A SINGLE-DOSE, OPEN-LABEL, RANDOMIZED, 2-WAY CROSS-OVER STUDY TO ASSESS THE BIOEQUIVALENCE BETWEEN BRIVARACETAM TABLET AND DRY SYRUP IN HEALTHY MALE JAPANESE STUDY PARTICIPANTS

PROTOCOL EP0110 AMENDMENT 1.0

PHASE 1

SHORT TITLE:

A single-dose study to assess the bioequivalence between brivaracetam tablet and dry syrup in healthy Japanese study participants

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Date**	**Type of amendment**
Original Protocol	25 Feb 2021	Not applicable
Amendment 1.0	11 Jan 2022	Not applicable

Amendment 1.0 (11 Jan 2022)

Overall Rationale for the Amendment

EP0110 Protocol Amendment 1.0, dated 11 Jan 2022, was completed to:

- Implement the appropriate COVID-19 precautions during the global pandemic.
- Add COVID-19 vaccination guidance.
- Align the time points for collection of 12-lead ECG and vital sign assessments and remove the nonessential 0.5h postdose ECG assessment.
- Reduce the volume of water ingested with the BRV tablet and dry syrup formulations to align with Japan's guideline for bioequivalence studies.
- Align the limits for blood loss resulting in exclusion from the study with Japan's blood donation standards.
- Add an excipient to the former list for the dry syrup preparation.
- Lengthen the allowable deviation from scheduled time for PK blood samples at predose (0h).
- Provide additional clarification for BRV background information and study-specific procedures.
- Correct minor typographical errors and inconsistencies.

Section # and name	Description of change	Brief rationale
Section 1.1 Synopsis	Corrected the primary endpoints presented in the Objectives and Endpoints table.	Error correction.
Section 1.1 Synopsis Section 3 Objectives and endpoints	Added that the secondary endpoints are the incidence of TEAEs and **treatment-emergent** SAEs	Clarification.
Section 1.1 Synopsis Section 1.2 Schema Section 1.3 Schedule of Activities Section 4.1 Overall design	Revised the duration of the Screening Period from 20 days (2 to 21 days before administration of IMP) to 27 days (2 to 28 days before administration of IMP).	Screening Period extended by 7 days to better disperse the number of potential study participants attending Screening Visits to minimize the spread of COVID-19 infection during the global pandemic.
Section 1.1 Synopsis	Revised the maximum total study duration from 41 to 48 days to reflect the 7-day extension of the Screening Period.	Screening Period extended by 7 days to better disperse the number of potential study participants attending Screening Visits to minimize the spread of COVID-19 infection during the global pandemic.
Section 1.2 Schema	Revised the treatment sequences for Dosing Period 2 (A-B or B-A).	Error correction.
Section 1.3 Schedule of Activities	Replaced the 12-hour post dose vital signs assessment with an 8-hour timepoint.	Adjusted to align with the 8-hour ECG measurement time point.
Section 1.3 Schedule of Activities	Removed the 0.5 hour postdose 12-lead ECG assessment.	Reduced the number of assessments based upon the PK of BRV.
Section 1.3 Schedule of Activities Section 8.2.3 Electrocardiograms	Clarified text describing the Screening (Visit 1) ECG, which includes the collection of 3 Baseline values, measured at 2- to 5-minute intervals.	Clarification of study procedures.
Section 1.3 Schedule of Activities	Clarified footnote ‘f’ to state that Randomization will occur for Dosing Period 1 only, either on Day -1 or Day 1 before any assessment of Day 1.	Clarification of study procedures.
Section 1.3 Schedule of Activities	Added that IMP administration will occur under fasting conditions.	Alignment with the descriptive text in Section 5.3.4.
Section 2.2 Background	Revised text to state that study N01258 has completed.	Update.

Section 2.2 Background	Added that the 1 BRV formulation currently used of the 2 oral formulations developed for the pediatric program is the oral solution (10mg/mL).	Clarification.
Section 5.2 Exclusion criteria	Exclusion criterion 8 was revised to include that participants will be excluded if they receive a COVID-19 vaccine within 7 days of the first administration of IMP.	Revised to reduce the impact of vaccination side reactions on evaluations conducted in this study.
Section 5.2 Exclusion criteria	For exclusion criterion 14, the former symbol (>) was revised to reflect that study participants would be excluded if they experienced blood loss of ≥400mL within 90 days or ≥200 within 30 days.	Alignment with blood donation standards in Japan.
Section 5.3.4 Food intake times	Clarified text to state that a predose blood sample will be obtained prior to the study participant's first dose of IMP.	Clarification of study procedures.
Section 5.3.4 Food intake times Section 6.1 Treatments administered	Adjusted the amount of water that would be administered with the BRV tablet from 240mL to 200mL. Adjusted the amount of water that the study participant would rinse the dosing container and then ingest from 140mL to 100mL.	Alignment with Japanese guideline for BE studies that provides the range of 100 to 200mL of water with IMP administration.
Section 5.3.5 Other restrictions	Revised text stating that all study participants would be contacted by telephone 1 day prior to admission for assessing COVID-19 signs and symptoms to state that this would occur before admission and as close to admission as feasible.	Enhanced flexibility for the Investigator/site staff.
Section 6.1 Treatments administered	Added light anhydrous silicic acid to the list of excipients for BRV dry syrup.	Revised due to changes in the composition of the BRV dry syrup administered in the study.
Section 6.5.1 Permitted concomitant treatments (medications and therapies)	Revised text stating that COVID-19 vaccines would be permitted during the study to specify that they would only be permitted up to 7 days prior to the initiation of IMP administration.	Revised to reduce the impact of vaccination side reactions on evaluations conducted in this study.

Section 6.5.2 Prohibited concomitant treatments (medications and therapies)	Clarify that COVID-19 vaccines are prohibited within 7 days of first IMP administration and during the study until SFU.	Revised to reduce the impact of vaccination side reactions on evaluations conducted in this study.
Section 8.1 Pharmacokinetics	Increased the allowable deviation from scheduled time for PK blood samples at predose (0h) from 15 minutes to 30 minutes.	Enhanced flexibility for the Investigator/site staff.
Section 8.2.2 Vital signs	Clarified text stating that vital signs will be assessed with the study participant in a supine position following at least 5 minutes of rest.	Clarification of study procedures.
Section 9.1 Definition of analysis sets	Revised text to state that study participants will be excluded from the PK-PPS if their predose concentrations are greater than 5% of the corresponding C_{max} value in **both** Dosing Period**s**, rather than in either Dosing Period.	Error correction.
Section 9.3.1 Pharmacokinetic analyses	Revised text to state that PK analyses will be performed on the SS and statistical analyses will be performed on the PK-PPS.	Clarification.
Section 9.5 Handling of protocol deviations	Added text to clarify that data will not yet be available at the time of the Data Evaluation Meeting to define the final PK-PPS, based upon the definition of PK-PPS provided in Section 9.1.	Clarification.
Section 9.8 Determination of sample size	Added text to clarify that a total of 19 participants will provide a power of 90% at the 5% significance level **(one-sided)** to declare BE.	Clarification
Section 10.2 Appendix 2: Clinical Laboratory Tests	Revised that clinical laboratory tests would be performed by a central laboratory to state that they will be performed by a local laboratory.	The single site for this study has a certified local clinical laboratory available.
Section 10.2 Appendix 2: Clinical Laboratory Tests	Added WBC count to the list of hematology parameters to be assessed.	Error correction.
Section 10.2 Appendix 2: Clinical Laboratory Tests	Revised that instead of a urine alcohol screen, an alcohol breath test would be performed.	Error correction.

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	+32 2 386 2421
Email	DS_ICT@ucb.com

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol title: A single-dose, open-label, randomized, 2-way cross-over study to assess the bioequivalence between brivaracetam (BRV) tablet and dry syrup in healthy male Japanese study participants.

Short Title: A single-dose study to assess the bioequivalence between BRV tablet and dry syrup in healthy Japanese study participants.

Rationale:

A dry syrup formulation of BRV is being developed specifically for the Japanese market to allow dose adjustment by body weight in pediatric patients. This study aims to assess the bioequivalence between the BRV 50mg tablet and BRV 50mg as dry syrup formulations.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To demonstrate the bioequivalence between the BRV 50mg tablet and BRV 50mg as dry syrup after a single oral dose in healthy Japanese male study participants	Primary Endpoints: • C_{max} • $AUC_{(0-t)}$
Secondary	
• To evaluate the safety and tolerability of 2 oral dosage forms of BRV in healthy Japanese male study participants	Secondary endpoints: • Incidence of TEAEs • Incidence of treatment-emergent SAEs
Other	
Other PK Objective: • To evaluate other PK parameters of 2 oral dosage forms of BRV in healthy Japanese male study participants	The other PK endpoints will be calculated: • AUC • AUC_{extr} • CL/F • V_z/F • MRT • t_{max} • $t_{½}$ • λ_z

Objectives	Endpoints
Other Safety Objective: • To further evaluate the safety and tolerability of 2 oral dosage forms of BRV in healthy Japanese male study participants	Other safety endpoints will be assessed during the study: • Changes in clinical laboratory test parameters (ie, hematology, clinical chemistry, and urinalysis) • Changes in vital signs (SBP, DBP, pulse rate, respiratory rate, and body temperature) • 12-lead ECG parameters and findings • Physical examinations

λ_z=first order terminal elimination rate constant; AUC=area under the curve from 0 to infinity; $AUC_{(0-t)}$=area under the curve from 0 to the time of the last quantifiable concentration; AUC_{extr}=extrapolated AUC; BRV=brivaracetam; CL/F=total clearance after oral administration; C_{max}=maximum concentration; DBP=diastolic blood pressure; ECG=electrocardiogram; MRT=mean residence time (ie, of the unchanged drug in the systemic circulation); PK=pharmacokinetics; SAE=serious adverse event; SBP=systolic blood pressure; $t_{1/2}$=terminal elimination half-life; TEAE=treatment-emergent adverse event; t_{max}=time of C_{max}; Vz/F=apparent volume of distribution

Overall Design

EP0110 is a single-center, single-dose, open-label, randomized, 2-way cross-over study designed to assess the bioequivalence between the BRV 50mg tablet and BRV 50mg as dry syrup formulations in healthy Japanese male study participants after oral administration under fasted conditions. In addition, safety and tolerability of BRV will be evaluated.

