Statistical analyses

9.2.1 General consideration

All analyses will be performed using SAS® version 9.4 or later (SAS Institute, Cary, North Carolina, United States).

9.2.1.1 Pharmacokinetic parameter calculation

For calculation of the plasma PK parameters of minzasolmin and metabolites, the actual sampling time points will be used to evaluate the PK parameters (Table 9–1).

The following PK parameters will be determined using the actual recorded sampling times and noncompartmental method(s) with Phoenix WinNonlin® (Version 8.3.4), as applicable: area under the plasma concentration-time curve from time 0 to t (AUC_{0-t}), AUC, C_{max}, t_{max}, $t_{½}$, CL/F (minzasolmin), Vz/F (minzasolmin), C_{max} metabolite to parent ratio, and AUC metabolite to parent ratio from the plasma concentration-time data.

Additional parameters (eg, AUC%Extrap, Lambda_z (λz)) will be calculated as appropriate.

Table 9–1: Noncompartmental PK parameters for minzasolmin in plasma

PK Parameter	Definition
AUC	The area under the plasma concentration-time curve from time zero to infinity (mass * time * volume^{-1}).
AUC_{0-t}	The AUC from time zero to the last measurable drug concentration sampling time (t_{last}) (mass * time * volume^{-1}).
C_{max}	The maximum (peak) observed drug concentration following a single dose administration (mass * volume^{-1}).
t_{max}	The time to reach maximum (peak) drug concentration following a single dose administration (time).
$t_{½}$	The elimination half-life associated with the terminal slope (λ_z) of a semi logarithmic 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 plasma concentration-time curve extrapolated from the time t to infinity as a percentage of total AUC.

Table 9–1: Noncompartmental PK parameters for minzasolmin in plasma

PK Parameter	Definition
Rsq_adj[c]	Square of the correlation coefficient (adjusted for the number of data points included) associated with λ_z.
MRC_{max}[d]	C_{max} metabolite to parent ratio.
MRAUC[d]	AUC metabolite to parent ratio.

[a] For minzasolmin only.
[b] AUC%Extrap was listed if AUC was presented.
[c] Rsq_adj was listed only.
[d] Metabolites only. Pharmcokinetic parameters will be derived after noncompartmental analysis.

The linear trapezoidal rule will be used for estimation of area under the curve (AUC and AUC_{0-t}). Regression analysis of the terminal plasma elimination phase for the determination of $t_{½}$ 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 0.8 or the AUC%Extrap value is greater than 20%, no value is to be reported for AUC, $t_{½}$, CL/F, and Vz/F.

9.2.2 Primary endpoints analysis

PK analyses will be performed on the PKS.

The plasma concentration-time profiles and PK parameters of minzasolmin will be summarized by formulation and feeding condition (fed vs fasting) using descriptive statistics (number of available observations, arithmetic mean, standard deviation, geometric mean, coefficient of variation (CV) of geometric mean, median, interquartile range, 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).

Individual concentration-time profiles will be displayed graphically on a linear-linear scale and on a semilogarithmic scale. Overall geometric mean plasma concentrations-time curves and corresponding 95% confidence intervals (CIs) will be displayed by formulation and feeding condition (fed vs fasting).

9.2.2.1 Definition of endpoint(s)

The primary PK parameters are AUC_{0-t}, AUC, and C_{max} for minzasolmin.

The primary comparisons of interest are:

- Tablet versus granules in capsule under fasting condition
- Tablet under fed condition versus tablet under fasting condition

9.2.2.2 Main analytical approach

9.2.2.2.1 Estimation of geometric mean ratios

Following log-transformation, the primary PK parameters (AUC_{0-t}, AUC, and C_{max}) will each be evaluated using a linear mixed effect model with a random intercept term for study participant

and fixed effect categorical terms for Treatment (3 formulation x feeding conditions), Sequence, and Period to account for the crossover nature of the study design.

