PROTOCOL EP0101 AMENDMENT 2

AN OPEN-LABEL, SINGLE-ARM STUDY TO EVALUATE THE PHARMACOKINETICS AND SAFETY OF A SINGLE AND MULTIPLE ORAL DOSES OF BRIVARACETAM IN HEALTHY ADULT CHINESE SUBJECTS

PHASE 1

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Protocol/Amendment number	Date	Type of amendment
Final Protocol	26 Sep 2016	Not applicable
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STUDY CONTACT INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve from 0 to infinite time
$AUC_{(0-12),ss}$	area under the curve from 0 to 12 hours at steady state
$AUC_{(0-t)}$	area under the plasma concentration-time curve from zero to the time of the last measured concentration above the limit of quantification
bpm	beats per minute
BRV	brivaracetam
$C_{av,ss}$	average plasma concentration at steady state
CDMS	clinical data management system
CI	confidence interval
CL/F	apparent total body clearance
CL_{ss}/F	apparent total body clearance at steady state
C_{max}	maximum plasma concentration
$C_{max,ss}$	maximum plasma concentration at steady state
$C_{min,ss}$	minimum plasma concentration at steady state
CPM	Clinical Project Manager
CPMP	Committee for Proprietary Medicinal Products
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
CV	coefficient of variation
CYP	cytochrome P450
DBP	diastolic blood pressure
DEM	Data Evaluation Meeting
ECG	electrocardiogram
eCRF	electronic Case Report form
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HRT	hormone replacement therapy

ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
IUD	intrauterine device
λ_z	rate constant of elimination
MedDRA®	Medical Dictionary for Regulatory Activities
MRT	mean residence time
OTC	over-the-counter
PD	pharmacodynamic(s)
PDILI	potential drug-induced liver injury
PK	pharmacokinetic(s)
PK-PPS	Pharmacokinetic Per-Protocol Set
PS	Patient Safety
PTF	peak trough fluctuation
R_{AUC}	accumulation ratio calculated from AUC at steady state and AUC after single dose
R_{max}	accumulation ratio calculated from C_{max} at steady state and C_{max} after single dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
SFU	Safety Follow-Up
SOP	Standard Operating Procedure
SPD	Specification of Protocol Deviations
SS	Safety Set
SV2A	synaptic vesicle protein 2A
$t_{½}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
t_{max}	time to reach maximum plasma concentration
ULN	upper limit of normal
V_z/F	apparent volume of distribution

1 SUMMARY

Brivaracetam (BRV) is a drug with a structure of a 2-pyrrolidinone derivative. Brivaracetam displays a high and selective interaction with synaptic vesicle protein 2A (SV2A), a protein involved in synaptic vesicle exocytosis and neurotransmitter release. This protein appears to be the primary target for BRV's pharmacological activity. Data in transgenic mice indicate that even partial SV2A deficiency may lead to increased seizure vulnerability and accelerated epileptogenesis. Brivaracetam demonstrated a potent suppression of seizure activity in a wide range of animal models of partial-onset and generalized seizures.

The clinical tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of BRV have been extensively studied up to 1400mg single dose and up to 800mg/day in repeated administration. It exhibits linear and dose-proportional PK, is rapidly and nearly completely absorbed orally, has a terminal elimination half-life ($t_{½}$) of about 9 hours, and has plasma protein binding of <20%. Brivaracetam is extensively metabolized (>90%), primarily by non-cytochrome P450 (CYP) dependent hydrolysis of the amide group to a carboxylic acid via amidase, and secondarily through CYP2C19-mediated hydroxylation of the side chain. A third hydroxyacid metabolite is preferentially generated by CYP2C9-mediated hydroxylation of the carboxylic acid metabolite. The 3 metabolites are pharmacologically inactive.

A Phase 1, placebo-controlled, single and multiple rising dose study in healthy Japanese volunteers (N01209) has shown that the disposition of BRV was similar to that in overseas populations. Brivaracetam was well tolerated and displayed linear and dose-proportional PK. No new observations were made relative to the safety and tolerability profile of BRV. In Japanese subjects bearing 2 nonfunctional alleles of the gene coding for the CYP2C19 isoenzyme (namely, *2/*2, *2/*3 or *3/*3; representing 25% of the study population), formation of the inactive hydroxy metabolite was decreased 10-fold but the plasma clearance (CL/F) of BRV was only decreased by 30% (0.70mL/min/kg compared to 0.99mL/min/kg in *1/*1 homozygous extensive metabolizers). It was concluded that no BRV dose adaptation is necessary in Japanese subjects compared to overseas populations, and, in particular, no dose reduction is needed for subjects bearing CYP2C19 mutations.

This is a Phase 1, single site, open-label, single-dose and multiple-dose PK study of BRV tablets in healthy male and female Chinese subjects. A total of 12 subjects (6 males and 6 females) will be enrolled in the study. Subjects will be confined to the unit from Day -1 (the day prior to first administration of study drug) until Day 13 (72h after the final dose of study drug). Subjects will receive a single dose of BRV 100mg under fasting conditions in the Single-Dose Period. Blood samples will be taken predose and at specified time points postdose for the determination of the PK profile of BRV and metabolites (ucb-42145, ucb-100406-1, and ucb107092-1).

In the Multiple-Dose Period, the same subjects as in the Single-Dose Period will receive BRV 200mg/day (100mg every 12h) under fasting conditions with 200mL of water. Blood samples will be taken predose and at specified time points postdose for the determination of the PK profile of BRV and metabolites (ucb-42145, ucb-100406-1, and ucb107092-1).

Subjects will be discharged from confinement in the morning of Day 13, approximately 72h after the final administration of study drug, provided there are no medical objections.

Safety and tolerability of BRV will be monitored throughout the study by monitoring of adverse events (AEs), collecting blood and urine samples for the evaluation of safety laboratory

parameters, vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate, respiratory rate, and body temperature), and electrocardiograms (ECGs).

A Safety Follow-Up (SFU) Visit will be performed after the final administration of BRV. The assessments performed for the SFU will also be performed for early withdrawals.

The study objectives are to assess the PK, safety, and tolerability of BRV after a single dose and multiple doses of 100mg for 6 days in healthy adult Chinese subjects (male and female).

2 INTRODUCTION

A clinical development program for BRV is underway in China and will support a market authorization application/new drug application for BRV in China for the indication of adjunctive treatment in subjects 16 years and older with partial-onset seizures whether or not secondarily generalized.

The clinical tolerability, PK, and PD of BRV have been extensively studied up to 1400mg single dose and up to 800mg/day in repeated administration. It exhibits linear and dose-proportional PK, is rapidly and nearly completely absorbed orally, has a $t_{½}$ of about 9h, and has plasma protein binding of <20%. Brivaracetam is extensively metabolized (>90%), primarily by hydrolysis of the amide group to a carboxylic acid supported by non-CYP dependent amidase, and secondarily through CYP2C19-mediated hydroxylation of the side chain. A third hydroxyacid metabolite is preferentially generated by CYP2C9-mediated hydroxylation of the carboxylic acid metabolite. The 3 metabolites are pharmacologically inactive.

A Phase 1, placebo-controlled, single and multiple rising dose study in healthy Japanese volunteers (N01209) has shown that the disposition of BRV was similar to that in overseas populations. Brivaracetam was well tolerated and displayed linear and dose-proportional PK. No new observations were made relative to the safety and tolerability profile of BRV. In Japanese subjects bearing 2 nonfunctional alleles of the gene coding for the CYP2C19 isoenzyme (namely, *2/*2, *2/*3 or *3/*3; representing 25% of the study population), formation of the inactive hydroxy metabolite was decreased 10-fold but the plasma clearance (CL/F) of BRV was only decreased by 30% (0.70mL/min/kg compared to 0.99mL/min/kg in *1/*1 homozygous extensive metabolizers). It was concluded that no BRV dose adaptation is necessary in Japanese subjects compared to overseas populations, and, in particular, no dose reduction is needed for subjects bearing CYP2C19 mutations.

3 STUDY OBJECTIVES

The study objectives are to assess the PK, safety, and tolerability of BRV after a single dose and multiple doses of 100mg for 6 days in healthy adult Chinese subjects (male and female).

4 STUDY VARIABLES

4.1 Primary pharmacokinetic variables

The primary PK variables are:

- Concentrations of BRV and 3 metabolites (ucb-42145, ucb-100406-1, and ucb107092-1) in plasma

- For the single dose:
  - $AUC_{(0-t)}$ of BRV
  - C_{max} of BRV
- For the multiple dose:
  - $AUC_{(0-12),ss}$ of BRV
  - $C_{max,ss}$ of BRV

4.2 Secondary pharmacokinetic variables

- For the single dose:
  - t_{max}, $t_{1/2}$, λ_z, MRT, AUC, CL/F, and V_z/F of BRV in plasma
  - C_{max}, t_{max}, $t_{½}$, λ_z, $AUC_{(0-t)}$, and AUC of metabolites in plasma
- For the multiple dose:
  - t_{max}, $t_{½}$, λ_z, $C_{min,ss}$, $C_{av,ss}$, CL_{ss}/F, and V_z/F of BRV in plasma
  - t_{max}, $t_{½}$, λ_z, $C_{max,ss}$, and $AUC_{(0-12),\ ss}$ of metabolites in plasma
  - PTF of BRV in steady-state
  - R_{AUC} and R_{max} of BRV

4.3 Safety variables

4.3.1 Primary safety variable

- Incidence of treatment-emergent AEs (TEAEs)

4.3.2 Other safety variables

- Changes in vital signs (SBP, DBP, pulse rate, respiratory rate, and body temperature)
- Standard 12-lead ECGs parameters and findings
- Changes in clinical laboratory test parameters (hematology, blood chemistry, and urinalysis)

5 STUDY DESIGN

5.1 Study description

This is a Phase 1, single site, open-label, single and multiple dose PK study of BRV tablets in healthy male and female Chinese subjects. Subjects will be confined to the unit from Day -1 (the day prior to first administration of study drug) until Day 13.

A total of 12 subjects (6 males and 6 females) who sign the Informed Consent form and fulfill all inclusion and none of the exclusion criteria will be enrolled and will start the Single-Dose Period. In the Single-Dose Period, each subject will receive BRV 100mg. In the Multiple-Dose Period, the multiple-dose PK and safety of BRV 200mg/day will be evaluated in the same subjects as in the Single-Dose Period.

In the Single-Dose Period, subjects will receive a single dose of BRV under fasting conditions with 200mL water. Blood samples will be taken for the determination of the PK profile of BRV and its metabolites (ucb-42145, ucb-100406-1, and ucb107092-1) at predose, and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16, 24, 36, 48, and 72h after study drug administration.

In the Multiple-Dose Period, subjects will receive BRV 200mg/day (100mg every 12h ±15min). Subjects will receive BRV under fasting conditions with 200mL water. Blood samples will be taken for the determination of the PK profile of BRV and its metabolites (ucb-42145, ucb-100406-1, and ucb107092-1) predose prior to the morning dose administration on Day 5 to Day 9, and at predosing and at the following time points after the last administration of the investigational medicinal product (IMP) on Day 10: 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16, 24, 36, 48, and 72h.

Subjects will be discharged from confinement in the morning of Day 13, approximately 72h after the final administration of study drug, provided there are no medical objections.

Safety and tolerability of BRV will be assessed throughout the study by monitoring of AEs, collecting blood and urine samples for the evaluation of safety laboratory parameters, measuring vital signs (SBP, DBP, pulse rate, respiratory rate, and body temperature), and ECG.

A SFU will be performed after the final administration of the IMP. The assessments performed for the SFU will also be performed for early withdrawals.

5.1.1 Study duration per subject

The anticipated maximum study duration per subject is 43 days (approximately 6 weeks), including the Screening Period (up to 28 days), confinement during the Single-Dose and Multiple-Dose Periods (13 days), and follow-up examination (2 days after clinic discharge).

The end of the study is defined as the date of the final visit of the final subject in the study.

5.1.2 Planned number of subjects and sites

A total of 12 healthy (6 male and 6 female) subjects will be enrolled at 1 site.

5.1.3 Anticipated regions and countries

The study will be conducted in China.