Study participants will enter a Screening Period (2 to 28 days before administration of investigational medicinal product [IMP]) and eligible study participants will start Dosing Period 1. The Dosing Period consists of 2 periods (Dosing Period 1 and Dosing Period 2) of 4 days each with a single administration on Day 1 of each Dosing Period. The Dosing Periods will be separated by a Wash-Out Period (at least 7 days and no more than 10 days between the 2 administrations for each study participant) and followed by a Safety Follow-Up (SFU) Visit, 7 to 9 days after the last administration of IMP. Study participants who prematurely discontinue the IMP/study are to return for a Withdrawal Visit, 7 to 9 days after the last IMP administration. Refer to the study schematic in Figure 1-1.

On Day 1 of each Dosing Period, the study participants will receive 1 of the following treatments in randomized order under fasting conditions:

- Treatment A – a single dose of BRV 50mg tablet
- Treatment B – a single dose of BRV 50mg as dry syrup (1.25g of granules for oral solution 4% w/w)

The activities to be performed during the Dosing Periods are presented in the Schedule of Activities (Table 1-1).

Number of Study participants

A total of 24 study participants are planned to be randomized and complete the study; however, additional study participants may be randomized in case some study participants discontinue the study early (not only limited to coronavirus disease 2019 [COVID-19] circumstances).

Treatment Groups and Duration

The total duration of the study for an individual study participant is 17 days to 48 days and will include:

- A Screening Period (2 to 28 days before IMP administration)
- Two Dosing Periods (4 days each, with IMP administration on Day 1 of each Dosing Period)
- A Wash-out Period following Dosing Period 1 (7 to 10 days between the 2 IMP administrations)
- An SFU Visit/Withdrawal Visit (7 to 9 days after the last IMP administration)

Refer to Figure 1-1 for the study design.

In the Treatment A/Treatment B sequence, on Day 1 of Dosing Period 1, each study participant will receive a single dose of BRV tablet formulation (50mg). On Day 1 of Dosing Period 2, these same study participants will receive a single dose of BRV 50mg as dry syrup formulation (1.25g of granules for oral solution 4% w/w).

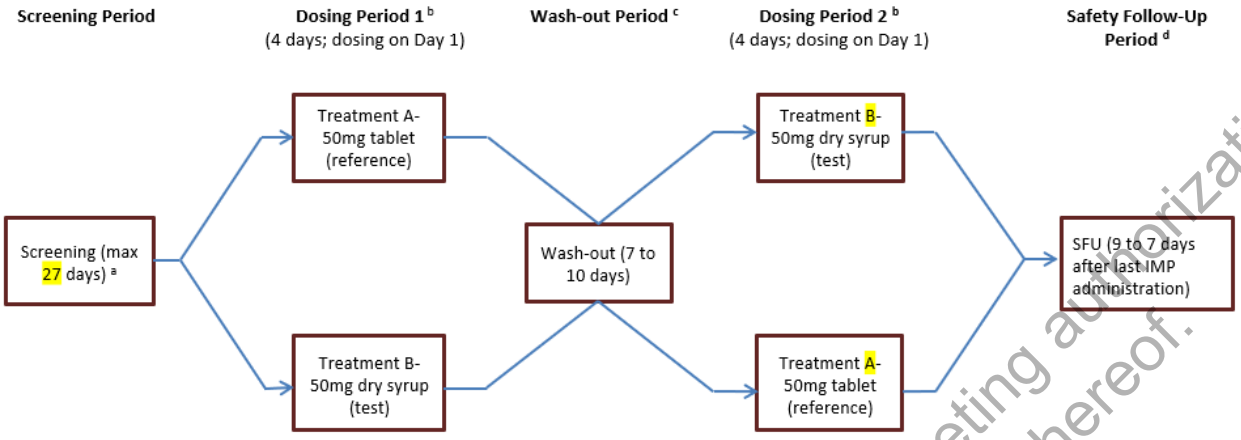
In the Treatment B/Treatment A sequence, on Day 1 of Dosing Period 1, each study participant will receive a single dose of BRV 50mg as dry syrup formulation (1.25g of granules for oral solution 4% w/w). On Day 1 of Dosing Period 2, these same study participants will receive a single dose of BRV tablet formulation (50mg).

The Dosing Periods will be separated by a Wash-out Period of at least 7 days and no more than 10 days between the 2 IMP administrations. Study participants will be discharged following Dosing Period 1 (on Day 3 of Dosing Period 1; 48 hours after IMP administration) with an appointment for their next check-in for Dosing Period 2. Study participants will check in 1 day before Dosing Period 2, which should start after the Wash-out Period (at least 7 days and no more than 10 days between the 2 IMP administrations). Study participants will be discharged after Dosing Period 2 (on Day 3 of Dosing Period 2; 48 hours after IMP administration) and will return to the study site for SFU Visit assessments, 7 to 9 days after the last IMP administration. Study participants who prematurely discontinue the IMP/study are to return for a Withdrawal Visit, 7 to 9 days after the last IMP administration.

1.2 Schema

A schematic of the study design is provided in Figure 1-1.

Figure 1-1: Schematic diagram



BRV=brivaracetam; IMP=investigational medicinal product; SFU=Safety Follow-Up

[a] Following a Screening Period (2 to 28 days before IMP administration), each study participant will be randomly assigned to 1 of 2 treatment sequences (A-B or B-A) before dosing in Dosing Period 1, after all Day -1 assessments have been completed. Treatment A – a single dose of BRV 50mg tablet and Treatment B – a single dose of BRV 50mg as dry syrup (1.25g of granules for oral solution 4% w/w).

[b] Each Dosing Period is 4 days (Day -1 to Day 3) with a single administration of IMP on Day 1 of each Dosing Period. For each Dosing Period, study participants will be admitted to the study site on Day -1 (1 day before dosing). Study participants will receive IMP on Day 1 and will be discharged in the morning of Day 3, approximately 48 hours after the administration of IMP.

[c] The 2 Dosing Periods will be separated by a Wash-Out Period of 7 to 10 days between IMP administrations.

[d] An SFU Visit will occur 7 to 9 days after the last administration of IMP. Study participants who prematurely discontinue the IMP/study will be encouraged to undergo Withdrawal Visit procedures within 7 to 9 days after the last administration of IMP.

1.3 Schedule of Activities

The Schedule of Activities is provided in Table 1-1.

Table 1-1: Schedule of Activities

Procedure	Screening	Dosing Period 1 or 2 [a]				SFU/Withdrawal [b]
	V1	V2 or V3				V4
	2 to 28 days before administration of IMP	Check in Day -1	Day 1	Day 2	Day 3	7 to 9 days after the last administration of IMP
Written informed consent	X					
Demographics, habits, and lifestyle	X					
Verification of inclusion/exclusion criteria	X	X				
Medical/surgical history	X					
Physical examination	X	X			X	X
Height and weight	X					
Viral serology (HBsAg, HCV, HIV, and syphilis)	X					
Urine drug test and alcohol breath test	X	X				
COVID-19 precautions [c]	X	X				X
Vital signs [d]	X		X	X	X	X
Clinical laboratory tests (hematology, clinical chemistry, and urinalysis)	X				X	X
Randomization [e]		X [f]				
12-lead ECG [g]	X		X	X	X	X
IMP administration [h]			X			
Blood sampling for PK [i]			X	X	X	

Table 1-1: Schedule of Activities

Procedure	Screening	Dosing Period 1 or 2 [a]				SFU/Withdrawal [b]
	V1	V2 or V3				V4
	2 to 28 days before administration of IMP	Check in Day -1	Day 1	Day 2	Day 3	7 to 9 days after the last administration of IMP
Recording of prior and concomitant medication and procedures	X	X	X	X	X	X
Recording of AEs	X	X	X	X	X	X
Confinement		X	X	X	X	

AE=adverse event; ECG=electrocardiogram; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IMP=investigational medicinal product; PK=pharmacokinetic(s); SFU=Safety Follow-Up

[a] Each study participant will enter 2 Dosing Periods, separated by a Wash-Out Period of 7 to 10 days between IMP administrations. Dosing Period 2 will start after the Wash-out Period (at least 7 days and no more than 10 days between the 2 IMP administrations).