Two separate analysis of variance (ANOVA) models, (1) one including data for the new formulation versus the reference formulation under the fasting condition and (2) the other one including data for the new tablet formulation under fed condition versus the tablet formulation under fasting condition will be used to align with the assumptions made for conditional power estimations (see Section 9.4 below).

The estimate of the geometric mean ratio (GMR) and associated 90% CI for the tablet (test) versus the capsule (reference) formulations given under fasting condition will be derived using the first ANOVA model in order to assess the minzasolmin relative bioavailability between the 2 formulations.

The estimate of the GMR and associated 90% CI for the tablet under fed condition (test) versus the tablet under fasting condition (reference) treatment will be derived using the second ANOVA model in order to assess the food effect.

Other sensitivity analyses may also be performed on the PK parameters, such as a common ANOVA model including all data.

9.2.3 Other PK endpoint analysis

The other PK parameters of minzasolmin and metabolites will be summarized by formulation and feeding condition (fed vs fasting) using descriptive statistics as below:

- For minzasolmin: 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 [redacted] metabolites: C_{max}, t_{max}, AUC_{0-t}, AUC, and each metabolite/parent C_{max} and AUC ratio (corrected for the molecular weight of the entities), as appropriate.
- Additional analyses of PK parameters might be conducted as appropriate.

9.2.4 Secondary safety endpoints analysis

Secondary safety endpoints in this study are the occurrence of TEAEs, treatment-emergent SAEs, and the occurrence of TEAEs leading to withdrawal from the study.

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 pre-treatment and treatment-emergent according to the intake of the IMP.

The occurrence and incidence of TEAEs will be summarized by MedDRA system organ class and preferred term and by treatment group. 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). Adverse events leading to discontinuation and SAEs will also be summarized by treatment group. 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.

9.2.4.1 Exploratory safety endpoints analysis

Laboratory variables and changes from Baseline (Day -1, or Day 1 before first treatment) will be summarized by time point and will be presented by treatment group. For categorized values according to the reference range, shift tables from Baseline 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, DBP, PR, respiration rate, and body temperature) and changes from Baseline (Day -1, or Day 1 before first treatment) will be summarized by time point and will be presented by treatment group.

The single 12-lead ECG will be recorded as timepoints defined in schedule of activities. Descriptive statistics will be presented for ECG values and changes from Baseline (Day -1, before first treatment, Day 6, and Day 11) through treatment periods.

9.3 Interim analysis

No interim analysis or data monitoring is planned for this study.

9.4 Sample size determination

The plan is to randomize 18 participants into the study; dropouts are assumed to be minimal and will not be replaced.

Conditional power was estimated for the key comparisons of interest based on the Primary PK Objective.

Primary comparison:

- To assess noninferiority of the AUC_{0-t} of a new tablet formulation versus the reference 'granules in capsule' formulation in fasting state (relative bioavailability)

Secondary comparison:

- To assess noninferiority of the AUC_{0-t} of a new tablet formulation in fed state versus the same formulation in fasting state (food effect)

Other comparisons:

- To assess nonsuperiority of the C_{max} of a new tablet formulation versus the reference 'granules in capsule' formulation in fasting state (relative bioavailability)
- To assess nonsuperiority of the C_{max} of a new tablet formulation in fed state versus the same formulation in fasting state (food effect)

The assessments were based on a one-sided noninferiority t-test, calculated exact via noncentral t-distribution for a 2-treatment 2-period crossover design for continuous response data on the log scale with significance level of 0.05 (5%), assuming:

- A ratio of geometric means (ρ) between the new tablet formulation and the reference formulation under the alternative hypothesis (H1) of 1.0 for AUC_{0-t} or 0.95 for C_{max}
- A lower margin of 0.8 for noninferiority and 1.25 for nonsuperiority

- A geometric intra-participant CV based on estimates of the residual variance obtained from linear mixed effect models (ANOVA) applied to the log-transformed AUC_{0-t} and C_{max} data from UP0073, a minzasolmin Phase 1 study with similar participant demographics (males and females aged 18 to 55 years) which used a crossover design

Relative bioavailability comparisons:

For the assessment of noninferiority of the AUC_{0-t} or the assessment of nonsuperiority of the C_{max}, for the new tablet formulation versus the reference 'granules in capsule' formulation, the estimates of variability were based on the UP0073 2-by-2 ANOVA models comparing the (nonencapsulated) fumaric acid tablet to the 'granules in capsule' formulation under condition of normal gastric pH (ie, relevant treatment periods from UP0073 Part A).