5.2 Schedule of study assessments

Table 5–1: Schedule of study assessments

Activity/Day	SV	Treatment Period															SFU
		Single-Dose						Multiple-Dose									
	D -28 to -2	D -1	D1		D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D15
			Pre	Post													
Informed consent	X																
Clinic admission		X															
Inclusion/exclusion criteria	X	X															
Demographic data	X																
Medical history	X																
Physical examination	X	X															X
Columbia-Suicide Severity Rating Scale	X	X															X
Vital signs	X		X[a]	X[a]			X[a]			X[b]			X[b]			X[b]	X
12-lead ECG	X	X[c]		X[a]			X[a]			X[b]			X[b]			X[b]	X
Safety laboratory assessments[d]	X		X			X								X			
Serology[e]	X																
Drug/alcohol test[f]	X	X															
Pregnancy test (serum)[g]	X																
Pregnancy test (urine)[g]		X				X										X	
IMP administration				X				X[h]	X[h]	X[h]	X[h]	X[h]	X[i]				
PK blood sampling			X	X[a]	X[a]	X[a]	X[a]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	

Adverse event/ concomitant medication/medical procedure	←																→
Discharge																X	

AE=adverse event; BRV=brivaracetam; D=day; ECG=electrocardiogram; HIV=human immunodeficiency virus; IMP=investigational medicinal product; PK=pharmacokinetics; Pre=predose; Post=postdose; SFU=Safety Follow-Up; SV=Screening Visit

[a] See Table 5–2 for the schedule for vital signs, ECGs, and PK sampling in the Single-Dose Period.

[b] See Table 5–3 for the schedule for vital signs and ECGs in the Multiple-Dose Period.

[c] Three ECGs to be performed at 15min (±5min) intervals within 24h prior to BRV dosing on Day 1 to provide a representative baseline.

[d] Hematology including coagulation parameters, clinical chemistry, and urinalysis

[e] Hepatitis B surface antigen, Hepatitis C virus antibody, HIV antibody, and syphilis

[f] Urine drug screen and alcohol breath test

[g] For females of childbearing potential only

[h] From Day 5 to Day 9, study drug will be administered in the morning and evening with an interval of 12h (±15min).

[i] On Day 10, study drug will be administered only in the morning 12h (±15min) after the last dose.

[j] See Table 5–4 for the schedule for plasma PK sampling in the Multiple-Dose Period.

Table 5–2: Single-Dose Period: schedule for ECGs, vital signs, and PK sampling

Assessment	Time relative to BRV administration															
		Postdose (h)														
	Day 1											Day 2			Day 3	Day 4
	Predose	0.25	0.5	1	1.5	2	3	4	6	9	12	16	24	36	48	72
12-lead ECG	X[a]	--	--	X	--	X	--	X	--	--	--	--	--	--	--	X
Vital signs[b]	X	--	--	X	--	X	--	X	--	--	--	--	--	--	--	X
Blood samples for PK	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

BRV=brivaracetam; DBP=diastolic blood pressure; ECG=electrocardiogram; PK=pharmacokinetics; SBP=systolic blood pressure
Note: A window of ±15min is allowed for all ECG and vital signs assessments postdose.
[a] Three ECGs to be performed at 15min (±5min) intervals within 24h prior to BRV dosing on Day 1 to provide a representative baseline.
[b] Vital sign assessments include SBP, DBP, pulse rate, respiratory rate, and body temperature.

Table 5–3: Multiple-Dose Period: schedule for ECGs and vital signs

Assessment	Day												
	5	6	7	8	9	10				11		12	13
			Pre			Pre	Postdose (h)						
							1	2	4	24	36	48	72
12-lead ECG	--	--	X[a]	--	--	X	X	X	X	--	--	--	X
Vital signs[b]	--	--	X[a]	--	--	X	X	X	X	--	--	--	X

DBP=diastolic blood pressure; ECG=electrocardiogram; Pre=predose; SBP=systolic blood pressure
Note: A window of ±15min is allowed for all ECG and vital signs assessments postdose.
[a] To be performed predose on the morning of Day 7.
[b] Vital sign assessments include SBP, DBP, pulse rate, respiratory rate, and body temperature.

Table 5–4: Multiple-Dose Period: schedule for PK sampling

Assessment	Day																				
	5	6	7	8	9	10											11			12	13
	Pre	Pre	Pre	Pre	Pre	Pre	Postdose (h)														
							0.25	0.5	1	1.5	2	3	4	6	9	12	16	24	36	48	72
Blood samples for PK	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

PK=pharmacokinetics; Pre=predose
[a] To be collected predose in the morning

5.3 Rationale for study design and selection of dose

In overseas studies, the clinical tolerability, PK, and PD of BRV have been extensively studied up to 1400mg single dose and up to 800mg/day in repeated administration. It exhibits linear and dose-proportional PK, is rapidly and nearly completely absorbed orally, has a $t_{½}$ of about 9h and has plasma protein binding of <20%.

A Phase 1, placebo-controlled, single- and multiple-rising dose study in healthy Japanese volunteers (N01209) has shown that the disposition of BRV was similar to that in overseas populations. See Section 2 for details.

Dose selection for the Multiple-Dose Period (200mg/day [100mg every 12h]) was based on the expectation that this would be the highest dose in the Phase 3 study. The study is designed to provide additional safety and PK data for this dose in Chinese subjects.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Inclusion criteria

To be eligible to participate in this study, all of the following criteria must be met:

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the subject.
2. Subject is considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, or medication intake according to the judgment of the Investigator.
3. Subjects are Chinese males and females born in China between 18 and 45 years of age (both inclusive) whose parents are of Chinese origin.

4a. Pregnancy waiver form signed by subject, if female of childbearing potential. Beta-human chorionic gonadotropin test is documented negative within 48 hours before Day 1 and a medically accepted method of contraception (hormonal contraception, intrauterine device (IUD), implant device, diaphragm with spermicide, bilateral tubal ligation, monogamous relationship with vasectomized [for at least 3 months] partner or using condoms with spermicidal gel, sexually inactive) is used during the entire duration of the study.

Male participants with a pregnant or breastfeeding partner or female partner of childbearing potential must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the study.

5. Subjects with body mass index from 19 to 24kg/m^2 (both inclusive). Minimum body weight is equal to or more than 50kg.
6. Subjects whose physical and mental conditions are judged to be favorable by the Investigators through physical examination and past history.
7. Subjects with supine blood pressure levels of between 90 to 150 and 60 to 90mmHg (inclusive) for systolic and diastolic, respectively, with pulse rate of 50 to 100 beats per minute (bpm) (supine position, inclusive) at Screening Visit.
8. Subjects without clinically relevant abnormalities in a standard 12-lead ECG at Screening Visit judged by the Investigators.

9. Subjects with laboratory values within the reference range at Screening Visit, or those with values exceeding the reference range but judged by the Investigators to be not clinically significant to their participation in the study.

6.2 Exclusion criteria

Subjects are not permitted to enroll in the study if any of the following criteria is met:

1. Subject has previously participated in this study or has previously been assigned to treatment with the medication under investigation in this study.
2. Subject has participated in another study of an IMP (or a medical device) within the previous 30 days or is currently participating in another study of an IMP (or a medical device).

3a. Subject has a history of chronic alcohol or drug abuse within the previous 6 months. Subject consumes on average more than 30g alcohol/day (amount corresponds to 750mL beer/day or 375mL wine/day or 90mL liquor/day) for men and 20g alcohol/day (amount corresponds to 500mL beer/day or 250mL wine/day or 60mL liquor/day) for women.

4. Subject has any medical or psychiatric condition that, in the opinion of the Investigator, could jeopardize or would compromise the subject's ability to participate in this study.
5. Pregnant, lactating, or sexually active women with childbearing potential who are not using a medically accepted birth control method.
6. Subject has a known hypersensitivity to any components of the IMP or any of its excipients.

7a. Subjects with any previous or current cardiovascular, respiratory, hepatic, renal, digestive, endocrine, or nervous system disorder that may affect absorption, secretion, metabolism, or excretion of the investigational product per Investigator judgment.

8. Subjects with a chronic or acute condition requiring treatment.
9. Subjects with known drug sensitivity or allergic reaction to any food.
10. Subjects who used other drugs including over-the-counter (OTC) products (excluding medicine for external use), with the exception of paracetamol, ibuprofen, aspirin, and the accepted methods of contraception and hormone replacement therapy (HRT), within 14 days before administration of the investigational drug.
11. Subjects who used hepatic enzyme-inducing drugs (eg, glucocorticoids, phenobarbital, isoniazid, phenytoin, rifampicin) within 2 months before the first administration of study drug.
12. Subjects from whom 400mL of blood or more is drawn within 3 months or 200mL or more within 1 month before administration of the IMP for blood donation or other reasons.

13a. Subject has a consumption of more than 600mg of caffeine/day on average (1 cup of coffee contains approximately 100mg of caffeine, 1 cup of tea approximately 30mg, and 1 glass of cola approximately 20mg).

14. Subject smokes more than 5 cigarettes per day or has done so within 6 months prior to Screening.

15. Subjects who consumed grapefruit (as beverage or fruit) within 1 week before administration of the IMP.
16. Subjects showing a positive result for hepatitis B surface antigen, hepatitis C virus antibody, human immunodeficiency virus antibody, or syphilis test at Screening Visit.
17. Subject has a lifetime history of suicide attempt (including an active attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the Columbia Suicide Severity Rating Scale (C-SSRS) at Screening.

18a. Subject has > upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

For subjects with a screening result >ULN for total bilirubin, a baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the electronic Case Report form (eCRF).

Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. If the repeat values are below ULN the subject will be considered to not meet the exclusion criteria.

19. Subjects who are considered ineligible for the present study by the Investigators.

6.3 Withdrawal criteria

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

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

1. Subject develops an illness that would interfere with his/her continued participation.
2. Subject is noncompliant with the study procedures or medications in the opinion of the Investigator.
3. Subject takes prohibited concomitant medications as defined in this protocol.
4. Subject withdraws his/her consent.
5. The Sponsor or a regulatory agency requests withdrawal of the subject.
6. The Investigators judge that continuation of the study is difficult because of occurrence of AEs, etc.
7. There is a protocol deviation that may affect study results markedly.
8. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.

Investigators should attempt to obtain information on subjects in the case of withdrawal or discontinuation. For subjects considered as lost to follow up, the Investigator should make an effort (at least 1 phone call and 1 written message to the subject), 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 subject, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal or discontinuation.

Investigators should contact the UCB Study Physician or designee, whenever possible, to discuss the withdrawal of a subject in advance.

6.3.1 Potential drug-induced liver injury IMP discontinuation criteria

Subjects with potential drug-induced liver injury (PDILI) must be assessed to determine if IMP must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

The PDILI criterion below requires immediate discontinuation of IMP:

- Subjects with ALT or AST ≥ 3 x ULN

Evaluation of PDILI must be initiated as described in Section 10.2.1. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

Investigators should attempt to obtain information on subjects in the case of IMP discontinuation to complete the final evaluation. Subjects 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 IMP discontinuation and subject withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for IMP discontinuation.

6.4 Other study restrictions

All BRV treatments will be administered under fasting conditions. For Day 1 and Day 10, subjects will be required to fast for ≥10h prior to dosing and until 3h after IMP administration. For Day 5 to Day 9, 2h fasting before and after dosing for morning and night dose is required. During fasting, no fluids are allowed except water; however, water is not allowed from 2h predose until 1h after the start of treatment (apart from the water taken with the oral dosing).

Subjects must refrain from smoking and consuming alcohol and caffeine-containing products (chocolate, cola, coffee, or tea) from 48h before treatment until Final Discharge from the study.

Subjects must refrain from consuming grapefruit, grapefruit juice, and grapefruit-containing products from 7 days before first drug administration through the end of the study.

7 STUDY TREATMENT

The IMP tablets will be distributed to the clinical study site by the Sponsor under the responsibility of UCB Clinical Trial Supplies.

7.1 Description of investigational medicinal product

Oral film-coated tablets of BRV 100mg will be used in this study.