[b] An SFU visit will occur 7 to 9 days after the last administration of IMP. Study participants who prematurely discontinue the IMP/study should be encouraged to undergo Withdrawal Visit procedures within 7 to 9 days after the last administration of IMP.

[c] COVID-19 precautions as described in Section 2.3.1 and Section 5.3.5.

[d] Vital signs are taken at the Screening Visit, at predose, 4, 8, 24, and 48 hours postdose, and at the SFU Visit/Withdrawal Visit.

[e] Each study participant will be randomly assigned to 1 of 2 treatment sequences (A-B or B-A) before dosing in Period 1, after all Day -1 assessments have been completed.

[f] Randomization occurs only for Dosing Period 1, either on Day -1 or Day 1 before any assessment of Day 1.

[g] 12-lead ECGs are recorded at Screening, at predose, 1, 4, 8, 24, and 48 hours postdose, and at the SFU Visit/Withdrawal Visit. At predose on Day 1 of each Dosing Period, 3 Baselines values will be measured at 2- to 5-minute intervals.

[h] IMP administration: BRV 50mg will be administered as a 50mg tablet (Treatment A [reference]) or as dry syrup (1.25g of BRV granules for oral solution 4% w/w; Treatment B [test]) under fasting conditions.

[i] Blood samples for PK analysis are collected at predose, and 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours postdose. Allowable deviations from these scheduled PK sampling times are provided in Table 8-2.

2 INTRODUCTION

Product description

Brivaracetam ((2S)-2-[(4R)-2-oxo-4-propyltetrahydro-1*H*-pyrrol-1-yl] butanamide) is a 2-pyrrolidone derivative. The targeted therapeutic indications for BRV in Japan are monotherapy and adjunctive therapy in the treatment of focal/partial-onset seizures (POS) with or without secondary generalization in patients from 4 years of age with epilepsy in Japan.

Brivaracetam displays a high and selective affinity for the synaptic vesicle protein 2A (SV2A) in the brain. Binding to SV2A is believed to be the primary mechanism for BRV anticonvulsant activity (Matagne et al, 2008).

More detailed information regarding the nonclinical and clinical development programs for BRV, including all completed and ongoing studies, can be found in the latest version of the Investigator's Brochure (IB).

Pharmacokinetics

Brivaracetam is rapidly and completely absorbed throughout the gastrointestinal tract. The median time to reach maximum plasma concentration (t_{max}) is 1h (range: 0.25 to 3h) after dosing in fasting study participants. The PK of BRV is dose proportional from 10mg to at least 600mg (for single dose). A food-effect study involving administration of BRV to healthy study participants under fasting conditions and with a high-fat, high-calorie meal indicated that under fed conditions the C_{max} was decreased by 28% and t_{max} occurred 3h later, while the AUC remained unchanged. The decrease in absorption rate is not clinically significant; therefore, BRV can be taken without regards to meals.

Brivaracetam follows single-compartment first-order PK, without an apparent distribution phase. The volume of distribution is 0.5L/kg, a value that is close to the volume of total body water. Brivaracetam is weakly bound to plasma proteins (<20%). The plasma half-life of BRV is approximately 9h in healthy adults. It decreases to 6.3h following repeated administration at high doses (800mg/day). More than 95% of the dose, including less than 9% as unchanged BRV, is excreted in the urine within 72h after dosing. Fecal and expired air excretion account for <1% of the dose.

The main disposition pathway of BRV is by cytochrome P450 (CYP)-independent hydrolysis of the acetamide group to the corresponding carboxylic acid (ucb42145) and is thought to be mediated by hydrolases. A second disposition pathway involves ω1-hydroxylation (ucb-101406-1), which is mediated by CYP2C19. Combination of these 2 pathways leads to the formation of the hydroxyacid metabolite (ucb-107092-1). These 3 metabolites are not pharmacologically active. Weak metabolic auto-induction, resulting in a 14% increase in BRV clearance, was only observed at high doses (800mg/day). There is no evidence of chiral inversion of BRV. In a PK and pharmacodynamic (PD) interaction study in healthy study participants, BRV increased the effects of alcohol on psychomotor function, attention, and memory, although there was no clinically relevant PK interaction.

Safety profile in clinical pharmacology studies

Over 25 clinical pharmacology studies with BRV have been conducted in healthy study participants, with the highest single dose given being BRV 1400mg.

Safety data were pooled (Pool Phase 1) for all completed clinical pharmacology studies with the exception of N01118 (elderly study participants), N01109 (study participants with renal impairment), and N01111 (study participants with hepatic impairment) due to the inherent differences in these study populations. N01209 and EP0117 studies in healthy male Japanese study participants, were also included in Pool Phase 1. N01069, a Phase 2a study in study participants with photosensitive epilepsy, is included in Pool Phase 1 due to its single-dose study design, which was similar to a clinical pharmacology study. Pool Phase 1 includes study participants who received BRV oral tablets, capsules, and solution, and study participants who received solution for intravenous (iv) injection. Pool Phase 1 included 220 study participants in the placebo group and 729 study participants in the BRV Overall group. Treatment-emergent adverse events (TEAEs) were reported for 67 study participants (30.5%) in the placebo group and 586 study participants (80.4%) in the BRV Overall group. The most frequently reported TEAEs in Pool Phase 1 included dizziness, somnolence, fatigue, headache, euphoric mood, and feeling drunk. Most study participants reported TEAEs with a maximum intensity of mild. There were no clinically meaningful differences in mean changes in hematology and clinical chemistry values or clinically meaningful observations in qualitative urinalysis parameters over time in the pooled Phase 1 data.

In N01209, a single- and multiple-dose PK study in healthy Japanese study participants, a total of 11 AEs were reported, in the following preferred terms: diarrhea, somnolence, pharyngolaryngeal pain, asthenia, rash, headache, and dizziness. In EP0117, a study that evaluated BRV PK after iv and oral administration in healthy male Japanese study participants, the most commonly reported TEAEs were somnolence, dizziness, and nausea.

A thorough QT study demonstrated the absence of an effect of BRV on cardiac repolarization at both therapeutic and supratherapeutic doses of BRV.

2.1 Study Rationale

Brivaracetam is being developed for adjunctive therapy in the treatment of POS with or without secondary generalization in pediatric study participants with epilepsy aged from 4 to <16 years of age in Japan. In addition to tablets and solution for injection, a dry syrup formulation is being developed specifically for the Japanese market mainly to allow dose adjustment by body weight in pediatric patients.

While the PK of the tablet has been studied extensively in healthy study participants and in patients with various forms of epilepsy, the PK of the dry syrup formulation has not been evaluated in studies.

As patients may switch from the dry syrup to the tablet, or vice versa, and as dry syrup is favorable in pediatric patients, it is important to know whether the same dose may be maintained and if the dry syrup formulation shows the PK performance of the tablet formulation.

For that reason, a bioequivalence study between the tablet and dry syrup formulations is required by the Pharmaceuticals and Medical Devices Agency. Since both formulations are of the [redacted], a single-dose study is sufficient to determine bioequivalence. The therapeutic dose will vary between patients, but a dose of 50mg bid is the most commonly used dose. For that reason, the dose of 50mg was selected for this study. Since the PK of BRV is linear over the therapeutic dose range, the bioequivalence results of this study should be applicable to other doses as well.

This study aims to assess the bioequivalence between the BRV 50mg tablet and BRV 50mg as dry syrup formulations in healthy adult male study participants.

A 2-treatment and 2-period randomized cross-over design will be used to compare the PK profile of single dosing of the BRV tablet formulation to the BRV dry syrup formulation. Study participants will be administered 1 of the 2 BRV formulations during each of the 2 Dosing Periods in a Treatment A (tablet [reference])/Treatment B (dry syrup [test]) or Treatment B (dry syrup [test])/Treatment A (tablet [reference]) sequence with a Wash-out Period in between.

2.2 Background

Brivaracetam is a chemical relative of the antiepileptic drug levetiracetam (LEV [Keppra®/E-Keppra®]). Like LEV, BRV displays a high and selective interaction with a binding site SV2A. However, the binding affinity of BRV for SV2A is approximately 10-fold higher. This binding site appears to be the major target for its pharmacological activity. Unlike LEV, BRV also reduces voltage-dependent sodium currents. Brivaracetam also reverses the inhibitory effects of negative allosteric modulators on gamma-aminobutyric acid- and glycine-induced currents. Brivaracetam is extensively metabolized, but seizure protection appears to be associated with the parent compound.

Brivaracetam has primarily been studied as oral (tablet) adjunctive therapy in study participants with refractory epilepsy, a conversion to monotherapy indication for POS, and adjunctive therapy for other indications (Unverricht–Lundborg disease, postherpetic neuralgia, acute repetitive seizures, and essential tremor). In addition, an iv formulation of BRV has been studied in study participants with epilepsy (N01258) and also has been evaluated as a replacement for oral BRV in adult Japanese study participants with POS with or without secondary generalization (EP0118). Two oral formulations of BRV were developed for the pediatric program; however, only 1 formulation (oral solution; 10mg/mL) is currently in use.

The BRV clinical development program includes 4 studies of BRV as adjunctive therapy in pediatric study participants with epilepsy (N01263, N01266, EP0065, and N01349).