This assumes homogenous variance for the 2 different formulations under fasting condition.

Food effect comparisons:

For the assessment of noninferiority of the AUC_{0-t} or the assessment of nonsuperiority of the C_{max}, for the new tablet formulation under fed state versus the fasting state, the estimates of variability were based on the UP0073 2-by-2 ANOVA models comparing the encapsulated fumaric acid tablet to the (nonencapsulated) fumaric acid tablet formulations under condition of normal gastric pH (ie, relevant treatment periods from UP0073 Part A).

This assumes homogenous variance for the encapsulated and the nonencapsulated forms of the fumaric acid tablet, homogenous variance for the nonencapsulated tablet with or without fumaric acid, and homogenous variance for the fed and fasting states of the new tablet.

Analyses were performed using the function power.noninf from the R package PowerTOST (https://CRAN.R-project.org/package=PowerTOST).

For the primary treatment comparison of interest, 12 completers would provide over 96% power to assess noninferiority of the AUC_{0-t} conditional on the GMR being 1.0. For a GMR of 0.95 (equivalent to the GMR observed in UP0073 for the fumaric acid tablet versus the 'granules in capsule' formulation), power would be 85% for 12 completers, 92% power for 15 completers and 96% for 18 completers.

For the secondary treatment comparison of interest, 12 completers would provide over 99% power to assess noninferiority of the AUC_{0-t} conditional on the GMR being 0.95, equivalent to the GMR observed in UP0073 for the encapsulated fumaric acid tablet versus (nonencapsulated) fumaric acid tablet.

Details of the conditional power estimations can be found in the "UP0152 sample size documentation form" located in the sample size folder of the electronic trial master file.

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 a Competent Authority (CA) and/or IRB/IEC, as defined in local regulations, ICH-GCP, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

UCB/the investigator will ensure that a CA and 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. Before 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/CA for their review and approval.

Before initiating a study, the investigator will have written and dated full approval from the responsible IRB/IEC/CA 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. UCB will submit relevant information to the CA in accordance with regulatory requirements.

The investigator/UCB will not make any changes in the study or study conduct without IRB/IEC/CA 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/UCB to obtain an expedited review by the IRB/IEC/CA, as allowed.

As part of the IRB/IEC/CA requirements for continuing review of approved studies, the investigator will be responsible for submitting periodic progress reports to the IRB/IEC according to local requirements and UCB will be responsible for submitting periodic progress reports to the CA, 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 and UCB should provide a final report to the CA following study completion.

UCB (or its representative) will communicate safety information to the appropriate regulatory authorities/CA 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.

Before 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.

Before participation in the study, the ICF should be signed and personally dated by the participant and by the person who conducted the informed consent discussion (investigator or designee). The participant 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.

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. A ClinBase entry 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 clinic center, as well as by advertisement.

10.1.5 Data protection

UCB staff (or designee) will affirm and uphold the participant's confidentiality. Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

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 will be informed how his/her personal data collected in the study will be used by the sponsor and that it will be used in accordance with local data protection laws. The level of disclosure will also be explained to the participant.

The participant will 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.

The personal data of the investigator and any site staff involved in the study will be processed by UCB in accordance with the UCB Data Protection Notice for Healthcare Professionals available at https://www.ucb.com/Privacy-policy-for-Healthcare-Professionals.

The contract between UCB or its designee and study sites specifies responsibilities of the parties and the timelines related to data protection, including handling of data security breaches and respective communication and cooperation of the parties in order to mitigate any possible deleterious consequences for the participants.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.6 Committees structure

No Safety Monitoring Committee will be included in this study.