7.2 Treatments to be administered

During the Single-Dose Period, subjects will receive a single dose of BRV 100mg under fasting conditions with 200mL of water. During the Multiple-Dose Period, subjects will receive BRV 200mg/day; study drug should be given as 2 equally divided doses administered twice daily. Subjects should take tablets according to instructions provided by the Investigator.

7.3 Packaging

Brivaracetam tablets are manufactured, packaged, and labeled according to Good Manufacturing Practice (GMP) guidelines and applicable laws or regulations. The IMP is suitably packaged in such a way as to protect the IMP from deterioration during transport and storage.

7.4 Labeling

Clinical drug supplies will be labeled in accordance with the current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and GMP and will include any locally required statements.

7.5 Handling and storage requirements

The Investigator (or designee) is responsible for the safe and proper storage of IMP at the site. Investigational medicinal product stored by the Investigator is to be kept in a secured area with limited access according to the storage conditions mentioned on the label.

Appropriate storage conditions must be ensured either by controlling the temperature (eg, room, refrigeration unit) or by completion of a temperature log in accordance with local requirements on a regular basis (eg, once a week), showing actual and minimum/maximum temperatures reached over the time interval.

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 subject to store the IMP following the instructions on the label.

7.6 Drug accountability

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

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

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

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

7.7 Procedures for monitoring subject compliance

The study drug will be administered under the Investigator's (or designee's) supervision. Study drug administration date and time will be recorded in the eCRF.

7.8 Concomitant medications/treatments

7.8.1 Permitted concomitant treatments (medications and therapies)

With approval from the Investigator, paracetamol, ibuprofen, and aspirin are permitted for the treatment of mild symptoms (eg, headache or pain), given at most every 6 to 8h, not exceeding 1g/day, and with a total of no more than 10g per 14 days.

Females are allowed to use hormonal contraceptives, implants, patches, or IUDs delivering progesterone or post-menopausal HRT.

Except for the medications noted above, no concomitant medication is allowed during this study.

7.8.2 Prohibited concomitant treatments (medications and therapies)

With the exception of paracetamol, ibuprofen, aspirin, and the accepted methods of contraception and HRT, all prescription or OTC medicines are prohibited within 14 days before first study drug administration and during the clinical part of the study, unless required to treat an AE. In addition, any hepatic enzyme-inducing drugs (eg, glucocorticoids, phenobarbital, isoniazid, phenytoin, rifampicin) are prohibited within 2 months before first study drug administration and during the clinical part of the study.

If a subject needs or takes any prohibited medication, the Investigator will (where possible) discuss with the Sponsor Study Physician and a decision will be made whether the subject can continue in the study or must be withdrawn.

7.9 Blinding

This is an open-label study.

7.10 Randomization and numbering of subjects

Subjects who have signed the Informed Consent form will be assigned a unique UCB-assigned 5-digit subject number that will be used to identify them and maintain subject confidentiality throughout the study.

8 STUDY PROCEDURES BY VISIT

8.1 Screening

Prior to the start of the any study procedures, the written informed consent form must be signed and personally dated by the subject and by the physician who informed the subject on the study.

Screening procedures (within 28 to 2 days before Day 1) will consist of the following:

- Verify inclusion and exclusion criteria
- Obtain demographic data
- Obtain medical history (past and concomitant diseases)

- Obtain vital sign measurements (SBP, DBP, pulse rate, respiratory rate, and body temperature)
- Perform physical examination
- Assess C-SSRS
- Perform 12-lead ECG
- Perform safety laboratory assessments for hematology, including coagulation, clinical chemistry, urinalysis, and serology
- Perform serum pregnancy test for females of childbearing potential only
- Perform alcohol breath test and urine drug screen
- Record AEs
- Record concomitant medication
- Record concurrent medical procedures

When all Screening procedures have demonstrated that all inclusion criteria have been met and none of the exclusion criteria apply, the subject can be invited to Day -1.

8.2 Day -1

The Treatment Period consists of 14 in-house days. Subjects will stay in-house from Day -1 (day before first dosing) to Day 13. During this time, they will remain under close medical surveillance. Throughout the study, subjects will be monitored for AEs, concomitant medication, and medical procedures.

- Check subject into the clinic
- Check subject eligibility
- Perform physical examination
- Assess C-SSRS
- Perform alcohol breath test and urine drug screen
- Perform urine dipstick pregnancy test for females of childbearing potential only
- Record concomitant medication and medical procedures
- Record AEs
- Perform 12-lead ECG (3 ECGs will be performed at 15min [±5min] intervals within 24h before dosing of BRV on Day 1)

8.3 Day 1

The following procedures will be performed predose:

- Perform 12-lead ECG (if not performed on Day -1, 3 ECGs will be performed at 15min [±5min] intervals within 24h before dosing of BRV on Day 1)
- Obtain blood samples for safety laboratory assessments and plasma PK

- Study drug administration (after all predose assessments are completed)

The following procedures will be performed postdose:

- Obtain vital sign measurements (SBP, DBP, pulse rate, respiratory rate, and body temperature) at 1, 2, and 4h postdose. A window of ±15min is allowed.
- Perform 12-lead ECG at 1, 2, and 4h postdose. A window of ±15min is allowed.
- Obtain blood samples for plasma PK at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, and 12h postdose
- Record concomitant medication and medical procedures
- Record AEs

8.4 Day 2

- Obtain blood sample for plasma PK at 16, 24, and 36h postdose
- Record concomitant medication and medical procedures
- Record AEs

8.5 Day 3

- Obtain blood samples for safety laboratory assessments
- Perform urine dipstick pregnancy test for females of childbearing potential only
- Obtain blood sample for plasma PK at 48h postdose
- Record concomitant medication and medical procedures
- Record AEs

8.6 Day 4

- Obtain vital sign measurements (SBP, DBP, pulse rate, respiratory rate, and body temperature) at 72h (±15min) postdose
- Perform 12-lead ECG at 72h (±15min) postdose
- Obtain blood sample for plasma PK at 72h postdose
- Record concomitant medication and medical procedures
- Record AEs

8.7 Day 5

The following procedures will be performed predose prior to the morning dose administration:

- Obtain blood sample for plasma PK
- Study drug administration (after all predose assessments are completed) in the morning

The following procedures will be performed postdose:

- Study drug administration 12h (±15min) after the morning dose
- Record concomitant medication and medical procedures

- Record AEs

8.8 Day 6

The following procedures will be performed predose prior to the morning dose administration:

- Obtain blood sample for plasma PK
- Study drug administration (after all predose assessments are completed) in the morning 12h (±15min) after the last dose

The following procedures will be performed postdose:

- Study drug administration 12h (±15min) after the morning dose
- Record concomitant medication and medical procedures
- Record AEs

8.9 Day 7

The following procedures will be performed predose prior to the morning dose administration:

- Obtain vital sign measurements (SBP, DBP, pulse rate, respiratory rate, and body temperature)
- Perform 12-lead ECG
- Obtain blood sample for plasma PK
- Study drug administration (after all predose assessments are completed) in the morning 12h (±15min) after the last dose

The following procedures will be performed postdose:

- Study drug administration 12h (±15min) after the morning dose
- Record concomitant medication and medical procedures
- Record AEs

8.10 Day 8

The following procedures will be performed predose prior to the morning dose administration:

- Obtain blood sample for plasma PK
- Study drug administration (after all predose assessments are completed) in the morning 12h (±15min) after the last dose

The following procedures will be performed postdose:

- Study drug administration 12h (±15min) after the morning dose
- Record concomitant medication and medical procedures
- Record AEs

8.11 Day 9

The following procedures will be performed predose prior to the morning dose administration:

- Obtain blood sample for plasma PK
- Study drug administration (after all predose assessments are completed) in the morning 12h (±15min) after the last dose

The following procedures will be performed postdose:

- Study drug administration 12h (±15min) after the morning dose
- Record concomitant medication and medical procedures
- Record AEs

8.12 Day 10

The following procedures will be performed predose:

- Obtain vital sign measurements (SBP, DBP, pulse rate, respiratory rate, and body temperature)
- Perform 12-lead ECG
- Obtain blood sample for plasma PK
- Study drug administration (after all predose assessments are completed) in the morning 12h (±15min) after the last dose

The following procedures will be performed postdose:

- Obtain vital sign measurements (SBP, DBP, pulse rate, respiratory rate, and body temperature) at 1, 2, and 4h postdose. A window of ±15min is allowed.
- Perform 12-lead ECGs at 1, 2, and 4h postdose. A window of ±15min is allowed.
- Obtain blood samples for plasma PK at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, and 12h postdose
- Record concomitant medication and medical procedures
- Record AEs

8.13 Day 11

- Obtain blood samples for safety laboratory assessments
- Obtain blood samples for plasma PK at 16, 24, and 36h postdose
- Record concomitant medication and medical procedures
- Record AEs

8.14 Day 12

- Obtain blood samples of plasma PK at 48h postdose
- Record concomitant medication and medical procedures
- Record AEs

8.15 Day 13

- Perform urine dipstick pregnancy test for females of childbearing potential only
- Obtain blood samples for safety laboratory assessments
- Obtain vital sign measurements (SBP, DBP, pulse rate, respiratory rate, and body temperature) at 72h (±15min) postdose
- Perform 12-lead ECG at 72h (±15min) postdose
- Obtain blood samples for plasma PK at 72h postdose
- Record concomitant medication and medical procedures
- Record AEs

After all scheduled procedures have been performed on Day 13, the subject may be discharged from the clinical unit provided that there are no safety concerns in the opinion of the Investigator.

8.16 Safety Follow-Up Visit

The subject will return to the clinic 2 days later (Day 15) for the SFU Visit. The following procedures will be performed:

- Perform physical examination
- Assess C-SSRS
- Obtain vital signs
- Perform 12-lead ECG
- Record concomitant medication and medical procedures
- Record AEs

9 ASSESSMENT OF PHARMACOKINETIC/ PHARMACODYNAMIC/PHARMACOGENOMIC VARIABLES

9.1 Blood sampling for determination of PK parameters

At the specified time points, 4mL of blood will be drawn from the subcutaneous vein of the forearm with a vacuum tube containing lithium heparin. Within 30 minutes after blood draw, samples will be centrifuged at 4°C at about 1600g for 10 minutes to separate plasma. At least 1mL of plasma will be collected into a polypropylene tube, and the remaining plasma into another tube. They will be frozen at −20°C or below until assay.

A label with the protocol number, Subject Identification Code, dose, sampling date, and sampling time will be put on each plasma sample tube. Plasma samples will be packed with dry ice and sent to the drug concentration assay center from the medical institution.

Unless otherwise indicated, any sample taken earlier or later than scheduled is considered a time deviation even if the deviation is pharmacokinetically irrelevant.

The maximum deviations from scheduled sampling times for PK are defined as follows:

- 0h (predose): within 30min before dosing
- 0.25h: ±1min
- 0.5h: ±2min
- 1 to 4h: ±3min
- 6 to 9h: ±6min
- 12 to 16h: ±12min
- ≥24h: ±20min

The unchanged drug and its metabolites (ucb-42145, ucb-100406-1, and ucb107092-1) in plasma will be determined with a validated liquid chromatography coupled with mass spectrometry/mass spectrometry method.

10 ASSESSMENT OF SAFETY

10.1 Adverse events

10.1.1 Definitions

10.1.1.1 Adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

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

Signs or symptoms of the condition/disease for which the IMP is being studied should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the Investigator from the subject's history.

10.1.1.2 Serious adverse event

Once it is determined that a subject experienced an AE, the seriousness of the AE must be determined. A serious adverse event (SAE) must meet 1 or more of the following criteria:

- Death
- Life-threatening

  (Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form.)

- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect (including that occurring in a fetus)
- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definition of serious

  (Important medical events may include, but are not limited to, potential Hy's Law [see Section 10.1.1.3], allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)
- Initial inpatient hospitalization or prolongation of hospitalization

  (A patient admitted to a hospital, even if he/she is released on the same day, meets the criteria for the initial inpatient hospitalization. An emergency room visit that results in admission to the hospital would also qualify for the initial inpatient hospitalization criteria. However, emergency room visits that do not result in admission to the hospital would not qualify for this criteria and, instead, should be evaluated for 1 of the other criteria in the definition of serious [eg, life-threatening adverse experience, important medical event].