The primary objective of this study is to demonstrate the bioequivalence between the BRV 50mg tablet and BRV 50mg as dry syrup formulations.

2.3 Benefit/Risk Assessment

The healthy study participants included in this study will receive no medical benefit from participation.

In addition to the most frequently reported adverse events (AEs) described in Section 2, the potential risks in the study include:

- Electrocardiogram stickers on the study participants' chests and limbs may cause some local irritation and may be uncomfortable to remove. Study participants will be closely monitored to ensure any local irritation does not persist.
- During cannulation, more than 1 attempt may be needed to insert the cannula in a vein of a study participant, and it is possible that bruising, and/or inflammation, and/or hematoma may occur at the site of cannulation.

In the BRV drug development program, the 50mg dose has been shown to be well tolerated in healthy study participants.

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

2.3.1 Risk assessment for coronavirus disease 2019

Brivaracetam is an inhibitor of SV2A in the brain. It has anticonvulsant activity and is marketed in several countries for treatment of certain forms of epilepsy (focal or POS). Brivaracetam is not expected to interact with the immune system or to inhibit innate or adaptive immunity.

The most frequently reported AEs in clinical pharmacology studies were effects on the central nervous system (eg, dizziness, somnolence, fatigue, headache, euphoric mood, and feeling drunk).

In this study, 2 BRV formulations (tablet and dry syrup) will be administered in 2 Dosing Periods as a single dose, on Day 1 of each Dosing Period (see Figure 1-1). Although effects on the central nervous system are possible, it appears to be unlikely that BRV has substantial effects that will worsen coronavirus disease 2019 (COVID-19) in infected study participants.

Therefore, the risk of the study participants to be exposed to the virus that causes COVID-19 is expected to be similar to the general population. However, the risk of exposure to infected people cannot be completely excluded as the study participants may have additional contact (eg, commute to the site) and have additional human contact (eg, with site staff and other study participants of the clinical study).

Screening for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection at the time of study entry is not currently recommended by the Sponsor and will only be conducted if required by local regulatory and healthcare guidance.

On each visit to the study site, study participants will be asked about their potential exposure to SARS-CoV-2 infection (contacts, family members, etc.) in accordance with the study site's own procedures and local regulatory/healthcare authority guidance. Refer to Section 5.3.5 for further details.

Study participants will be closely monitored for any signs and symptoms of COVID-19 (eg, fever, dysgeusia [taste loss/change], dysosmia [loss or distortion/change of smell], persistent cough, and dyspnea) throughout the study. If symptoms and/or clinical signs of infection are identified, the Investigator will decide whether these findings will be handled as suspected or confirmed COVID-19. The use of testing for SARS-CoV-2 will be determined by reference to the regulatory and healthcare guidance in place locally at the time. In the case that COVID-19 is suspected or confirmed, administration of further IMP to that study participant will be suspended, and the Investigator will determine (ideally in discussion with the UCB Study Physician) how soon the study participant may be discharged from the study site, and whether this will be to their home or another healthcare facility.

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To demonstrate the bioequivalence between the BRV 50mg tablet and BRV 50mg as dry syrup after a single oral dose in healthy Japanese male study participants	Primary Endpoints: • C_{max} • $AUC_{(0-t)}$
Secondary	
• To evaluate the safety and tolerability of 2 oral dosage forms of BRV in healthy Japanese male study participants	Secondary endpoints: • Incidence of TEAEs • Incidence of treatment-emergent SAEs
Other	
Other PK Objective: • To evaluate other PK parameters of 2 oral dosage forms of BRV in healthy Japanese male study participants	The other PK endpoints will be calculated: • AUC • AUC_{extr} • CL/F • V_z/F • MRT • t_{max} • $t_{½}$ • λ_z
Other Safety Objective: • To further evaluate the safety and tolerability of 2 oral dosage forms of BRV in healthy Japanese male study participants	Other safety endpoints will be assessed during the study: • Changes in clinical laboratory test parameters (ie, hematology, clinical chemistry, and urinalysis) • Changes in vital signs (SBP, DBP, pulse rate, respiratory rate, and body temperature) • 12-lead ECG parameters and findings • Physical examinations

λ_z=first order terminal elimination rate constant; AUC=area under the curve from 0 to infinity; $AUC_{(0-t)}$=area under the curve from 0 to the time of the last quantifiable concentration; AUC_{extr}=extrapolated AUC; BRV=brivaracetam; CL/F=total clearance after oral administration; C_{max}=maximum concentration; DBP=diastolic blood pressure; ECG=electrocardiogram; MRT=mean residence time (ie, of the unchanged drug in the systemic circulation); PK=pharmacokinetics; SAE=serious adverse event; SBP=systolic blood pressure; $t_{1/2}$=terminal elimination half-life; TEAE=treatment-emergent adverse event; t_{max}=time of C_{max}; Vz/F=apparent volume of distribution

4 STUDY DESIGN

4.1 Overall design

EP0110 is a single-center, single-dose, open-label, randomized, 2-way cross-over study designed to assess the bioequivalence between the BRV 50mg tablet and BRV 50mg as dry syrup formulations in healthy Japanese male study participants after oral administration under fasted conditions. In addition, safety and tolerability of BRV will be evaluated.

Study participants will enter a Screening Period (2 to 28 days before administration of IMP) and eligible study participants will start Dosing Period 1. The Dosing Period consists of 2 periods (Period 1 and Period 2) of 4 days each with a single administration on Day 1 of each Dosing Period. The Dosing Periods will be separated by a Wash-Out Period (at least 7 days and no more than 10 days between the 2 administrations for each study participant) and followed by an SFU Visit, 7 to 9 days after the last administration of IMP. Study participants who prematurely discontinue the IMP/study are to return for a Withdrawal Visit, 7 to 9 days after the last IMP administration.

On Day 1 of each Dosing Period, the study participants will receive 1 of the following treatments in randomized order under fasting conditions:

- Treatment A – a single dose of BRV 50mg tablet
- Treatment B – a single dose of BRV 50mg as dry syrup (1.25g of granules for oral solution 4% w/w)

During each of the 2 Dosing Periods (ie, Period 1 and Period 2), study participants will be admitted to the study site 1 day before administration of IMP. After an overnight fast of at least 10 hours, in the morning of Day 1 of each Dosing Period, a blood sample for PK assessments will be obtained to determine the Baseline value, and then study participants will receive the dose of IMP (Treatment A or Treatment B). Study participants will remain fasting for 4 hours after dosing. Blood samples will be taken at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours after administration of IMP for the determination of the plasma concentrations of BRV. A total of 17 blood samples will be taken from each study participant per each Dosing Period for PK assessments. Study participants will be discharged in the morning of the final day (Day 3) of each Dosing Period, approximately 48 hours after the administration of IMP, provided there are no medical objections in the opinion of the Investigator (refer to study schematic in Figure 1-1).

Safety and tolerability will be monitored throughout the study by monitoring of AEs, collecting blood and urine samples for the examination of safety laboratory parameters, measurement of vital signs (SBP, DBP, pulse rate, respiratory rate, and body temperature), electrocardiogram (ECGs), and completion of physical examinations.

A detailed time and events schedule is presented in Section 1.3.

A total of 24 study participants are planned to be randomized and complete the study; however, additional study participants may be randomized in case some study participants discontinue the study early (not only limited to COVID-19 circumstances).

4.2 Scientific rationale for study design

The primary objective of this study is to demonstrate the bioequivalence between the BRV 50mg tablet and BRV 50mg as dry syrup formulations. Therefore, this study employs a standard 2-treatment and 2-period randomized cross-over design (where a single dose of treatment is given in each Dosing Period under fasted conditions).

4.3 Justification for dose

The Japanese bioequivalence guideline recommends a single-dose study with a usual clinical dose. Therefore, this study employs a 50mg dose of BRV.

4.4 End of study definition

A study participant is considered to have completed the study if he has completed both Dosing Periods of the study as well as the SFU Visit assessments.

The end of the study is defined as the date of the last visit of the last study participant in the study.

5 STUDY POPULATION

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

5.1 Inclusion criteria

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

Age

1. Study participant must be between 20 to 50 years of age (inclusive) at the time of signing the Informed Consent Form (ICF).

Type of study participant and disease characteristics

2. Study participant is overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.
3. Study participant has laboratory values within the reference range at the Screening Visit, or has values exceeding the reference range but judged by the Investigator to be not clinically significant for participation in the study.
4. Study participant is of Japanese descent as evidenced by appearance and verbal confirmation of familial heritage (a study participant has all 4 Japanese grandparents born in Japan).

Weight

5. Body weight of at least 50kg and body mass index (BMI) within the range 18 to 30kg/m^2 (inclusive) at the Screening Visit.

Sex

6. Study participant is male.
7. Study participant must agree to use contraception as detailed in Appendix 4 (Section 10.4) of the protocol starting from Screening through at least 2 days after the last dose of IMP and refrain from donating sperm during this period.