10.1.7 Dissemination of clinical study data

This study will be registered and results posted on public registries as required and in line with UCB policies. A plain language summary of results may also be written. Investigators may request access to anonymized individual participant-level data and redacted study documents after product approval in the United States and Europe. However, once the study completes, if the risk of re-identifying study participants is determined to be too high, then individual participant-level data will not be made available.

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

A summary of the results is planned to be posted to the EU database within 1 year of study completion, in accordance with international standards and irrespective of the outcome of the clinical study.

10.1.8 Data quality assurance

All participant data relating to the study will be recorded on printed case report form (CRF) or in ClinBase 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 signing the CRF or electronically signing in ClinBase.

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 participant that supports the information entered in the ClinBase. 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.

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

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

UCB assumes accountability for actions delegated to other individuals (eg, CROs).

Study monitors will perform ongoing source data verification to confirm that data entered into ClinBase by authorized site personnel are accurate, legible, contemporaneous, original, 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 before 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 ClinBase completion

The investigator is responsible for prompt reporting of accurate, complete, and legible data in ClinBase and in all required reports.

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

10.1.8.2 Apps

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). Photocopies and/or printouts of CRFs are not considered acceptable source documents.

The investigator must maintain accurate documentation (source data) that supports the information entered in ClinBase.

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.

Electronic data records, such as Holter monitor records or electroencephalogram records, must be saved and stored as instructed by UCB (or designee).

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 or 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:

For study termination:

- Discontinuation of further study intervention development.

For site termination:

- 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 or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator.
- Individual recruitment goal for site reached earlier than expected.
- 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.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow up.

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 below in Table 10–1 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.

Table 10–1: Protocol-required safety laboratory tests

Laboratory tests	Parameters			
Hematology[a]	Platelet count RBC count Hemoglobin Hematocrit		RBC indices: Mean corpuscular volume Mean corpuscular hemoglobin %Reticulocytes	WBC count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical chemistry[a,b]	Blood urea nitrogen	Potassium	AST/serum glutamic-oxaloacetic transaminase[c]	Total and direct bilirubin[c]
	Creatinine	Sodium	ALT/serum glutamic-pyruvic transaminase[c]	Total protein
	Glucose (fasting)	Calcium	ALP[c, d]	Creatine phosphokinase, Lactate dehydrogenase, serum aldolase, Cystatin C
	Coagulation (INR, PT, and aPTT)	Estimated glomerular filtration rate[e]		
Routine urinalysis	• Specific gravity • Albumin/creatinine ratio • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Upon a positive urine test from leucocytes, blood, nitrite, or protein, the investigator may require further urine analysis, such as flow cytometry. Results of additional urine analyses			

Table 10–1: Protocol-required safety laboratory tests

Laboratory tests	Parameters
	will be included in the database. If the flow cytometry examination shows a different result than the urine sticks, the urine will be investigated by fully automated digital imaging where leucocytes, erythrocytes, casts in urine will be analyzed.
Pregnancy testing	• Highly sensitive serum human chorionic gonadotropin pregnancy test (as needed for women of childbearing potential)
Other screening tests	• Total immunoglobulin E test • Urine alcohol and cotinine test • Follicle stimulating hormone and estradiol (females only) • Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines, creatinine [to exclude dilution of urine samples]) • Serology (HIV antibody, HBsAg, HCV-Ab, and HBcAb [IgG and IgM]) The results of each test must be entered into ClinBase.

ALP=alkaline phosphatase; ALT=alanine aminotransferase; aPTT=activated partial prothrombin time; AST=aspartate aminotransferase; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HCV-Ab=hepatitis C virus antibody; HIV=human immunodeficiency virus; IgG=immunoglobulin G; IgM=immunoglobulin M; INR=international normalized ratio; PT=prothrombin time; RBC=red blood cell; ULN=upper limit of normal; WBC=white blood cell

[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 are given in Section 7.1.1 and Section 10.6. All events of ALT [or AST] ≥3 × ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT [or AST] ≥3 × ULN and INR >1.5, (if INR measured) which may indicate severe liver injury (possible Hy's Law), must be reported to UCB in an expedited manner (excluding studies of hepatic impairment or cirrhosis).