  Hospitalizations for reasons not associated with the occurrence of an AE [eg, preplanned surgery or elective surgery for a pre-existing condition that has not worsened or manifested in an unusual or uncharacteristic manner] do not qualify for reporting. For example, if a subject has a condition recorded on his/her medical history and later has a preplanned surgery for this condition, it is not appropriate to record the surgery or hospitalization as an SAE, since there is no AE upon which to assess the serious criteria. Please note that, if the pre-existing condition has worsened or manifested in an unusual or uncharacteristic manner, this would then qualify as an AE and, if necessary, the seriousness of the event would need to be determined.)

10.1.1.3 Adverse events of special interest

An AE of special interest is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound. For this study, the AEs of special interest include:

- Autoimmune nephritis
- Nephritis
- Nephritis allergic
- Tubulointerstitial nephritis
- Tubulointerstitial nephritis and uveitis syndrome
- 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, must ALWAYS be reported to UCB as an AE of special interest (ie, without waiting for any additional etiologic investigations to have been concluded). In the event of

this occurring, permission to contact the subject's primary healthcare professional would be sought to ensure further investigation and follow up.

10.1.2 Procedures for reporting and recording adverse events

The subject will be given the opportunity to report AEs spontaneously. A general prompt will also be given at each study visit to detect AEs. For example:

"Did you notice anything unusual about your health (since your last visit)?"

In addition, the Investigator should review any self-assessment procedures (eg, diary cards) employed in the study.

10.1.2.1 Description of adverse events

When recording an AE, the Investigator should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The eCRF and source documents should be consistent. Any discrepancies between the subject's own words on his/her own records (eg, diary card) and the corresponding medical terminology should be clarified in the source documentation.

Details for completion of the Adverse Event eCRF (including judgment of relationship to IMP) are described in the CRF Completion Guidelines.

10.1.2.2 Rule for repetition of an adverse event

An increase in the intensity of an AE should lead to the repetition of the AE being reported with:

- The outcome date of the first AE that is not related to the natural course of the disease being the same as the start date of the repeated AE, and the outcome of "worsening"
- The AE verbatim term being the same for the first and repeated AE, so that the repeated AE can be easily identified as the worsening of the first one

10.1.2.3 Additional procedures for reporting serious adverse events

If an SAE is reported, UCB must be informed within 24 hours of receipt of this information by the site (see contact information for SAE reporting listed in the Serious Adverse Event Reporting section at the front of the protocol). The Investigator must forward to UCB (or its representative) a duly completed "Investigator SAE Report Form for Development Drug" (SAE report form) provided by UCB, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions. Information recorded on this form will be entered into the global safety database.

An Investigator SAE report form will be provided to the Investigator. The Investigator SAE Report form must be completed in English.

It is important for the Investigator, when completing the SAE report form, to include the assessment as to a causal relationship between the SAE and the IMP administration. This insight from the Investigator is very important for UCB to consider in assessing the safety of the IMP and in determining whether the SAE requires reporting to the regulatory authorities in an expedited manner.

Additional information (eg, autopsy or laboratory reports) received by the Investigator must be provided within 24 hours. All documents in the local language must be accompanied by a

translation in English, or the relevant information included in the same document must be summarized in the Investigator SAE report form.

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

Upon receipt of the SAE report form, UCB will perform an assessment of expectedness of the reported SAE. The assessment of the expectedness of the SAE is based on the Investigator's Brochure.

10.1.3 Follow up of adverse events

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 subject is lost to follow up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest; further details regarding follow up of PDILI events is provided in Section 10.2.1.

If an AE is ongoing at the end of the study for a subject, follow up should be provided until resolution/stable level of sequelae is achieved, or until the Investigator no longer deems that it is clinically significant, or until the subject is lost to follow up. If no follow up is provided, the Investigator must provide a justification. The follow up will usually be continued for 30 days after the subject has discontinued his/her IMP.

Information on SAEs obtained after clinical database lock will be captured through the Patient Safety (PS) database without limitation of time.

10.1.4 Pregnancy

If an Investigator is notified that a subject has become pregnant after the first intake of any IMP, the Investigator must immediately notify UCB's PS department by providing the completed Pregnancy Report and Outcome form (for contact details see Serious Adverse Event reporting information at the beginning of this protocol). The subject should be withdrawn from the study as soon as pregnancy is known (by positive pregnancy test), and the following should be completed:

- The subject should return for an early discontinuation visit.
- The subject should immediately stop the intake of the IMP.
- An SFU Visit should be scheduled 14 days after the subject has discontinued IMP.

The Investigator must inform the subject of information currently known about potential risks.

The pregnancy will be documented on the Pregnancy Report and Outcome form provided to the Investigator. The progression of the pregnancy and the eventual birth (if applicable) must be followed up using the Pregnancy Report and Outcome form in which the Investigator has to report on the health of the mother and of the child. Every reasonable attempt should be made to follow the health of the child for 30 days after birth for any significant medical issues. In certain circumstances, UCB may request that follow up is continued for a period longer than 30 days. If

the subject is lost to follow up and/or refuses to give information, written documentation of attempts to contact the subject needs to be provided by the Investigator and filed at the site. UCB's PS department is the primary contact for any questions related to the data collection for the pregnancy, eventual birth, and follow up.

In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, the Investigator or designee is asked to contact the subject to request consent of the partner via the Partner Pregnancy Consent form that has been approved by the responsible IRB/IEC and should be available in the Investigator site file. In case of questions about the consent process, the Investigator may contact the UCB/contract research organization (CRO) contract monitor for the study. The Investigator will complete the Pregnancy Report and Outcome form and send it to UCB's PS department (for contact details see Serious Adverse Event reporting information at the beginning of this protocol) only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form. UCB's PS department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow up.

A pregnancy becomes an SAE in the following circumstances: miscarriage, abortion (elective or spontaneous), 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. Those SAEs must be additionally reported using the Investigator SAE Report form.

10.1.5 Suspected transmission of an infectious agent via a medicinal product

For the purposes of reporting, any suspected transmission of an infectious agent via a medicinal product should be considered as an SAE; such cases must be reported immediately, recorded in the AE module of the eCRF, and followed as any other SAE. Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

10.1.6 Overdose of investigational medicinal product

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the eCRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or nonserious AE. These events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess medicine itself is an AE or SAE (eg, suicide attempt).

10.1.7 Safety signal detection

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

The Study Physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the PS representative.

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

10.2 Laboratory measurements

The following laboratory parameters will be measured:

Table 10–1: Laboratory measurements

Hematology	Chemistry	Urinalysis
Basophils	Calcium	Albumin
Eosinophils	Chloride	Bacteria
Lymphocytes	Creatinine	Crystals
Atypical lymphocytes	Magnesium	Glucose
Monocytes	Potassium	pH
Neutrophils	Sodium	RBC
Hematocrit	Glucose	WBC
Hemoglobin	BUN	Protein
MCH	AST	Bilirubin
MCHC	ALP	Nitrite
MCV	ALT	Urobilinogen
Platelet count	GGT	Ketones
RBC count	Total bilirubin	
WBC count	LDH	
	Total cholesterol	
	Albumin	

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT=gamma-glutamyltransferase; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; WBC=white blood cell

10.2.1 Evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 6.3.1, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and Sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 10.1.1.3), and, if applicable, also reported as an SAE (see Section 10.1.1.2).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 10–2 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 10.2.1.1). The local

hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 10.2.1.3).

The results of all monitoring, including laboratory testing and other testing, should be made available to the study site and Sponsor.

All initial tests resulting in abnormal hepatic laboratory values need to be repeated, but appropriate medical action must not be delayed waiting for the repeat result.

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. In these cases, the Investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

The table below summarizes the approach to investigate PDILI.

Table 10–2: Required investigations and follow up for PDILI

Laboratory value					
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Required testing**	**Continued evaluation**
Requires immediate and permanent IMP discontinuation					
≥3xULN	<2xULN	No	Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Must have repeat liver chemistry values and additional testing completed ASAP (see Section 10.2.1.3); recommended to occur within 24 hours at Phase 1 unit or with HCP.	Monitoring of liver chemistry values required once per week until values normalize, stabilize, or return to within baseline values.[b]
≥3xULN	NA	Yes	Hepatology consult.[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.		Monitoring of liver chemistry values required at least twice per week until values normalize, stabilize, or return to within baseline values.[b]
≥3xULN	≥2xULN[d]	NA			

ALP=alkaline phosphatase; ALT=alanine aminotransferase; ASAP=as soon as possible; AST=aspartate aminotransferase; HCP=healthcare practitioner; IMP=investigational medicinal product; NA=not applicable; PDILI=potential drug-induced liver injury; ULN=upper limit of normal

[a] Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

[b] Unless an alternative monitoring schedule is agreed by the Investigator and UCB responsible physician. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

[c] Details provided in Section 10.2.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

[d] If the subject also has ≥2xULN ALP, the possibility of an indication of biliary obstruction should be discussed with the Medical Monitor.

10.2.1.1 Consultation with Medical Monitor and local hepatologist

Potential drug-induced liver injury events require notification of the Medical Monitor within 24 hours (eg, by laboratory alert), and the subject must be discussed with the Medical Monitor as soon as possible. If required, the subject must also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section 10.2.1.3) and SAE report (if applicable).

10.2.1.2 Immediate action: determination of IMP discontinuation

All PDILI events require immediate action, testing, and monitoring.

The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and requires permanent IMP discontinuation (see Section 6.3.1 and Table 10–2 for details).

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. The Investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

10.2.1.3 Testing: identification/exclusion of alternative etiology

The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are detailed in Table 10–3 (laboratory measurements) and Table 10–4 (additional information). Results of the laboratory measurements and information collected are to be submitted to the Sponsor on the corresponding eCRF. If the medical history of the subject indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable.

All blood samples should be stored, if possible.

The following measurements are to be assessed:

Table 10–3: PDILI laboratory measurements

Virology-related	Hepatitis A IgM antibody
	HBsAg
	Hepatitis E IgM antibody
	HBcAb-IgM
	Hepatitis C RNA
	Cytomegalovirus IgM antibody
	Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophile antibody or monospot testing)
Immunology	Anti-nuclear antibody (qualitative and quantitative)
	Anti-smooth muscle antibody (qualitative and quantitative)
	Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative)
Hematology	Eosinophil count
Urinalysis	Toxicology screen
Chemistry	Amylase
	If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
Additional	Prothrombin time/INR[a]
	Serum pregnancy test
	PK sample

ALT=alanine aminotransferase; CPK=creatine phosphokinase; HBcAb-IgM=hepatitis B core antibody-IgM; HBsAg=hepatitis B surface antigen; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PDILI=potential drug-induced liver injury; PK=pharmacokinetic; RNA=ribonucleic acid; ULN=upper limit of normal

a Measured only for subjects with ALT >8xULN, elevations in total bilirubin, and symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

The following additional information is to be collected:

Table 10–4: PDILI information to be collected

New or updated information
Concomitant prescription and over-the-counter medications (eg, acetaminophen, herbal remedies, vitamins); dosages and dates should be included.
Pertinent medical history, including the following: • History of liver disease (eg, autoimmune hepatitis, nonalcoholic steatohepatitis or other "fatty liver disease") • Adverse reactions to drugs • Allergies • Relevant family history or inheritable disorders (eg, Gilbert's syndrome, alpha-1 antitrypsin deficiency) • Recent travel • Progression of malignancy involving the liver (Note: Metastatic disease to the liver, by itself, should not be used as an explanation for significant AST and/or ALT elevations.)
The appearance or worsening of clinical symptoms of hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, decreased appetite, abdominal pain, jaundice, fever, or rash)
Recent clinically significant hypotension or hypoxemia with compromised cardiopulmonary function
Alcohol and illicit drug use
Results of liver imaging or liver biopsy, if done
Results of any specialist or hepatology consult, if done
Any postmortem/pathology reports

ALT=alanine aminotransferase; AST=aspartate aminotransferase; PDILI=potential drug-induced liver injury

10.2.1.4 Follow-up evaluation

Potential drug-induced liver injury events require follow-up monitoring as described in Table 10–2. Monitoring should continue until liver chemistry values normalize, stabilize, or return to baseline. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

10.3 Other safety measurements

10.3.1 Physical examination

A standard physical examination will be performed according to Table 5–1. Clinically significant new or worsened abnormalities will have to be reported as AEs.