Informed consent

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

5.2 Exclusion criteria

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

Medical conditions

1. Study participant has any medical or psychiatric condition including previous or current episode of suicidal ideation that, in the opinion of the Investigator, could jeopardize or would compromise the study participant's ability to participate in this study.
2. Study participant has any previous or current cardiovascular, respiratory, hepatic, renal, digestive, endocrine, or nervous system disorder that may affect absorption, secretion, metabolism, or excretion of IMP.
3. Study participant has a current history of alcohol or drug use disorder, as defined in Diagnostic and Statistical Manual of Mental Disorders (DSM) V, or within the previous 6 months.
4. Study participant has a known hypersensitivity to any components of the IMP formulations.
5. Alanine transaminase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) >1.0x upper limit of normal (ULN).
6. Bilirubin >1.0xULN (isolated bilirubin <1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
7. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

   For randomized study participants with a Baseline 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. This includes rescreening. If the repeat values are below ULN the study participant will be considered to not meet the exclusion criteria.

Prior/Concomitant therapy

8. Study participant has used other drugs, including over-the-counter medications, herbal/traditional medicines, or dietary supplements (excluding medicines for external use),

with the exception of paracetamol (Section 6.5.1), within 14 days before first administration of IMP or has received a COVID-19 vaccine within 7 days of initiating IMP.

9. Study participant has used hepatic enzyme-inducing drugs (eg, glucocorticoids, phenobarbital, isoniazid, phenytoin, rifampicin) within 2 months before the first administration of IMP.

Prior/Concurrent clinical study experience

10. Study participant has participated in another study of an IMP (and/or an investigational device) within the previous 30 days or 5 times the half-life (whichever is longer) or is currently participating in another study of an IMP (and/or an investigational device).

Diagnostic assessments

11. Study participants with clinically relevant abnormalities in a standard 12-lead ECG at Screening Visit as judged by the Investigator.
12. Study participant has a positive result for hepatitis B surface antigen, hepatitis C virus antibody test, human immunodeficiency virus antibody test, or syphilis at Screening Visit.
13. Study participant tests positive for alcohol breath test and/or urine drug test at the Screening Visit or on Day -1.

Other exclusions

14. Study participant has donated blood or plasma or has experienced blood loss ≥400mL within 90 days, ≥200mL within 30 days, or has donated any blood or plasma within 14 days before first administration of IMP.
15. Study participant is a current smoker or has used nicotine-containing products (eg, tobacco, patches, gum) within 30 days before the first administration of IMP.
16. 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).
17. Consumption of restricted food specified in Section 5.3.1 within 7 days before first administration of the IMP.

5.3 Lifestyle restrictions

5.3.1 Meals and dietary restrictions

- Study participants must refrain from consumption of grapefruit within 7 days before the start of IMP until completion of the study.

5.3.2 Caffeine, alcohol, and tobacco

- During each Dosing Period, study participants must abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for 48 hours before the start of dosing until after collection of the final pharmacokinetic (PK) sample.

- During each Dosing Period, study participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK sample.
- Use of nicotine-containing products will not be allowed from within 30 days before IMP administration until after the final follow-up visit.

5.3.3 Activity

- Study participants will abstain from strenuous exercise for 96 hours before each blood collection for clinical laboratory tests. Study participants may participate in light recreational activities during studies (eg, watching television, reading).

5.3.4 Food intake times

The food intake schedule is applicable only on the days of IMP administration and PK sampling.

Study participants will fast overnight (≥10 hours) in the study site the day before IMP dosing. A predose blood sample will be obtained before they receive the dose of IMP. Study participants will remain fasting for 4 hours after IMP dosing.

Study participants will be allowed water up to 1 hour before the scheduled dosing time. The BRV tablet will be administered with 200mL of water.

The dry syrup will be mixed with 50mL of water; after intake, the dosing container will be rinsed with 50mL of water, which will also be taken. Then, the dosing container will be rinsed with 100mL of water and taken by the study participant. Water will be allowed ad libitum after 2 hours postdose.

5.3.5 Other restrictions

Due to the exceptional circumstance of the evolving COVID-19 pandemic, study participants are advised to adhere to local requirements to minimize potential exposure to and/or transmission of the virus that causes COVID-19 while ambulatory.

All study participants will be contacted by telephone before admission to the study site (as close to admission as feasible) to assess COVID-19 signs and symptoms and will be asked not to come to the site in case of suspected infection.

In addition, study participants will be asked for any contact with a person who has confirmed infection. If applicable, study participants may be referred to the local health care system.

Physical distancing and person-to-person contact restrictions will be applied and explained to study participants while staying at the study site. Study participants will be asked to use surgical face masks and/or gloves as guided by local requirements.

For details on the risk assessment for COVID-19, refer to Section 2.3.1.

5.4 Screen failures

Screen failures are defined as study participants who consent to participate in the clinical study but are not subsequently randomly assigned to an IMP treatment sequence. A minimal set of screen failure information is required to ensure transparent reporting of screen failure study participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information

includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. This includes rescreening. If the repeat values are above ULN the study participant will be considered as a screen failure.

6 STUDY TREATMENTS

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

6.1 Treatments administered

A summary of the treatments administered is provided in Table 6-1.

Table 6-1: Treatments administered

Treatment	Treatment A (Reference)	Treatment B (Test)
Intervention name	BRV	BRV
Type	Drug	Drug
Dose formulation	Tablet	Dry syrup
Active dose	BRV 50mg	BRV 50mg
Unit dose strength	1 tablet of 50mg	1.25g of granules for oral solution 4% w/w
Dosage level	Single dose	Single dose
Route of administration	Oral	Oral
Dosing instructions	Tablet will be administered with 200mL water.	Dry syrup will be mixed with 50mL of water; after intake, the dosing container will be rinsed with 50mL of water, which will also be taken. Then, the dosing container will be rinsed with 100mL of water and taken by the study participant.
Use	Experimental	Experimental
IMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and labeling	Tablets will be provided in high-density polyethylene bottles and polypropylene caps. Each bottle will be labeled as required per country requirements.	Dry syrup will be provided in high-density polyethylene bottles and polypropylene caps. Each bottle will be labeled as required per country requirements.
Excipients	• Croscarmellose sodium • Lactose monohydrate • Betadex • Lactose anhydrous • Magnesium stearate • Polyvinyl alcohol • Titanium dioxide (E171) • Macrogol 3350 • Talc • Iron oxide yellow (E172) • Iron oxide black (E172)	• [redacted]

BRV=brivaracetam; IMP=investigational medicinal product

6.2 Preparation, handling, storage, and accountability requirements

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

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

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

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

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

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

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

6.2.1 Drug accountability

A Drug Accountability Form will be used to record IMP dispensing 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.

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

6.3 Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. Randomization will be involved only in the assignment of study participants to the treatment sequence as per the crossover design, Treatment A/Treatment B or Treatment B/Treatment A.

The study site will generate the randomization lists (a main list and a replacement list) for the treatment sequence (Treatment A/Treatment B or Treatment B/Treatment A) allocation. These randomization lists will be reviewed by the Clinical Trial Statistician at UCB to ensure that the code meets the study requirements.

In addition to the main randomization list, a randomization replacement list will be provided in order to replace withdrawn study participants; the replacement study participant will receive the same treatment sequence as the corresponding withdrawn study participant.

6.3.1 Procedures for maintaining and breaking the treatment blind

Not applicable; this is an open-label study.

6.4 Treatment compliance

Study participant compliance to treatment will be ensured by the administration of IMP under the Investigator's (or designated site personnel's) supervision. Drug accountability must be recorded on the Drug Accountability Form.

6.5 Concomitant medication(s)/treatment(s)

6.5.1 Permitted concomitant treatments (medications and therapies)

Paracetamol (acetaminophen) for the treatment of mild symptoms (eg, headache or pain relief) not exceeding 1g per dose is permitted with a total of 10g within 2 weeks and until 48 hours before the first administration of IMP.

Study participants will be allowed to receive a COVID-19 vaccine up to 7 days prior to the initiation of IMP administration. Vaccine administration will be entered as a prior medication in the eCRF. Study participant continuation in case of a vaccine-related AE will be as per Investigator judgement.

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

6.5.2 Prohibited concomitant treatments (medications and therapies)

With the exception of paracetamol, all prescription or OTC medicines (including herbal/traditional medicines and dietary supplements) are prohibited within 14 days before first IMP administration and during the study until SFU, unless required to treat an AE. COVID-19 vaccines are prohibited within the 7 days prior to the initiation of IMP administration and for the duration of the study until SFU. In addition, any hepatic enzyme-inducing drugs (eg, glucocorticoids, phenobarbital, isoniazid, phenytoin, rifampicin) are prohibited within 2 months before first IMP administration and during the clinical part of the study.

If a study participant 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 study participant can continue in the study or must be withdrawn.

6.6 Dose modification

No dose modifications are allowed during the study.

6.7 Criteria for study hold or dosing stoppage

Not applicable.

6.8 Treatment after the end of the study

Not applicable. This is a Phase 1 study in healthy study participants; therefore, no treatment will be provided after the end of the study.