[c] The following parameters are part of hepatic function testing: ALP, ALT, AST, and bilirubin.

[d] If ALP is elevated, consider fractionating.

[e] Estimated glomerular filtration rate, based on the Chronic Kidney Disease Epidemiology Collaboration 2021 equation, only at screening.

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

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- 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 intervention.

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, or more severe than expected for the participant's condition).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention 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 intervention 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 <u>not</u> meeting the AE definition

- Any abnormal laboratory findings or other abnormal safety assessments that 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 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 pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:

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 admitted 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 pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant 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) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that 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, invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions not resulting in hospitalization, or development of intervention dependency or intervention abuse.

10.3.3 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.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to UCB in lieu of completion of the ClinBase.
- 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:

  A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

- Moderate:

  A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

- Severe:

  A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. 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 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 intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- 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.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. There may be situations in which an 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 their opinion of causality in light of follow-up information and send an 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 postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed ClinBase.
- The investigator will submit any updated SAE data to UCB immediately and under no circumstance should this exceed 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to UCB via paper data collection tool

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- 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 follicle stimulating hormone (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 nonestrogen 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 during the protocol-defined time frame in Section 5.1:

- 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 WOCBP 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 final dose of study intervention.

Male participants with a pregnant or breastfeeding (including pumping breastmilk to feed a child) 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 final 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 10–2 below.

Table 10–2: Highly effective contraceptive methods[a]

Highly effective contraceptive methods that are user dependent[b,c,d] Failure rate of <1% per year when used consistently and correctly.
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[c,d] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly effective methods that are user independent[c,d]
• Implantable progestogen only hormonal contraception associated with inhibition of ovulation • IUD • 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 intervention. 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.

IUD=intrauterine device; IUS=intrauterine hormone-releasing system; WOCBP=woman of childbearing potential

[a] In case of newly started contraception pills/IUDs, the principal investigator 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] If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

[d] Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In this case, male condoms must be used in addition to hormonal contraception during the Treatment Period and for at least 1 week after the final dose of study intervention.

Pregnancy testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test at the Screening Visit.
- Additional pregnancy testing should be performed on Day -1 and at the SFU Visit after the final dose of study intervention and as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Pregnancy testing, with a sensitivity of 25 mIU/mL will be performed.

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 intervention. If the study 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 intervention.
- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Upon notification of a pregnancy, the investigator must immediately (within 24 hours) notify UCB's Patient Safety department by entering all pregnancy information on the appropriate pregnancy paper forms provided by UCB. 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 via an update to ClinBase. 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, any pregnancy will need to be reported to UCB Patient Safety. In some circumstances a pregnancy-related AE or outcome should be considered as an SAE: miscarriage, elective abortion when medically indicated (eg, when pregnancy is endangering life or health of mother or when fetus will be born with severe abnormalities), unintended pregnancy after hormonal contraceptive failure (if the hormonal contraceptive was correctly used), ectopic pregnancy, fetal demise, or any congenital anomaly/birth defect of the baby. Any post-study pregnancy-related SAE in either the mother or the neonate considered reasonably related to the study intervention by the investigator will

be reported to the sponsor as described in Section 8.4.5. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

10.5 Appendix 5: Genetics

Use and analysis of deoxyribonucleic acid (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.
- Deoxyribonucleic acid samples will only be used for research related to exposure and response to minzasolmin. They may also be used to develop tests/assays including diagnostic tests related to minzasolmin. Genetic research may consist of the analysis of 1 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 minzasolmin 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 minzasolmin 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 intervention 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 study participants in the case of study intervention discontinuation to complete the final evaluation.

Study 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 intervention discontinuation and/or participant withdrawal (if applicable), must be recorded in the source documents. ClinBase must document the primary reason for discontinuation of study intervention.

A specific monitoring plan must be agreed between the study physician and the investigator for study 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 10–3).