10.3.2 ECG

At time points specified in Table 5–2 and Table 5–3, 12-lead ECGs will be recorded at supine rest (at least 5 minutes), and normal or abnormal will be judged. Heart rate, PR, QRS, QT, and time from the beginning of the Q wave to the end of the T wave corrected for heart rate will also be recorded.

10.3.3 Vital signs

At time points specified in Table 5–2 and Table 5–3, SBP, DBP, pulse rate, respiratory rate, and body temperature in supine and standing positions will be recorded at supine rest (at least 5 minutes) and 1 minute after standing.

10.3.4 Assessment of suicidality

Suicidality will be assessed by trained study personnel using the C-SSRS. This scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be completed according to Table 5–1.

11 STUDY MANAGEMENT AND ADMINISTRATION

11.1 Adherence to protocol

The Investigator should not deviate from the protocol. However, the Investigator should take any measure necessary in deviation from or not defined by the protocol in order to protect clinical study subjects from any immediate hazard to their health and safety. In this case, this action should be taken immediately, without prior notification of the regulatory authority, IRB/IEC, or Sponsor.

After implementation of such measure, the Investigator must notify the Clinical Project Manager (CPM) of the Sponsor within 24 hours and follow any local regulatory requirements.

11.2 Monitoring

UCB (or designee) will monitor the study to meet the Sponsor's monitoring Standard Operating Procedures (SOPs), ICH-GCP guideline, and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate. Monitoring of the study may be delegated by UCB to a CRO or a contract monitor.

The Investigator and his/her staff are expected to cooperate with UCB (or designee) and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information. The Investigator(s)/institution(s) will permit direct access to source data/documents for study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s).

The Investigator will allow UCB (or designee) to periodically review all eCRFs and corresponding source documents (eg, hospital and laboratory records for each study participant). Monitoring visits will provide UCB (or designee) with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of eCRFs, ensure that all protocol requirements, applicable authorities regulations, and Investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

11.2.1 Definition of source data

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 eCRFs are not considered acceptable source documents.

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, or quality of life questionnaires, for example. Source documents should be kept in a secure, limited access area.

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

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

11.2.2 Source data verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (eg, subject files, recordings from automated instruments, tracings [ECG], x-ray films, laboratory notes). All data reported on the eCRF should be supported by source documents, unless otherwise specified in Section 11.2.1.

11.3 Data handling

11.3.1 Case Report form completion

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

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

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

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

Detailed instructions will be provided in the CRF Completion Guidelines.

11.3.2 Database entry and reconciliation

Case Report forms/external electronic data will be entered/loaded into a validated electronic database using a clinical data management system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. The data are entered into the eCRFs once and are subsequently verified if the study is performed using electronic data capture.

An electronic audit trail system will be maintained within the CDMS to track all data changes in the database once the data have been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

11.3.3 Subject Screening and Enrollment log/Subject Identification Code list

The subject's screening and enrollment will be recorded in the Subject Screening and Enrollment Log.

The Investigator will keep a Subject Identification Code list. This list remains with the Investigator and is used for unambiguous identification of each subject.

The subject's consent and enrollment in the study must be recorded in the subject's medical record. These data should identify the study and document the dates of the subject's participation.

11.4 Termination of the study

UCB reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, or unsatisfactory enrollment with respect to quality or quantity.

If the study is prematurely terminated or suspended, UCB (or its representative) will inform the Investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The IRB/IEC should also be informed and provided with reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for the return of all unused IMP and other material in accordance with UCB procedures for the study.

11.5 Archiving and data retention

The Investigator will maintain adequate records for the study, including CRFs, medical records, laboratory results, Informed Consent documents, drug dispensing and disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

All essential documents are to be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB (Committee for Proprietary Medicinal Products [CPMP]/ICH/135/95, 2002 [Section 4.9.5]). The Investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The Investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the Sponsor's trial master file.

11.6 Audit and inspection

The Investigator will permit study-related audits mandated by UCB, after reasonable notice, and inspections by domestic or foreign regulatory authorities.

The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects enrolled have been protected, that enrolled subjects (ie, signing consent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of the IMP have been processed and reported in compliance with the planned arrangements, the protocol, investigational site, and IRB/IEC SOPs, ICH-GCP, and applicable regulatory requirements.

The Investigator will provide direct access to all study documents, source records, and source data. If an inspection by a regulatory authority is announced, the Investigator will immediately inform UCB (or designee).

11.7 Good Clinical Practice

Noncompliance with the protocol, ICH-GCP, or local regulatory requirements by the Investigator, institution, institution staff, or designees of the Sponsor will lead to prompt action by UCB to secure compliance. Continued noncompliance may result in the termination of the site's involvement in the study.

12 STATISTICS

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

12.1 Definition of analysis sets

The Safety Set (SS) will consist of all subjects who received at least 1 dose of the IMP.

The Pharmacokinetic Per-Protocol Set (PK-PPS) will consist of all subjects who are included in the SS and also have a sufficient number of bioanalytical assessments to calculate reliable estimates for the primary PK parameters.

The reasons for exclusion of subjects from either of the analysis sets will be listed.

12.2 General statistical considerations

All analysis will be performed using SAS version 9.3 or higher.

A complete set of raw data listings containing all documented data and all calculated data (eg, difference from Baseline) will be generated. In general, summary statistics (n [number of available measurements], arithmetic mean, standard deviation [SD], median, minimum, and maximum) for quantitative variable and frequency tables for qualitative data will be presented.

12.3 Planned pharmacokinetic analyses

12.3.1 Analysis of the primary pharmacokinetics variable

In general, all PK parameter variables will be summarized using the PK-PPS.

The plasma concentration-time profiles and PK parameters of BRV will be summarized by dosage (single and multiple) using descriptive statistics (number of observations [n], geometric mean, lower and upper 95% confidence interval [CI], geometric coefficient of variation [CV], arithmetic mean, SD and CV, median, and minimum and maximum value).

Individual concentration-time profiles will be displayed graphically on a linear scale and semi-logarithmic scale. Plasma concentrations will be displayed superimposed in 1 plot for both dosages. Geometric mean profiles (including corresponding lower and upper limit of 95% CI for the linear scale, without CI on the semi-logarithmic scale) will be displayed in the same way.

On the basis of plasma concentrations of the unchanged BRV and its metabolites obtained for each subject, the PK parameter values will be calculated. Pharmacokinetic parameter values will be calculated with Phoenix WinNonlin™. The methodology of PK parameter calculations will be detailed in the SAP.

12.4 Planned safety and other analyses

In general, all safety variables will be summarized using the SS.

12.4.1 Adverse events

All AEs will be characterized as pretreatment or treatment-emergent according to the intake of BRV.

Treatment-emergent AEs will be defined as those events that start on or after the date-time of first IMP administration, or whose severity worsens on or after the date of first administration of the IMP. Adverse Events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®).

The occurrence and incidence of TEAEs will be summarized by MedDRA system organ class and preferred term. The incidence of TEAEs will also be summarized by intensity and relationship to BRV.

Listings of all pretreatment AEs and TEAEs will be provided.

12.4.2 Clinical laboratory test

Laboratory variables and changes from Baseline (Day 1 pre-dose assessment) will be descriptively summarized at each time point. Shift tables from Baseline to each post-Baseline time point will be presented. Values outside the reference ranges will be flagged in the listings.

12.4.3 Vital signs and ECG

Vital sign variables and changes from Baseline will be descriptively summarized at each time point.

Electrocardiogram parameters (RR interval, PR interval, QRS interval, QT, corrected interval between Q and T waves on ECG [Bazett's Formula Correction], and corrected interval between Q and T Waves on ECG [Fridericia Correction]) and change from Baseline will be descriptively summarized by scheduled time point. Hereby, Baseline is defined as the mean of triplicate measurements of the ECG parameters prior to the first dose of study drug.

12.5 Handling of protocol deviations

In accordance with ICH E3, UCB will report only deviations from the protocol deemed by the study team as important. In general, important protocol deviations are those considered to have an impact on key safety or PK parameters, or study conduct, and will be identified from various sources such as programmed edit checks, programmed listings, and monitoring reports. The categories (safety, PK, and conduct) are not fixed and can be adapted, extended, or reduced according to the needs of the study.

The Specification of Protocol Deviations (SPD) document defines the criteria for identifying important protocol deviations.

The SPD and any amendments are authored by the CRO CPM and are based on the final protocol and protocol amendment(s), if any. The CRO CPM works in close collaboration with the CRO Lead Study Biostatistician and in consultation with the Partner Study Physician.

The important protocol deviations are to be reviewed and finalized during the Data Evaluation Meeting (DEM). The DEM will take place prior to database lock. Search criteria for potential protocol deviations will be detailed in the SPD.

All important protocol deviations will be listed by subject.

12.6 Handling of dropouts or missing data

If single data points for plasma concentrations are missing, the AUC parameters will be derived by interpolating with regard to the 2 neighboring nonmissing concentrations.

Subjects who drop out from the study before completion of study procedures and for any other reason than for safety issues will be replaced with subjects of the same gender after consultation with the Sponsor.

The handling of other missing data will be detailed in the SAP.

12.7 Planned interim analysis and data monitoring

No interim analysis and data monitoring are planned.

12.8 Determination of sample size

Twelve subjects will be allocated to treatment.

Due to the primary objective of the study being related to PK and safety, no power calculation of the study sample size was performed. In the event of dropouts, subjects will be replaced with subjects of the same gender after consulting with the Sponsor.

13 ETHICS AND REGULATORY REQUIREMENTS

13.1 Informed consent

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

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

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

If the Informed Consent form 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 Informed Consent form by the IRB/IEC and use of the amended form.

13.2 Subject identification cards

Upon signing the Informed Consent and Assent form (as applicable), the subject or legal representative will be provided with a subject identification card in the language of the subject. The Investigator will fill in the subject identifying information and medical emergency contact information. The Investigator will instruct the subject to keep the card with him/her at all times.

13.3 Institutional Review Boards and Independent Ethics Committees

The study will be conducted under the auspices of an 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.

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

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

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

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

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

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

13.4 Subject privacy

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

The Investigator agrees that representatives of UCB, its designee, representatives of the relevant IRB/IEC, or representatives of regulatory authorities will be allowed to review that portion of the subject'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 subject's study participation, and autopsy reports for deaths occurring during the study).

13.5 Protocol amendments

Protocol changes may affect the legal and ethical status of the study and may also affect the statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective.

Significant changes to the protocol will only be made as an amendment to the protocol and must be approved by UCB, the IRB/IEC, and the regulatory authorities (if required), prior to being implemented.

14 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

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

15 REFERENCES

CPMP/ICH/135/95 Note for guidance on Good Clinical Practice (EMEA) Jul 2002.

Food and Drug Administration. Guidance for Industry. Drug-induced liver injury: premarketing clinical evaluation. US Dept of Health and Human Services, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, 07/2009.

16 APPENDICES

16.1 Protocol amendment 1

This protocol has been amended to incorporate the following:

- To remove the urine PK sample collection and analysis throughout the protocol.
- To update the study contact information
- To update the company name from SPRL to SRL
- To clarify study variables

In addition, minor administrative edits including typographical changes for formatting and/or spelling errors have been made.