7 DISCONTINUATION OF IMP AND STUDY PARTICIPANT DISCONTINUATION/WITHDRAWAL

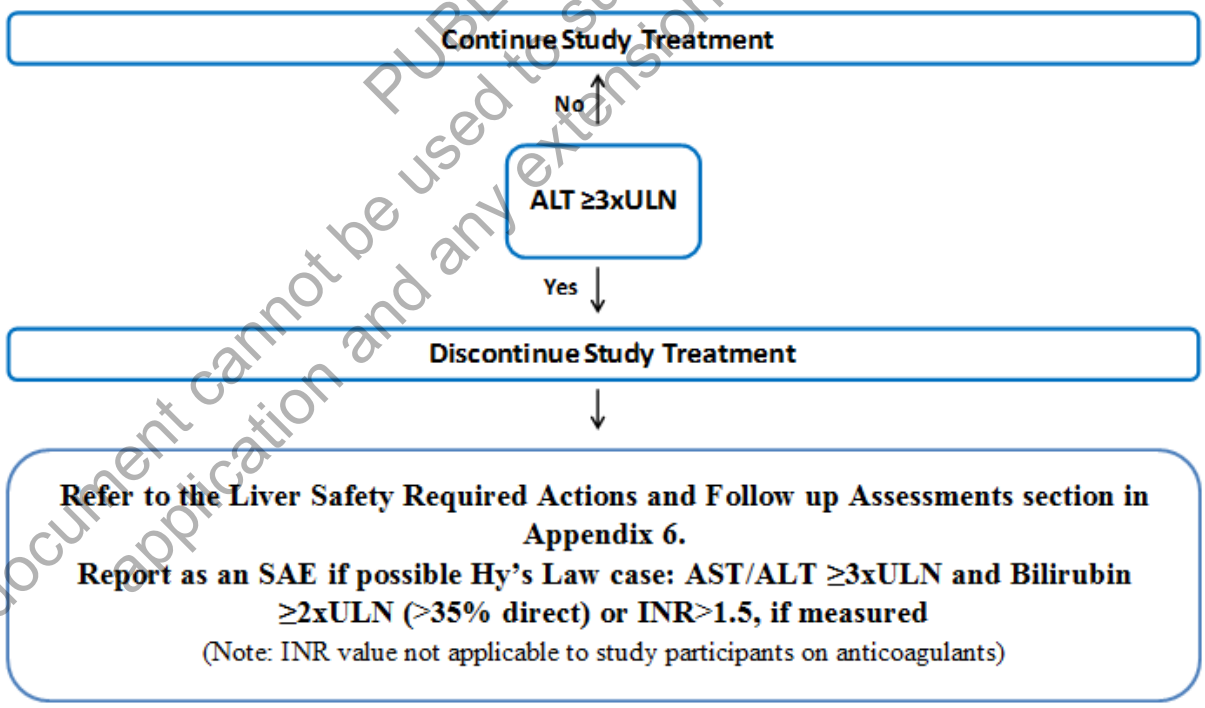
7.1 Discontinuation of IMP

7.1.1 Liver chemistry stopping criteria

Discontinuation of IMP for abnormal liver function should be considered by the Investigator when a study participant meets one of the conditions outlined (Figure 7-1) or if the Investigator believes that it is in the best interest of the study participant.

Investigational medicinal product will be discontinued immediately and permanently for a study participant if liver chemistry stopping criteria are met.

Figure 7-1: Liver chemistry stopping algorithm



ALT=alanine transaminase; AST=aspartate aminotransferase; INR=international normalized ratio; SAE=serious adverse event; ULN=upper limit of normal

Evaluation of potential drug-induced liver injury (PDILI) must be initiated as described in the protocol. If study participants are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

Specific assessments and follow up actions for PDILI are provided in Appendix 6 (Section 10.6).

7.2 Study participant discontinuation/withdrawal from the study

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

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

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

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

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

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

1. Study participant withdraws his consent.
2. Study participant develops an illness that would interfere with his continued participation.
3. Study participant is noncompliant with the study procedures in the opinion of the Investigator.
4. Study participant takes prohibited concomitant medications as defined in this protocol.
5. The Sponsor or a regulatory agency requests withdrawal of the study participant.

Participants must be withdrawn by the Investigator based on discussion with the Sponsor and Medical Monitor under the following circumstance:

Any confirmed COVID-19 case that warrants discontinuation in the judgment of the Investigator or Sponsor to protect the safety of the participant, other participants, or study site staff (see Section 2.3.1 for further details).

Study participants who discontinue the study early for reasons other than IMP-related safety may be replaced upon agreement with the Investigator and Sponsor. Replacement study participants will receive the same treatment sequence that was assigned to the study participant who dropped out.

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

7.3 Lost to follow up

A study participant will be considered lost to follow up if he fails to return for Dosing Period 2 or the SFU Visit and is unable to be contacted by the study site.

The following actions must be taken if a study participant fails to return to the study site for Dosing Period 2 or the SFU Visit:

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Activities (Table 1-1).

Protocol waivers or exemptions are not allowed.

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

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

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

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

The maximum amount of blood collected from each study participant over the duration of the study, including any extra assessments that may be required, will not exceed 250mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Pharmacokinetics

Blood samples of approximately 4mL will be collected for measurement of plasma concentrations of BRV as specified in the Schedule of Activities (Table 1-1) Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24h clock time) of each sample will be recorded.

Samples will be used to evaluate the PK of BRV. Each blood sample will be divided into 2 aliquots (1 for PK and 1 as a backup). Samples collected for analyses of BRV plasma concentration may also be used to evaluate safety aspects related to concerns arising during or after the study.

The primary and other PK endpoints are provided in Section 3. These will be calculated by the Quantitative Clinical Development within the contract research organization (CRO). Details of the PK methods used for the calculations of the parameters are outlined in the Statistical Analysis Plan (SAP). Definitions for these PK endpoints are as follows:

- AUC Area under the curve from 0 to infinity
- $AUC_{(0-t)}$ Area under the curve from 0 to the time of the last quantifiable concentration
- AUC_{extr} Extrapolated AUC
- MRT Mean residence time (ie, of the unchanged drug in the systemic circulation)
- C_{max} Maximum concentration
- t_{max} Time of C_{max}
- $t_{½}$ Terminal elimination half-life
- V_z/F Apparent volume of distribution
- CL/F Total clearance after oral administration
- λ_z First order terminal elimination rate constant

Brivaracetam concentration will be determined in study plasma samples using a validated liquid chromatography electrospray ionization tandem mass spectrometry bioanalytical method. The lower limit of quantification will be 2ng/mL. The assays will be performed in accordance with Good Laboratory Practice regulations of the Organisation for Economic Co-operation and Development.

Blood sampling time for PK analysis is provided in Table 8-1.

Table 8-1: Pharmacokinetic blood sampling scheme

BRV Formulation	Dose	Collection time (per Dosing Period)	Number of samples (per Dosing Period)
Tablet (reference)	Single	On Day 1 at 0 (predose), 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48h postdose	17
Dry syrup (test)	Single	On Day 1 at 0 (predose), 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48h postdose	17
Total			34

BRV=brivaracetam; h=hours

Study site should aim to collect PK samples at the nominal time points to the extent possible. However, the following maximum deviations from scheduled sampling times considered irrelevant for PK are defined in Table 8-2.

Table 8-2: Irrelevant time deviations for PK sampling

PK blood sampling times	Deviation from scheduled time considered irrelevant
0h (predose)	Within 30min
0.25 to 1.5h	2min
2 to 8h	5min
12 to 16h	30min
24 to 48h	60min

h=hours; min=minutes; PK=pharmacokinetic

8.2 Safety assessments

Planned time points for all safety assessments are provided in the Schedule of Activities (Table 1-1).

8.2.1 Clinical safety laboratory assessments

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and the Schedule of Activities for the timing and frequency of these tests (Table 1-1).

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE Section of the Case Report Form (CRF). The laboratory reports must be filed with the source documents. Abnormal laboratory findings (ie, outside the normal range) will be considered clinically significant based on the Investigator's judgment.

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

If such values do not return to normal within a period of time judged reasonable by the Investigator, the study participant will be referred to his General Practitioner for assessment and the Sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the Laboratory Manual and the Schedule of Activities (Table 1-1).

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

8.2.2 Vital signs

Systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, respiratory rate, and axillary body temperature will be assessed.

Vital signs will be measured in a supine position after the study participant has rested for at least 5 minutes and will include SBP and DBP, pulse and respiratory rate, and body temperature. Blood pressure and pulse measurements will be assessed in a quiet setting without distractions (eg, television, cell phones), with a completely automated device. Manual techniques will be used only if an automated device is not available.

8.2.3 Electrocardiograms

Single 12-lead ECG (except at predose on Day 1 of each Dosing Period, when 3 Baseline values will be measured at 2- to 5-minute intervals) will be obtained as outlined in the Schedule of Activities (see Table 1-1) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT intervals, and QT interval corrected (QTc).

All ECG recordings should be taken with the study participant resting in the supine position for at least 10 minutes before the recording.

8.2.4 Physical examination

A complete physical examination will include, at a minimum, general appearance; ear, nose, and throat; eyes, hair, and skin; and assessments of the cardiovascular, respiratory, gastrointestinal neurological, musculoskeletal, and hepatic systems. height and weight will also be measured and recorded at screening only.

A brief physical examination will include, at a minimum, assessments of the skin, respiratory system, cardiovascular system, and abdomen (liver and spleen).

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

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

8.3 Adverse events and serious adverse events

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

Adverse events will be reported by the study participant (or, when appropriate, by a caregiver, surrogate, or the study participant's legally authorized representative).

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

Confirmed COVID-19 cases will be recorded as AEs.

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs and SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the Schedule of Activities (Section 1.3).

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the ICF), including any pretreatment and posttreatment periods required by the

protocol, must be reported in the CRF 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.