Table 10–3: 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 ClinBase, 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**) • Consider the need for a toxicology screening.	• 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 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48, 72, and 96 hours after minzasolmin administration[d] • CPK and LDH • Fractionate bilirubin, if total bilirubin ≥ 2xULN

Table 10–3: Phase 1 liver chemistry stopping criteria and follow up assessments table

MONITORING: **If ALT ≥3xULN AND bilirubin ≥2xULN or INR >1.5** • Repeat liver function tests (include ALT, AST, ALP, 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, ALP, 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 • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) • Record alcohol use **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 assay, when available, to assess potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week. **NOTE: Not required in China**. • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease

AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=serum creatine phosphokinase; HBsAg=hepatitis B surface antigen; HBcAb=hepatitis B core antibody; HPLC=high performance liquid chromatography; IgG=immunoglobulin G; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PK=pharmacokinetic(s); RNA=ribonucleic acid; 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.

[c] Includes: Hepatitis A 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 noncomparator interventions. Record the date/time of the PK blood sample draw and the date/time of the final dose of study intervention before the PK blood sample draw. If the date or time of the final dose is unclear, provide the participant's best approximation. If the date/time of the final cannot be approximated OR a PK sample cannot be collected in the

Table 10–3: Phase 1 liver chemistry stopping criteria and follow up assessments table

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: Device adverse events (AEs), adverse device effects (ADEs), serious adverse events (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: Protocol amendment history

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

10.10.1 Amendment 1 (16 May 2024)

Overall Rationale for the Amendment

UP0152 Protocol Amendment 1 was completed to clarify protocol procedures.

Section # and name	Description of change	Brief rationale
Title page – Regulatory agency identifying number(s) table and Section 1.1 Regulatory agency identifying numbers table	The EU CT Number was updated to remove trailing zeros.	Administrative change.
Section 1.3 Schedule of Activities	Physical examination: Footnote 'd' was moved from the assessment name to each X in the Treatment Period (D1, D2-5, D6, D7-10, D11, D12-14; D15).	To clarify protocol procedures.
	Blood pregnancy test (females only) was changed to Blood pregnancy test (**WOCBP** only).	To align with Appendix 2 Table 10-1.
	Laboratory assessments: The parenthetical addition to the assessment name was updated to include estradiol to align with Table 10-1.	To clarify protocol procedures.
	Laboratory assessments: Xs were added for D5 and D10; refer to the related update of footnote 'e' below.	To clarify protocol procedures.
	SARS-CoV-2 testing (PCR): Testing was removed from Screening (D -28 to -2) and will only be done at D -1.	To clarify protocol procedures.
	Footnote 'd': Day -1 was added to complete the list of time points for the complete physical examination.	Minor correction to align with the Schedule of Activities.
Section 1.3 Schedule of Activities	The second sentence in footnote 'e' was updated to clarify when hepatic function tests will be done.	To clarify protocol procedures.

Section # and name	Description of change	Brief rationale
	A third sentence was added to footnote 'e' to provide the following clarification: Note that FSH and estradiol will only be determined for females at the Screening Visit.	To clarify protocol procedures.
Section 5.2 Exclusion criteria	Exclusion criterion #15a (previously #15) was updated to include normal ranges for vital signs.	To clarify eligibility criteria.
	Exclusion criterion #16a (previously #16) was updated to remove text on hepatic enzyme baseline results >ULN that do not apply.	To clarify eligibility criteria.
Section 5.4 Screen failures	The second paragraph was updated to note that participants who are screen failures may be rescreened **once** at the discretion of the investigator.	To clarify protocol procedures.
Section 7.1.1 Liver chemistry stopping criteria	Introductory text to Figure 7-1 was updated to clarify that study intervention will be discontinued immediately and permanently for a participant if liver chemistry stopping criteria are met.	To clarify liver chemistry stopping criteria and align with current UCB protocol template.
Section 7.1.2 Corrected QT interval stopping criteria	Discontinuation criteria for participants with underlying bundle branch block were removed.	To remove discontinuation criteria that do not apply in a healthy volunteer study.
Section 7.2 Participant discontinuation/withdrawal from the study	The criteria for participant withdrawal from the study were separated into those for which participants **must** be withdrawn and those for which participants **should** be withdrawn.	To clarify protocol procedures.
Section 8 STUDY ASSESSMENTS AND PROCEDURES	A paragraph referring to the participant's routine clinical management was removed.	To remove text that does not apply in a healthy volunteer study.
Section 8.1 Administrative and general/baseline procedures	In the second sentence, 'viral serology (HBsAg, hepatitis C virus antibody, HIV, and HBcAb)' was removed from the list of Baseline procedures done at Screening and Day -1 (only done at Screening).	To align with the schedule of activities.