Modifications and changes

Global changes

Clarification of the study protocol title from “single oral dose and multiple oral doses” to “a single and multiple oral doses”

Specific changes

Change 1: Update Study contact information			
STUDY CONTACT INFORAMTION	Clinical Project Manager [redacted] UCB Trading (Shanghai) Co. Ltd. Suite 2802, Raffles City Shanghai Office Tower 268 Tibet Road Central, Shanghai 200001 PEOPLE'S REPUBLIC OF CHINA [redacted] [redacted]	**TBD** [redacted] ~~UCB Trading (Shanghai) Co. Ltd.~~ ~~Suite 2802, Raffles City Shanghai Office Tower~~ ~~268 Tibet Road Central, Shanghai 200001~~ ~~PEOPLE'S REPUBLIC OF CHINA~~ [redacted] [redacted]	Remove clinical project manager
STUDY CONTACT INFORAMTION	Clinical Trial Biostatistician [redacted] UCB Japan Co. Ltd. Shinjuku Grand Tower 8-17-1 Nishi-Shinjuku Shinjuku-ku Tokyo 160-0023 JAPAN [redacted] [redacted]	Clinical Trial Biostatistician [redacted] **Suite 2802, Raffles City, Shanghai Office Tower,** **268 Tibet Road Central, Shanghai 200001 PRC** [redacted]	Update Clinical Trial Biostatistician

Protocol section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Change 2: Removed urine concentration of BRV and metabolites text			
Section 1	1 Summary In addition, all urine will be collected and will be used to evaluate the urinary concentration of BRV and its metabolites. In the Multiple-Dose Period, the same subjects as in the Single-Dose Period will receive BRV 200mg/day (100mg every 12h) under fasting conditions with 200mL of water. Blood samples will be taken predose and at specified time points postdose for the determination of the PK profile of BRV and metabolites (ucb-42145, ucb 100406-1, and ucb107092-1). In addition, all urine will be collected and will be used to evaluate the urinary concentration of BRV and metabolites. Blood and urine samples will also be used to evaluate the urinary excretion of BRV.	1 Summary ~~In addition, all urine will be collected and will be used to evaluate the urinary concentration of BRV and its metabolites.~~ In the Multiple-Dose Period, the same subjects as in the Single-Dose Period will receive BRV 200mg/day (100mg every 12h) under fasting conditions with 200mL of water. Blood samples will be taken predose and at specified time points postdose for the determination of the PK profile of BRV and metabolites (ucb-42145, ucb 100406-1, and ucb107092-1). ~~In addition, all urine will be collected and will be used to evaluate the urinary concentration of BRV and metabolites~~. Blood and urine samples will also be used to evaluate the urinary excretion of BRV.	Remove urine PK text
Change 3: Removed urine PK associated tests			
Section 4.1	4.1 Primary pharmacokinetic variables • Concentrations of BRV and 3 metabolites (ucb-42145, ucb-100406-1, and ucb107092-1) in plasma and urine	Concentrations of BRV and 3 metabolites (ucb-42145, ucb-100406-1, and ucb107092-1) in plasma ~~and urine~~	Remove urine PK text

Protocol section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 4.2	4.2 Secondary pharmacokinetic variables • For the single dose: – t_{max}, $t_{1/2}$, λ_z , MRT, AUC, CL/F, and Vz/F of BRV in plasma – C_{max}, t_{max}, $t_{½}$, λ_z, $AUC_{(0-t)}$, and AUC of metabolites in plasma – Ae, f_e, and CL_R of BRV and metabolites in urine • For the multiple dose: – t_{max}, $t_{½}$, λ_z, $C_{min,ss}$, $C_{av,ss}$, CL_{ss}/F, and Vz/F of BRV in plasma – t_{max}, $t_{½}$, λ_z, $C_{max,ss}$, and $AUC_{(0-12),\ ss}$ of metabolites in plasma – Ae, f_e, and CL_R of BRV and metabolites in urine – PTF of BRV in steady-state	4.2 Secondary pharmacokinetic variables • For the single dose: – t_{max}, $t_{1/2}$, λ_z , MRT, AUC, CL/F, and Vz/F of BRV in plasma – C_{max}, t_{max}, $t_{½}$, λ_z, $AUC_{(0-t)}$, and AUC of metabolites in plasma ~~– Ae, f_e, and CL_R of BRV and metabolites in urine~~ • For the multiple dose: – t_{max}, $t_{½}$, λ_z, $C_{min,ss}$, $C_{av,ss}$, CL_{ss}/F, and Vz/F of BRV in plasma – t_{max}, $t_{½}$, λ_z, $C_{max,ss}$, and $AUC_{(0-12),\ ss}$ of metabolites in plasma ~~– Ae, f_e, and CL_R of BRV and metabolites in urine~~ – PTF of BRV in steady-state	Remove urine PK text
Change 4: Clarified study variables			
Section 4.3	4.3 Pharmacogenomic variable	4.3 ~~Pharmacogenomic~~ **Other** variable	Clarify study variables

Protocol section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 4.4	4.4 Safety variables • Adverse events • Vital signs (blood pressure and pulse rate in supine and standing positions) • Standard 12-lead ECGs • Clinical laboratory values (hematology, blood chemistry, and urinalysis)	4.4 Safety variables 4.4.1 Primary safety variable ~~The following will be assessed as primary safety variable:~~ • **Incidence of** TEAEs ~~from Baseline to SFU~~ 4.4.2 Other safety variables • Changes in vital signs (**systolic blood pressure [SBP], diastolic blood pressure [DBP],** ~~blood pressure and~~ pulse rate, ~~in supine and standing positions~~ **respiratory rate, and body temperature**) • Standard 12-lead ECGs **parameters and findings** • **Changes in** clinical laboratory ~~values~~ test parameters (hematology, blood chemistry, and urinalysis)	Clarify study variables
Change 5: Removed urine PK associated tests			

Protocol section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 5.1	5.1 Study description In addition, all urine will be collected (predosing, 0 to 6h, 6 to 12h, 12 to 24h, 24 to 36h, 36 to 48h, and 48 to 72h after administration) and will be used to evaluate the urinary concentration of BRV and metabolites. In the Multiple-Dose Period, subjects will receive BRV 200mg/day (100mg every 12 hours). Subjects will receive BRV under fasting conditions with 200mL water. Blood samples will be taken for the determination of the PK profile of BRV and its metabolites (ucb-42145, ucb 100406-1, and ucb107092-1) predose prior to the morning dose administration on Day 5 to Day 9, and at predosing and at the following time points after the last administration of the IMP on Day 10: 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16, 24, 36, 48, and 72h. In addition, all urine will be collected (0 to 12h, 12 to 24h, 24 to 48h, and 48 to 72h after the final study drug administration) and will be used to evaluate the urinary concentration of BRV and its metabolites. Blood and urine samples will be collected to evaluate the urinary excretion of BRV.	~~In addition, all urine will be collected (predosing, 0 to 6h, 6 to 12h, 12 to 24h, 24 to 36h, 36 to 48h, and 48 to 72h after administration) and will be used to evaluate the urinary concentration of BRV and metabolites.~~ In the Multiple-Dose Period, subjects will receive BRV 200mg/day (100mg every 12 hours). Subjects will receive BRV under fasting conditions with 200mL water. Blood samples will be taken for the determination of the PK profile of BRV and its metabolites (ucb-42145, ucb 100406-1, and ucb107092-1) predose prior to the morning dose administration on Day 5 to Day 9, and at predosing and at the following time points after the last administration of the IMP on Day 10: 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16, 24, 36, 48, and 72h. ~~In addition, all urine will be collected (0 to 12h, 12 to 24h, 24 to 48h, and 48 to 72h after the final study drug administration) and will be used to evaluate the urinary concentration of BRV and its metabolites. Blood and urine samples will be collected to evaluate the urinary excretion of BRV.~~	Remove urine PK text
Change 6: Removed urine PK from study related tables			

Protocol section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 5.2	Table 5-1 Schedule of study assessments	The PK urine activity was removed from the table to include footnote j	Remove urine PK activity
Section 5.2	Table 5-2 Single-Dose Period: schedule for ECGs, vital signs, and PK sampling	The urine sample for PK and associated footnote b was removed from the table.	Remove urine PK activity
Section 5.2	Table 5-4 Multiple-Dose Period: schedule for PK sampling	The urine sample for PK and associated footnote b was removed from the table.	Remove urine PK activity
Change 7: Removed urine PK from study visits			
Section 8.3	8.3 Day 1	The following bullets were removed: • ~~Obtain urine sample for urine PK~~ • ~~Obtain urine samples for urine PK at the following intervals: 0 to 6h, 6 to 12h, and 12 to 24h postdose~~	Remove urine PK activity
Section 8.4	8.4 Day 2	The following bullet was removed: • ~~Obtain urine samples for urine PK at the following intervals: 12 to 24h, 24 to 36h, 36 to 48h postdose~~	Remove urine PK activity
Section 8.5	8.5 Day 3	The following bullet was removed: • ~~Obtain urine samples for urine PK at the following interval: 36 to 48h postdose~~	Remove urine PK activity
Section 8.6	8.6 Day 4	The following bullet was removed: • ~~Obtain urine samples for urine PK at the following intervals: 48 to 72h postdose~~	Remove urine PK activity

Protocol section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 8.12	8.12 Day 10	The following bullets were removed: ~~• Obtain urine sample for urine PK~~ ~~• Obtain urine samples for urine PK at the following intervals: 0 to 12h and 12 to 24h postdose~~	Remove urine PK activity
Section 8.13	8.13 Day 11	The following bullet was removed: ~~• Obtain urine samples for urine PK at the following intervals: 12 to 24h and 24 to 48h postdose~~	Remove urine PK activity
Section 8.14	8.14 Day 12	The following bullet was removed: ~~• Obtain urine samples for urine PK at the following intervals: 24 to 48h and 48 to 72h postdose~~	Remove urine PK activity
Section 8.15	8.15 Day 13	The following bullet was removed: ~~• Obtain urine samples for urine PK at the following intervals: 48 to 72h postdose~~	Remove urine PK activity
Change 8: Removed urine from PK parameters			
Section 9.1	9.1 Blood sampling for determination of PK parameters The unchanged drug and its metabolites (ucb-42145, ucb-100406-1, and ucb107092-1) in plasma and urine will be determined with a validated liquid chromatography coupled with mass spectrometry/mass spectrometry (LC-MS/MS) method.	The unchanged drug and its metabolites (ucb-42145, ucb-100406-1, and ucb107092-1) in plasma ~~and urine~~ will be determined with a validated liquid chromatography coupled with mass spectrometry/mass spectrometry (LC-MS/MS) method.	Remove urine PK text

Protocol section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 9.2	9.2 Urine for determination of PK parameters	The entire section 9.2 was deleted and following section numbers were adjusted accordingly	Remove urine PK text
Change 9: Clarified statistical analysis			
Section 12.2	Section 12.2 General statistical considerations All statistical analyses of the PK and safety variables will be considered exploratory. Datasets will be analyzed using SAS version 9.1.3 or higher.	All statistical analyses ~~of the PK and safety variables~~ will be ~~considered exploratory. Datasets will be analyzed~~ **performed** using SAS version 9.~~1.~~3 or higher.	Clarification of analysis
Change 10: Removed urine concentration of BRV and metabolites text and clarified dosages			
Section 12.3.1	12.3.1 Analysis of the primary pharmacokinetics variable Individual concentration-time profiles will be displayed graphically on a linear scale and semi logarithmic scale. Plasma concentrations will be displayed superimposed in 1 plot for both treatments.	Individual concentration-time profiles will be displayed graphically on a linear scale and semi logarithmic scale. Plasma concentrations will be displayed superimposed in 1 plot for both ~~treatments~~ **dosages**. The fifth paragraph was deleted: ~~On the basis of urine concentrations of the unchanged drug and its metabolites obtained for each subject, the PK parameter values will be calculated.~~	Remove urine PK text
Change 11: Clarified statistical analysis			
Section 12.4	12.4 Planned safety and other analyses In general, all safety variables will be summarized by treatment using the SS.	In general, all safety variables will be summarized ~~by treatment~~ using the SS.	
Change 12: Created a section sub-header for laboratory information			