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

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

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

8.3.2 Method of detecting AEs and SAEs

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

8.3.3 Follow up of AEs and SAEs

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

8.3.4 Regulatory reporting requirements for SAEs

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

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IMP under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB), and investigators.

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

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

8.3.5 Pregnancy

Details of all pregnancies in female partners of male study participants will be collected after the start of IMP and until the end of the study.

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

8.3.6 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 BRV.

The AEs of special interest for BRV (by preferred term) are as follows: autoimmune nephritis, nephritis, nephritis allergic, tubulointerstitial nephritis, and uveitis syndrome.

"Potential Hy's Law" (ie, the finding of ≥3xULN ALT and/or AST in conjunction with ≥2xULN bilirubin [in absence of ≥2xULN ALP] with no alternative explanation for the biochemical abnormality) must ALWAYS be reported to UCB as a serious unexpected AE (ie, not waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the study participant.

8.4 Safety signal detection

Not applicable for this study.

8.5 Treatment of overdose

Not applicable; all single doses will be administered by study staff.

8.6 Efficacy assessments

Efficacy will not be assessed in this study.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.9 Biomarkers

Biomarkers are not evaluated in this study.

8.10 Health economics

Not applicable.

9 STATISTICAL CONSIDERATIONS

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

9.1 Definition of analysis sets

The following analysis sets will be defined:

Enrolled Set

All study participants who sign the ICF will be included in the Enrolled Set.

Randomized Set

All enrolled study participants who are randomized will be included in the Randomized Set.

Safety Set

All randomized study participants who receive at least 1 dose of the IMP will be included in the Safety Set (SS).

Pharmacokinetic Per-Protocol Set

All randomized study participants who are included in the SS, have no important protocol deviations that are considered to impact the study participant's data validity for analysis of the primary study objective, and have a sufficient number of bioanalytical assessments to calculate reliable estimates for the primary pharmacokinetic parameters for both treatments will be included in the Pharmacokinetic Per-Protocol Set (PK-PPS).

If a study participant's predose concentration is greater than 5% of the corresponding C_{max} value in both Dosing Periods, the study participant will be excluded from the PK-PPS. If this occurs in 1 of the 2 Dosing Periods, but not in the other Dosing Period, data of the other Dosing Period will be used. Furthermore, since the study participant will be entered as a random effect in the ANOVA, the data of the single Dosing Period can still be used for the bioequivalence assessment.

If vomiting occurs at or before 2 times of the median t_{max}, the study participant will be excluded from the PK-PPS.

The reasons for exclusion of study participants from any of the analysis sets will be listed.

9.2 General statistical considerations

Statistical evaluation will be performed by the Sponsor or designee and supervised by the Exploratory Statistics Department of UCB. Statistical analysis and generation of tables, figures, and study participant data listings will be performed using SAS Version 9.3 or higher. A noncompartmental analysis (NCA) will be performed using Phoenix WinNonlin® Version 8.0 or higher (Certara L.P., Princeton, NJ, USA) for PK parameter estimation.

A complete set of listings containing both all documented data and all calculated data will be generated. Missing data will not be imputed. Outlier detection and statistical analysis of outliers will not be performed.

For categorical endpoints, the number and percentage of study participants in each category will be presented. The denominator for percentages will be based on the number of study participants appropriate for the purpose of the analysis. For continuous endpoints, descriptive statistics will include number of study participants, mean, standard deviation, median, minimum, and maximum. Geometric mean, geometric coefficient of variation (CV), and 95% confidence

interval (CI) for the geometric mean will also be presented in the descriptive statistics for plasma concentrations and PK parameters.

9.3 Planned outcome analyses

9.3.1 Pharmacokinetic analyses

Pharmacokinetic analyses will be performed on the SS. Statistical analyses will be performed on the PK-PPS.

Descriptive statistics will be used to describe PK parameters for each treatment.

Listing of sampling time deviations, individual concentration-time data, and individual PK parameters will be generated. Graphical displays of individual and mean concentrations by time will also be presented on semi-logarithmic and linear scales.

The bioavailability of BRV dry syrup (1.25g of granules for oral solution 4% w/w, corresponding to 50mg of BRV) (test) will be compared with BRV 50mg dose administered as a 50mg tablet (reference).

The parameters C_{max} and $AUC_{(0-t)}$ will be evaluated according to a univariate model of analysis of variance, adapted to crossover experimental designs. The model will include the treatment, the period, and sequence as fixed effects. The study participant (nested to the sequence) will be the random effect. The dependent variables will be logarithmically (ln) transformed prior to statistical testing, following the usual recommendations. The 90% confidence intervals (CIs) of the adjusted test/reference geometric mean ratio will be calculated. Bioequivalence between the test (dry syrup) and reference (tablet) formulations will be concluded if the 90% CI limits for C_{max} and $AUC_{(0-t)}$ fall fully within 80% to 125%.

The MIXED procedure in SAS software will be used for this analysis.

For t_{max}, a distribution-free 90% CI (Hodges-Lehmann's method) will be calculated for the median differences between each test and the reference.

9.4 Planned safety analyses

All safety analyses will be performed using the SS. All safety variables will be summarized by BRV formulation (tablet and dry syrup). Safety variables will be listed individually for detailed clinical review, when needed.

9.4.1 Primary safety analyses

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) and characterized as pretreatment and treatment emergent according to the intake of the IMP. Adverse events with a start date prior to the first dose of IMP will be defined as pretreatment AEs. A TEAE is defined as any AE with a start date/time on or after the first dose of IMP or any unresolved event already present before administration of IMP that worsens in intensity following exposure to IMP. Further detail on the rules for attributing AEs to a Dosing Period, and to single dose within a Dosing Period, will be included in the SAP.

Adverse events will be summarized descriptively by treatment (tablet or dry syrup), Primary System Organ Class, and Preferred Term according to the MedDRA terminology. Additional tables will summarize AEs by severity and relationship to IMP as well as, if applicable, separate tables for AEs leading to withdrawal from the study and SAEs.

9.4.2 Other safety analyses

9.4.2.1 Clinical laboratory assessments

Clinical laboratory variables (hematology and clinical chemistry) and changes from Baseline will be summarized using descriptive statistics by BRV formulation at each time point, as applicable. Urinalysis data and laboratory values outside the reference range will be listed.

9.4.2.2 Vital signs

Vital signs variables (SBP, DBP, pulse rate, respiratory rate, and body temperature) and changes from Baseline will be summarized using descriptive statistics by BRV formulation at each time point.

9.4.2.3 Electrocardiograms

Twelve-lead ECG variables (PR, QRS, QT intervals, and QTc) and changes from Baseline will be summarized using descriptive statistics by BRV formulation at each time point.

9.4.2.4 Physical examination

Physical examination data will be listed.

9.5 Handling of protocol deviations

All protocol deviations will be reviewed on an ongoing basis as part of the data cleaning and evaluation process. After all data have been verified/entered into the database, and prior to database lock, a Data Evaluation Meeting will be performed. The purpose of this review meeting will be to examine all protocol deviations, define the PK-PPS (see Section 9.1), and to verify the quality of the data. If PK parameters are needed to define PK-PPS, it will be performed based on the ADPP (Pharmacokinetic Parameters Analysis Data). The data evaluation will also help in guiding decisions on how to manage data issues on a case-by-case basis (eg, missing values, dropouts, and protocol deviations). Protocol deviations (eg, missing assessments or visits) related to COVID-19 will be listed separately.

Accepted deviations from theoretical time points will be described in the appropriate documents and included in the electronic Trial Master File. After the data review, resolution of all issues, and documentation of all decisions, the database will be locked.

9.6 Handling of dropouts or missing data

Handling of missing data will be detailed in the SAP.

9.7 Planned interim analysis and data monitoring

Not applicable.

9.8 Determination of sample size

A total of 24 study participants are planned to be randomized and complete the study; however, additional study participants may be randomized in case some study participants discontinue the study early (not only limited to the COVID-19 circumstances).

Previous BRV PK studies (N01287, N01185, N01118, N01081, and N01075) provide estimates of the intrastudy study participant variability (CV%) approximately ranging from 10% to 23% (median 18%) for C_{max} and from 4% to 12% (median 6%) for AUC.

Provided that the ratio of expected means is equal to 1.00 and assuming a CV% of 20%, 19 study participants in total provide a power of 90%, at the 5% level of significance (one-sided), to declare that the true geometric means ratio is in the range of 80% to 125%.

In the case of the true mean difference of 5% (the ratio of 0.95 or 1.05), a power of 90% would be reached with 24 study participants completing the study.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Regulatory and ethical considerations

The study will be conducted under the auspices of an IRB, as defined in local regulations, International Council for Harmonisation-Good Clinical Practice (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 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 (ICF), IB, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other study participant-related documents to be used for the study to the IRB for its review and approval.

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

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

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

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

10.1.2 Financial disclosure

Insurance coverage will be handled according to local requirements.

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

10.1.3 Informed consent process

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

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

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

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

10.1.4 Data protection

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

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

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

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

10.1.5 Data quality assurance

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

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

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

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

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, legible, contemporaneous, original, and attributable from source documents; that the safety and rights of study participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH-GCP, and all applicable regulatory requirements.

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

10.1.5.1 Case Report Form completion

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

Any change or correction to the CRF 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 CRF.