Section # and name	Description of change	Brief rationale
Section 8.3.1 Physical examination	In the fourth paragraph, the assessment of skin, lungs, cardiovascular system, and abdomen (liver and spleen) was removed as a minimum requirement for symptom-directed physical examination in case of emerging symptoms.	To clarify protocol procedures.
Section 8.3.2 Vital signs	The first sentence was updated to remove the reference to 'a completely automated device.' This only applies to heart rate and blood pressure, as noted in the second sentence, and not to all vital signs measurements.	Minor correction.
Section 8.4.5 Pregnancy	The seventh paragraph was updated to remove text on continuing in the study off treatment.	To remove a protocol procedure that does not apply to the study.
Section 8.4.6.1.5 Blood sampling	The second sentence in the first paragraph on specific laboratory parameters to be collected at baseline (Day -1) was removed.	To remove a protocol procedure that does not apply to the study.
Section 8.7 Biomarkers	Text on biomarkers was inadvertently deleted during protocol development and was added back to the protocol.	Correction.
Section 10.1.8.1 ClinBase completion	The section was updated to remove procedures that do not apply for reporting in ClinBase.	To remove procedures that do not apply to the study.
Section 10.1.9 Source documents	The fourth paragraph about printed source documents was removed.	To remove procedures that do not apply to the study.
Section 10.2 Appendix 2: Clinical laboratory tests Table 10-1: Protocol-required safety laboratory tests	Clinical chemistry: A new footnote 'c' was added to ALP, ALT, AST, and bilirubin to identify the parameters included in hepatic function tests. Subsequent footnotes were renumbered.	To clarify protocol procedures.
Section 10.2 Appendix 2: Clinical laboratory tests Table 10-1 Protocol-required safety laboratory tests	Clinical chemistry: The parenthetical addition for glucose was updated to clarify this will be assessed in the fasting state throughout. The enzyme name of 'phosphokinase' was corrected to 'Creatine phosphokinase.'	Minor corrections.

Section # and name	Description of change	Brief rationale
	Other screening tests: The parenthetical addition for 'Follicle stimulating hormone and estradiol' was changed to 'females only' to align with the Schedule of Activities. Creatinine was removed as separate bullet and integrated into the urine drug screen (to exclude dilution of urine samples).	Minor clarifications.
	In footnote 'e' (previously 'd') the year 2021 was added in the reference to the equation for the estimated glomerular filtration rate.	Minor clarification.
	Footnote 'f' (previously 'e') was removed because the information is already included in the table.	To remove an unnecessary footnote.
Section 10.3.4 Reporting of SAEs	Text on reporting of SAEs via facsimile was removed.	To remove protocol procedures that do not apply to the study.
Section 10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information	Text on **Female participants who become pregnant** was updated to clarify that pregnancy information is entered on the appropriate forms provided by UCB, not in ClinBase.	To clarify protocol procedures.
Section 10.6 Appendix 6: Liver safety – Suggested actions and follow-up assessments Table 10-3 Phase 1 liver chemistry stopping criteria and follow up assessments table	Text on the serum acetaminophen adduct assay was updated. The cited literature reference of James et al, 2009 was removed from the REFERENCES section (not listed separately).	To allow for flexibility in the assay used.
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized.

11 REFERENCES

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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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