Protocol section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 12.4.1	12.4.1 Adverse events Laboratory variables and changes from Baseline (Day 1 pre-dose assessment) will be descriptively summarized at each time point. Shift tables from Baseline to each post-Baseline time point will be presented. Values outside the reference ranges will be flagged in the listings.	**12.4.2 Clinical laboratory test** Laboratory variables and changes from Baseline (Day 1 **pre-dose** assessment) will be descriptively summarized at each time point. Shift tables from Baseline to each post-Baseline time point will be presented. Values outside the reference ranges will be flagged in the listings.	Clarify laboratory information
Change 13: Clarified ECG parameters measurement			
Section 12.4.3	12.4.3 Vital signs and ECG Hereby, Baseline is defined as the mean of triplicate measurements of the ECG parameters at predose of Day 1.	Hereby, Baseline is defined as the mean of triplicate measurements of the ECG parameters ~~at predose of Day 1~~ **prior to the first dose of study drug**~~.~~	Clarify ECG parameters
Change 14: Clarified impact on safety parameters			
Section 12.5	12.5 Handling of protocol deviations In general, important protocol deviations are those considered to have an impact on safety or PK parameters, or study conduct, and will be identified from various sources such as programmed edit checks, programmed listings, and monitoring reports. The CRO CPM works in close collaboration with the CRO Lead Study Biostatistician and in consultation with the Partner Study Physician and other CRO study team members as appropriate.	In general, important protocol deviations are those considered to have an impact on **key** safety or PK parameters, or study conduct, and will be identified from various sources such as programmed edit checks, programmed listings, and monitoring reports. The CRO CPM works in close collaboration with the CRO Lead Study Biostatistician and in consultation with the Partner Study Physician ~~and other CRO study team members as appropriate~~.	Clarify safety parameters
Change 15: Removed urine as a plasma concentration data point			

Protocol section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 12.6	12.6 Handling of dropouts or missing data If single data points for plasma or urine concentrations are missing, the AUC parameters will be derived by interpolating with regard to the 2 neighboring nonmissing concentrations.	If single data points for plasma ~~or urine~~ concentrations are missing, the AUC parameters will be derived by interpolating with regard to the 2 neighboring nonmissing concentrations.	Remove urine PK text

16.2 Protocol amendment 2

This protocol has been amended to incorporate the following:

- To update the study contact information
- To clarify the vital sign measurements
- To remove the genotype sample collection and analysis throughout the protocol
- To clarify assessment windows for vital signs and ECGs
- To modify the contraceptive inclusion criterion to include male subjects
- To change the maximum pulse rate for eligible subjects
- To clarify exclusion criteria for alcohol and drug abuse, medical history, and caffeine intake
- To clarify retesting for liver function tests
- To clarify fasting conditions for study drug administration
- To remove the optional hepatic investigation sample collection

In addition, minor administrative edits including typographical changes for formatting and/or abbreviations have been made.

Modifications and changes

Specific changes

Protocol section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Change 1: Update Study contact information			
STUDY CONTACT INFORMATION	Suite 4106	Suite ~~4106~~**2802**	Update contact information
STUDY CONTACT INFORMATION	Clinical Project Manager [redacted]	Clinical Project Manager [redacted] **Suite 2802** **Raffles City Shanghai Office Tower** **268 Tibet Road Central** **Shanghai 200001** **People's Republic of China** [redacted] [redacted]	Add clinical project manager

Protocol section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Change 2: Clarified background information			
Section 1	Brivaracetam is extensively metabolized (>90%), primarily by hydrolysis of the amide group to a carboxylic acid supported by non-cytochrome P450 (CYP) dependent amidase, and secondarily through CYP2C19-mediated hydroxylation of the side chain.	Brivaracetam is extensively metabolized (>90%), primarily by ~~hydrolysis of the amide group to a carboxylic acid supported by~~ **non-cytochrome P450 (CYP) dependent hydrolysis of the amide group to a carboxylic acid via amidase**~~non-cytochrome P450 (CYP) dependent amidase~~, and secondarily through CYP2C19-mediated hydroxylation of the side chain.	Clarify background information
Change 3: Clarified vital sign measurements			
Section 1	vital signs (pulse rate, blood pressure)	vital signs (**systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate, respiratory rate, and body temperature**~~pulse rate, blood pressure~~)	Clarify vital signs measurements
Section 5.1	vital signs (pulse rate, blood pressure)	vital signs (**SBP, DBP, pulse rate, respiratory rate, and body temperature**~~pulse rate, blood pressure~~)	Clarify vital signs measurements
Table 5-2	Vital signs (BP, pulse)	Vital signs[b] ~~(BP, pulse)~~ [b] **Vital sign assessments include SBP, DBP, pulse rate, respiratory rate, and body temperature.**	Clarify vital signs measurements

Protocol section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Table 5-3	Vital signs (BP, pulse)	Vital signs[b] ~~(BP, pulse)~~ [b] **Vital sign assessments include SBP, DBP, pulse rate, respiratory rate, and body temperature.**	Clarify vital signs measurements
Section 8.1	• Obtain vital sign measurements (blood pressure [BP] and pulse rate)	• Obtain vital sign measurements (**SBP, DBP, pulse rate, respiratory rate, and body temperature**~~blood pressure [BP] and pulse rate~~)	Clarify vital signs measurements
Section 8.3	• Obtain vital sign measurements (BP and pulse rate)	• Obtain vital sign measurements (**SBP, DBP, pulse rate, respiratory rate, and body temperature**~~blood pressure [BP] and pulse rate~~)	Clarify vital signs measurements
Section 8.6	• Obtain vital sign measurements (BP and pulse rate)	• Obtain vital sign measurements (**SBP, DBP, pulse rate, respiratory rate, and body temperature**~~blood pressure [BP] and pulse rate~~)	Clarify vital signs measurements
Section 8.9	• Obtain vital sign measurements (BP and pulse rate)	• Obtain vital sign measurements (**SBP, DBP, pulse rate, respiratory rate, and body temperature**~~blood pressure [BP] and pulse rate~~)	Clarify vital signs measurements
Section 8.12	• Obtain vital sign measurements (BP and pulse rate)	• Obtain vital sign measurements (**SBP, DBP, pulse rate, respiratory rate, and body temperature**~~blood pressure [BP] and pulse rate~~)	Clarify vital signs measurements
Section 8.15	• Obtain vital sign measurements (BP and pulse rate)	• Obtain vital sign measurements (**SBP, DBP, pulse rate, respiratory rate, and body temperature**~~blood pressure [BP] and pulse rate~~)	Clarify vital signs measurements

Protocol section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 10.3.3	At time points specified in Table 5–2 and Table 5–3, blood pressure and pulse rate in supine and standing positions will be recorded at supine rest (at least 5 minutes) and 1 minute after standing.	At time points specified in Table 5–2 and Table 5–3, **SBP, DBP, pulse rate, respiratory rate, and body temperature**~~blood pressure and pulse rate~~ in supine and standing positions will be recorded at supine rest (at least 5 minutes) and 1 minute after standing.	Clarify vital signs measurements
Change 4: Clarified indication			
Section 2	A clinical development program for BRV is underway in China and will support a market authorization application/new drug application for BRV in China for the indication of adjunctive treatment in subjects 16 years and older with refractory partial-onset seizures whether or not secondarily generalized.	A clinical development program for BRV is underway in China and will support a market authorization application/new drug application for BRV in China for the indication of adjunctive treatment in subjects 16 years and older with ~~refractory~~ partial-onset seizures whether or not secondarily generalized.	Clarify indication
Change 5: Removed genotype variable			
Section 4.3	4.3 Other variable CYP2C19 (*2,*3) alleles (Genotype) will be evaluated.	~~4.3 Other variable~~ ~~CYP2C19 (*2,*3) alleles (Genotype) will be evaluated.~~	Remove the genotype sample collection and analysis
Table 5-1	Genotyping	~~Genotyping~~	Remove the genotype sample collection and analysis

Protocol section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 8.3	• Obtain blood samples for safety laboratory assessments, genotyping, and plasma PK	• Obtain blood samples for safety laboratory assessments~~, genotyping,~~ and plasma PK	Remove the genotype sample collection and analysis
Change 6: Clarified assessment windows for vital signs and ECGs and for study drug administration			
Section 5.1	In the Multiple-Dose Period, subjects will receive BRV 200mg/day (100mg every 12 hours).	In the Multiple-Dose Period, subjects will receive BRV 200mg/day (100mg every 12**h ±15min**).	Clarify study drug administration window
Table 5-1	[c] Three ECGs to be performed at 15min intervals within 24h prior to BRV dosing on Day 1 to provide a representative baseline. [h] From Day 5 to Day 9, study drug will be administered in the morning and evening with an interval of 12h. [i] On Day 10, study drug will be administered only in the morning.	[c] Three ECGs to be performed at 15min **(±5min)** intervals within 24h prior to BRV dosing on Day 1 to provide a representative baseline. [h] From Day 5 to Day 9, study drug will be administered in the morning and evening with an interval of 12h **(±15min)**. [i] On Day 10, study drug will be administered only in the morning **12h (±15min) after the last dose**.	Clarify assessment windows for vital signs and ECGs and for study drug administration
Table 5-2	[a] Three ECGs to be performed at 15min intervals within 24h prior to BRV dosing on Day 1 to provide a representative baseline.	**Note: A window of ±15min is allowed for all ECG and vital signs assessments postdose.** [a] Three ECGs to be performed at 15min **(±5min)** intervals within 24h prior to BRV dosing on Day 1 to provide a representative baseline.	Clarify assessment windows for vital signs and ECGs

Protocol section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Table 5-3	None	**Note: A window of ±15min is allowed for all ECG and vital signs assessments postdose.**	Clarify assessment windows for vital signs and ECGs
Change 7: Modified the contraceptive inclusion criteria to include male subjects			
Section 6.1	4. Pregnancy waiver form signed by subject, if female of childbearing potential. Beta-human chorionic gonadotropin test is documented negative within 48 hours before Day 1 and a medically accepted method of contraception (hormonal contraception, intrauterine device (IUD), implant device, diaphragm with spermicide, bilateral tubal ligation, monogamous relationship with vasectomized [for at least 3 months] partner or using condoms with spermicidal gel, sexually inactive) is used during the entire duration of the study.	4**a**. Pregnancy waiver form signed by subject, if female of childbearing potential. Beta-human chorionic gonadotropin test is documented negative within 48 hours before Day 1 and a medically accepted method of contraception (hormonal contraception, intrauterine device (IUD), implant device, diaphragm with spermicide, bilateral tubal ligation, monogamous relationship with vasectomized [for at least 3 months] partner or using condoms with spermicidal gel, sexually inactive) is used during the entire duration of the study. **Male participants with a pregnant or breastfeeding partner or female partner of childbearing potential must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the study.**	Modify contraceptive inclusion criterion to include male subjects

Protocol section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Change 8: Changed the maximum pulse rate for eligible subjects			
Section 6.1	7. Subjects with supine blood pressure levels of between 90 to 150 and 60 to 90mmHg (inclusive) for systolic and diastolic, respectively, with pulse rate of 50 to 90bpm (supine position, inclusive) at Screening Visit.	7. Subjects with supine blood pressure levels of between 90 to 150 and 60 to 90mmHg (inclusive) for systolic and diastolic, respectively, with pulse rate of 50 to ~~90~~**100** beats per minute (bpm) (supine position, inclusive) at Screening Visit.	Change the maximum pulse rate for eligible subjects
Change 9: Clarified exclusion criteria for alcohol and drug abuse, medical history, and caffeine intake			
Section 6.2	3. Subject has a history of chronic alcohol or drug abuse within the previous 6 months. Subject consumes more than 30g alcohol/day (amount corresponds to 750mL beer/day or 375mL wine/day or 90mL liquor/day) for men and 20g alcohol/day (amount corresponds to 500mL beer/day or 250mL wine/day or 60mL liquor/day) for women.	3**a**. Subject has a history of chronic alcohol or drug abuse within the previous 6 months. Subject consumes **on average** more than 30g alcohol/day (amount corresponds to 750mL beer/day or 375mL wine/day or 90mL liquor/day) for men and 20g alcohol/day (amount corresponds to 500mL beer/day or 250mL wine/day or 60mL liquor/day) for women.	Clarify exclusion criterion for alcohol and drug abuse
Section 6.2	7. Subjects with any previous or current cardiovascular, respiratory, hepatic, renal, digestive, endocrine, or nervous system disorder that may affect absorption, secretion, metabolism, or excretion of the investigational product.	7**a**. Subjects with any previous or current cardiovascular, respiratory, hepatic, renal, digestive, endocrine, or nervous system disorder that may affect absorption, secretion, metabolism, or excretion of the investigational product **per Investigator judgment**.	Clarify exclusion criterion for medical history
Section 6.2	13. Subject has a consumption of more than 600mg of caffeine/day (1 cup of coffee contains approximately 100mg of caffeine, 1 cup of tea approximately 30mg, and 1 glass of cola approximately 20mg).	13**a**. Subject has a consumption of more than 600mg of caffeine/day **on average** (1 cup of coffee contains approximately 100mg of	Clarify exclusion criterion for caffeine intake