Detailed instructions will be provided in the CRF Completion Guidelines.

10.1.5.2 Apps

No apps will be used in the study.

10.1.6 Source documents

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

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

Source documents that are computer generated and stored electronically must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated by the Investigator and become a permanent part of the study participant's source documents.

The Investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

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

10.1.7 Study and site closure

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

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

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

- Failure of the Investigator to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of study participants by the Investigator
- Discontinuation of further IMP development

10.1.8 Publication Policy

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

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in the table below will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of study participants are detailed in Section 5.1 and Section 5.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Protocol-Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="4">Parameters</th></tr>
<tr><td>Hematology</td><td>Platelet Count
RBC Count
WBC Count
Hemoglobin
Hematocrit</td><td colspan="2">RBC Indices:
MCV
MCH
%Reticulocytes</td><td>WBC Count with Differential:
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td rowspan="3">Clinical Chemistry [a]</td><td>Blood Urea Nitrogen (BUN)</td><td>Potassium</td><td>Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)</td><td>Total and direct bilirubin</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td>Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)</td><td>Total Protein</td></tr>
<tr><td>Glucose</td><td>Calcium</td><td>Alkaline phosphatase</td><td></td></tr>
<tr><td>Routine Urinalysis</td><td colspan="4">• Specific gravity
• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick
• Microscopic examination (if blood or protein is abnormal)</td></tr>
<tr><td>Other Screening Tests</td><td colspan="4">• Alcohol breath test and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines)
All study-required laboratory assessments will be performed by a local laboratory.
The results of each test must be entered into the eCRF.</td></tr>
</table>

ALT=alanine aminotransferase; eCRF=electronic Case Report Form; INR=international normalized ratio; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; SAE=serious adverse event; ULN=upper limit of normal; WBC=white blood cell

[a] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.1 and Section 10.6. All events of ALT ≥3×ULN and bilirubin ≥2×ULN (>35% direct bilirubin) or ALT ≥3×ULN and INR >1.5, if INR is measured, may indicate severe liver injury (possible Hy's Law), and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

10.3 Appendix 3: Adverse Events – Definitions and Procedures for Recording, Evaluating, Follow up, and Reporting

Definition of AE

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

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

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

Definition of SAE

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

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

Recording and follow up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the Investigator to send photocopies of the study participant's medical records to UCB in lieu of completion of the UCB/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by UCB. In this case, all study participant identifiers, with the exception of the study participant number, will be redacted on the copies of the medical records before submission to UCB.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the study participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe (eg, a severe AE may be either serious or not serious, depending on whether these criteria are also met).

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) should be used as a supportive standardization instrument to evaluate AEs and SAEs but the final intensity grading by the Investigator must be mild, moderate, or severe.

Assessment of Causality

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

Follow up of AEs and SAEs

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

Reporting of SAEs

SAE Reporting to UCB via Paper CRF
• The primary mechanism for reporting an SAE to UCB will be the paper SAE data collection tool. • Facsimile transmission of the sop-af-004166 SAE Report Form for Development Product is the preferred method to transmit this information to UCB Drug Safety. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the SERIOUS ADVERSE EVENT REPORTING section at the front of the protocol.

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Contraception Guidance

Male study participants

Male study participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following (during the protocol-defined time frame in Section 5.1):

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 10-1 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

In addition, male study participants must refrain from donating sperm for the duration of the study and for 2 days after the last dose of IMP.

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

Table 10-1: Highly Effective Contraceptive Methods for female partners

Highly Effective Contraceptive Methods That Are User Dependent [a] Failure rate of <1% per year when used consistently and correctly.
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent [c]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the IMP. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the study participant.

IMP=investigational medicinal product; IUD=intrauterine device; IUS=intrauterine hormone-releasing system

[a] In case of newly started contraception pills/IUDs, the Investigator should consider the correct timing of starting/applying such methods in relation to the menstrual cycle and the manufacturing instruction as when these newly started methods would become effective.

[b] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for study participants participating in clinical studies.

[c] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the Dosing Period and for at least 3 months after the last dose of IMP

Collection of pregnancy information

Male study participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male study participant's female partner who becomes pregnant while the male study participant is in this study.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 1 working day of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to UCB. Generally, the follow up will be at least 12 months after the delivery date. Any termination of the pregnancy will be

reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.5 Appendix 5: Genetics

Not applicable.

10.6 Appendix 6: Liver Safety – Suggested Actions and Follow-up Assessments

Study participants with potential drug-induced liver injury 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.

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

Study participants with potential drug-induced liver injury 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/or study participant withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for discontinuation of IMP.

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

Phase 1 liver chemistry stopping criteria are designed to assure study participant safety and to evaluate liver event etiology.

Table 10-2: Liver Chemistry Stopping Criteria and Follow-Up Assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	**ALT ≥3xULN** **If ALT ≥3xULN AND bilirubin ≥ 2xULN (>35% direct bilirubin) or INR >1.5, report as a serious adverse event (SAE)** [a,b] **See additional actions and follow-up assessments below**
Required Actions and Follow-up Assessments	
Actions	**Follow-Up Assessments**
• **Immediately** discontinue study intervention • Report the event to UCB **within 24 hours** • Complete the liver event electronic Case Report From (eCRF), and complete an SAE data collection tool if the event also met the criteria for an SAE [b] • Perform liver function follow-up assessments • Monitor the study participant until liver function test abnormalities resolve, stabilize, or return to Baseline (see **MONITORING**) • Consider the need for a toxicology screening **MONITORING:**	• Viral hepatitis serology [c] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain blood sample for pharmacokinetic (PK) analysis within 1 hour after the most recent dose[d] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) • Fractionate bilirubin if total bilirubin ≥ 2xULN • Complete blood count with differential to assess eosinophilia

Table 10-2: Liver Chemistry Stopping Criteria and Follow-Up Assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	**ALT ≥3xULN** **If ALT ≥3xULN AND bilirubin ≥ 2xULN (>35% direct bilirubin) or INR >1.5, report as a serious adverse event (SAE)** [a,b] **See additional actions and follow-up assessments below**

Required Actions and Follow-up Assessments	
Actions	**Follow-Up Assessments**
If ALT ≥3xULN AND bilirubin ≥2xULN or INR >1.5 • Repeat liver function tests (include ALT, AST, ALP, bilirubin) and perform liver function follow-up assessments within **24 hours** • Monitor study participant twice weekly until liver function test abnormalities resolve, stabilize, or return to Baseline • A specialist or hepatology consultation is recommended **If ALT ≥3xULN AND bilirubin <2xULN and INR ≤1.5:** • Repeat liver function tests (include ALT, AST, ALP, bilirubin) and perform liver function follow-up assessments within **24 to 72 hours** • Monitor study participants weekly until liver function abnormalities resolve, stabilize, or return to Baseline	• Record the appearance or worsening of clinical symptoms of liver injury (eg, fatigue, nausea, vomiting, right upper quadrant pain), or hypersensitivity, on the adverse event (AE) eCRF • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications eCRF • Record alcohol use on the liver event alcohol intake eCRF **If ALT ≥3xULN AND bilirubin ≥2xULN or INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in study participants with definite or likely acetaminophen use in the preceding week [James et al, 2009]) **NOTE: Not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete liver imaging and/or liver biopsy eCRFs

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; eCRF=electronic Case Report Form; INR=international normalized ratio; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; SAE=serious adverse event; ULN=upper limit of normal; WBC=white blood cell

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

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

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

[d] Record the date/time of the PK blood sample draw and the date/time of the last dose of IMP prior to the PK blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the study participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Study Reference Manual.

10.7 Appendix 7: Medical Device Adverse Events (AEs), Adverse Device Effects (ADEs), Serious Adverse Events (SAEs) and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow up, and Reporting

Not applicable.

10.8 Appendix 8: Rapid Alert Procedures

Not applicable.

10.9 Appendix 9: Country-specific Requirements

The country-specific requirements for Japan will be provided separately.

10.10 Appendix 10: Abbreviations and Trademarks

ADE	adverse device effect
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
app	application
AST	aspartate aminotransferase
BRV	brivaracetam
CRF	Case Report Form
CRO	contract research organization
CYP	cytochrome P450
COVID-19	coronavirus disease 2019
ECG	electrocardiogram
eCRF	electronic Case Report Form
GCP	Good Clinical Practice
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IRB	Institutional Review Board
iv	intravenous
LEV	levetiracetam
PDILI	potential drug-induced liver injury
PK-PPS	Pharmacokinetic Per-Protocol Set
POS	partial-onset seizures
QTc	QT interval corrected
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SS	Safety Set
SV2A	synaptic vesicle protein 2A
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

10.11 Appendix 11: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current global amendment 1.0 is located directly before the Table of Contents.

11 REFERENCES

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.

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SPONSOR DECLARATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol and according to current Good Clinical Practice.

Approval Signatures

Name: ep0110-protocol-amendment-1.0

Version: 1.0

Document Number: CLIN-000182810

Title: EP0110 Protocol Amendment 1.0

Approved Date: 12 Jan 2022

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 11-Jan-2022 22:15:06 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 12-Jan-2022 00:58:38 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 12-Jan-2022 03:18:48 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 12-Jan-2022 06:47:43 GMT+0000