Protocol section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
		caffeine, 1 cup of tea approximately 30mg, and 1 glass of cola approximately 20mg).	
Change 10: Clarified retesting for liver function tests			
Section 6.2	18. Subject has > upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%). For subjects with a baseline result >ULN for ALT, AST, ALP, or total bilirubin, a baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the electronic Case Report form (eCRF). If subject has >ULN ALT, AST, or ALP that does not meet the exclusion limit at screening, repeat the tests, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the subject must be discussed with the Medical Monitor.	18a. Subject has > upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%). ~~For subjects with a baseline result >ULN for ALT, AST, ALP, or total bilirubin, a baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the electronic Case Report form (eCRF).~~ ~~If subject has >ULN ALT, AST, or ALP that does not meet the exclusion limit at screening, repeat the tests, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the subject must be discussed with the Medical Monitor.~~	Clarify retesting for liver function tests

Protocol section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
		Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). **For subjects with a screening result >ULN for total bilirubin, a baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the electronic Case Report form (eCRF).** **Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. If the repeat values are below ULN the subject will be considered to not meet the exclusion criteria.**	
Change 11: Clarified fasting conditions for study drug administration			
Section 6.4	None	**6.4 Other study restrictions** **All BRV treatments will be administered under fasting conditions. For Day 1 and Day 10, subjects will be required to fast for ≥10h prior to dosing and until 3h after IMP administration. For Day 5 to Day 9, 2h fasting before and after dosing for morning and night dose is required. During fasting, no fluids are allowed except water; however, water is not allowed from 2h predose until 1h after the**	Clarify fasting conditions for study drug administration

Protocol section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
		start of treatment (apart from the water taken with the oral dosing). **Subjects must refrain from smoking and consuming alcohol and caffeine-containing products (chocolate, cola, coffee, or tea) from 48h before treatment until Final Discharge from the study.** **Subjects must refrain from consuming grapefruit, grapefruit juice, and grapefruit-containing products from 7 days before first drug administration through the end of the study.**	
Change 12: Clarified assessment windows for vital signs and ECGs and for study drug administration during study visits			
Section 8.2	• Perform 12-lead ECG (3 ECGs will be performed at 15min intervals within 24h before dosing of BRV on Day 1)	Perform 12-lead ECG (3 ECGs will be performed at 15min **[±5min]** intervals within 24h before dosing of BRV on Day 1)	Clarify assessment window for ECGs

Protocol section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 8.3	The following procedures will be performed predose: • Perform 12-lead ECG (if not performed on Day -1, 3 ECGs will be performed at 15min intervals within 24h before dosing of BRV on Day 1) The following procedures will be performed postdose: • Obtain vital sign measurements (BP and pulse rate) at 1, 2, and 4h postdose • Perform 12-lead ECG at 1, 2, and 4h postdose	The following procedures will be performed predose: • Perform 12-lead ECG (if not performed on Day -1, 3 ECGs will be performed at 15min **[±5min]** intervals within 24h before dosing of BRV on Day 1) The following procedures will be performed postdose: • Obtain vital sign measurements (**SBP, DBP, pulse rate, respiratory rate, and body temperature**~~BP and pulse rate~~) at 1, 2, and 4h postdose**. A window of ±15min is allowed.** • Perform 12-lead ECG at 1, 2, and 4h postdose**. A window of ±15min is allowed.**	Clarify assessment windows for vital signs and ECGs
Section 8.6	• Obtain vital sign measurements (BP and pulse rate) at 72h postdose • Perform 12-lead ECG at 72h postdose	• Obtain vital sign measurements (**SBP, DBP, pulse rate, respiratory rate, and body temperature**~~BP and pulse rate~~) at 72h **(±15min)** postdose • Perform 12-lead ECG at 72h **(±15min)** postdose	Clarify assessment windows for vital signs and ECGs
Section 8.7	The following procedures will be performed postdose: • Study drug administration 12h after the morning dose	The following procedures will be performed postdose: • Study drug administration 12h **(±15min)** after the morning dose	Clarify assessment windows for vital signs and ECGs

Protocol section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 8.8	• Study drug administration (after all predose assessments are completed) in the morning The following procedures will be performed postdose: • Study drug administration 12h after the morning dose	• Study drug administration (after all predose assessments are completed) in the morning **12h (±15min) after the last dose** The following procedures will be performed postdose: • Study drug administration 12h **(±15min)** after the morning dose	Clarify assessment windows for vital signs and ECGs and for study drug administration
Section 8.9	• Study drug administration (after all predose assessments are completed) in the morning The following procedures will be performed postdose: • Study drug administration 12h after the morning dose	• Study drug administration (after all predose assessments are completed) in the morning **12h (±15min) after the last dose** The following procedures will be performed postdose: • Study drug administration 12h **(±15min)** after the morning dose	Clarify assessment windows for vital signs and ECGs and for study drug administration
Section 8.10	• Study drug administration (after all predose assessments are completed) in the morning The following procedures will be performed postdose: • Study drug administration 12h after the morning dose	• Study drug administration (after all predose assessments are completed) in the morning **12h (±15min) after the last dose** The following procedures will be performed postdose: • Study drug administration 12h **(±15min)** after the morning dose	Clarify assessment windows for vital signs and ECGs and for study drug administration

Protocol section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 8.11	• Study drug administration (after all predose assessments are completed) in the morning The following procedures will be performed postdose: • Study drug administration 12h after the morning dose	• Study drug administration (after all predose assessments are completed) in the morning **12h (±15min) after the last dose** The following procedures will be performed postdose: • Study drug administration 12h **(±15min)** after the morning dose	Clarify assessment windows for vital signs and ECGs and for study drug administration
Section 8.12	• Study drug administration (after all predose assessments are completed) in the morning The following procedures will be performed postdose: • Obtain vital sign measurements (BP and pulse rate) at 1, 2, and 4h postdose • Perform 12-lead ECGs at 1, 2, and 4h postdose	• Study drug administration (after all predose assessments are completed) in the morning **12h (±15min) after the last dose** The following procedures will be performed postdose: • Obtain vital sign measurements (**SBP, DBP, pulse rate, respiratory rate, and body temperature**~~BP and pulse rate~~) at 1, 2, and 4h postdose**. A window of ±15min is allowed.** • Perform 12-lead ECGs at 1, 2, and 4h postdose**. A window of ±15min is allowed.**	Clarify assessment windows for vital signs and ECGs and for study drug administration
Section 8.15	• Obtain vital sign measurements (BP and pulse rate) at 72h postdose • Perform 12-lead ECG at 72h postdose	• Obtain vital sign measurements (**SBP, DBP, pulse rate, respiratory rate, and body temperature**~~BP and pulse rate~~) at 72h **(±15min)** postdose • Perform 12-lead ECG at 72h **(±15min)** postdose	Clarify assessment windows for vital signs and ECGs

Protocol section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Change 13: Removed genotype analysis			
Section 9.2	9.2 Genotype analysis For the genotype analysis, 2.0mL of whole blood will be collected in a test tube containing ethylene diamine tetraacetic acid disodium salt (EDTA2Na). The sample will be sent to a genetic testing facility in a condition where individual identification is not impossible.	~~9.2 Genotype analysis~~ ~~For the genotype analysis, 2.0mL of whole blood will be collected in a test tube containing ethylene diamine tetraacetic acid disodium salt (EDTA2Na). The sample will be sent to a genetic testing facility in a condition where individual identification is not impossible.~~	Remove the genotype sample collection and analysis
Change 14: Removed the optional hepatic investigation sample collection			
Section 10.2.1.5	10.2.1.5 Optional hepatic investigation sample collection If a subject is undergoing further investigation for PDILI and has consented to retrospective genetic analysis per local regulations, the subject's blood sample will be shipped to a secure storage facility. The blood sample will be retained in the UCB Hepatic Investigation Biobank to solely support retrospective genetic analyses associated with an adverse therapeutic response to BRV. Genetic analyses of deoxyribonucleic acid isolated from the blood will be contracted by UCB to specialized third-party laboratories and analysis will be limited to:	~~10.2.1.5 Optional hepatic investigation sample collection~~ ~~If a subject is undergoing further investigation for PDILI and has consented to retrospective genetic analysis per local regulations, the subject's blood sample will be shipped to a secure storage facility. The blood sample will be retained in the UCB Hepatic Investigation Biobank to solely support retrospective genetic analyses associated with an adverse therapeutic response to BRV.~~ ~~Genetic analyses of deoxyribonucleic acid isolated from the blood will be contracted by UCB to specialized third-party laboratories and analysis will be limited to:~~ ~~• Uridine 5′-diphospho-glucuronosyltransferase loci − the loci~~	Remove the optional hepatic investigation sample collection

Protocol section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
	• Uridine 5′-diphospho-glucuronosyltransferase loci − the loci responsible for Gilbert's syndrome (hyperbilirubinemia) • Human leukocyte antigen (HLA) loci − for example, HLA-B5701 that has been associated with abacavir- and flucloxacillin-induced liver injury • Absorption, distribution, metabolism, and excretion gene loci associated with abnormal pharmacokinetics Genetic analysis of samples may be performed immediately, on a per-study basis, or as part of combined analyses across multiple studies belonging to the same clinical development program. As a result, samples will be retained for 15 years unless clinical development of the IMP is terminated, at which point all samples will be destroyed. The results determined using clinically approved diagnostic tests will be made available to the Investigator upon request. Subjects may request at any time that their sample be removed from the UCB Hepatic Investigation Biobank and destroyed, though data from analyses already performed will remain on file. All samples, associated materials, and data will be kept securely by UCB and its agents. A sample destruction request should be made in writing to the Investigator who will notify the UCB Biorepository Manager (Global Exploratory Development, UCB, Slough, SL1 3WE, United Kingdom).	~~responsible for Gilbert's syndrome (hyperbilirubinemia)~~ ~~• Human leukocyte antigen (HLA) loci − for example, HLA-B5701 that has been associated with abacavir- and flucloxacillin-induced liver injury~~ ~~• Absorption, distribution, metabolism, and excretion gene loci associated with abnormal pharmacokinetics~~ ~~Genetic analysis of samples may be performed immediately, on a per-study basis, or as part of combined analyses across multiple studies belonging to the same clinical development program. As a result, samples will be retained for 15 years unless clinical development of the IMP is terminated, at which point all samples will be destroyed. The results determined using clinically approved diagnostic tests will be made available to the Investigator upon request.~~ ~~Subjects may request at any time that their sample be removed from the UCB Hepatic Investigation Biobank and destroyed, though data from analyses already performed will remain on file. All samples, associated materials, and data will be kept securely by UCB and its agents. A sample destruction request should be made in writing to the Investigator who will notify the UCB Biorepository Manager (Global~~	

Protocol section(s) impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
		~~Exploratory Development, UCB, Slough, SL1 3WE, United Kingdom).~~	
Change 15: Removed genotype analysis			
Section 12.3.1	If CYP2C19 poor metabolizers are identified in the study, data may also be summarized by CYP2C19 poor or extensive metabolizer status.	~~If CYP2C19 poor metabolizers are identified in the study, data may also be summarized by CYP2C19 poor or extensive metabolizer status.~~	Remove the genotype sample collection and analysis

17 DECLARATION AND SIGNATURE OF INVESTIGATOR

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.

I will ensure that all subinvestigators and other staff members read and understand all aspects of this protocol.

I have received and read all study-related information provided to me.

The objectives and content of this protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by UCB.

All rights of publication of the results reside with UCB, unless other agreements were made in a separate contract.

Investigator:

Printed name	Date/Signature

18 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 and according to current Good Clinical Practice.

Approval Signatures

Name: ep0101-protocol-amend-2

Version: 1.0

Document Number: CLIN-000166592

Title: EP0101 Protocol Amendment 2

Approved Date: 10 Jan 2021

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 08-Jan-2021 18:46:49 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 09-Jan-2021 00:40:08 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Subject Matter Expert Date of Signature: 10-Jan-2021 08:36:35 GMT+0000