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

PROTOCOL EP0231 AMENDMENT 1.0

PHASE 1

SHORT TITLE:

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

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History	
Document	**Date**
Amendment 1	14 Dec 2023
Original Protocol	28 Jul 2023

Amendment 1 (14 Dec 2023)

Overall rationale for the amendment

The purpose of this protocol amendment is to include a description of the option of dissolution testing that could be used to determine bioequivalence and to align the protocol with the excipients for the development formulation.

Section # and name	Description of change	Brief rationale
Section 6.1, Treatments administered	The excipients for the BRV 50mg tablet and BRV dry syrup were updated as described below. BRV 50mg tablet: Hypromellose and saccharin sodium were added. Polyvinyl alcohol, iron oxide yellow (E172), and iron oxide black (E172) were removed. Dry syrup: [redacted] was added.	Aligned to include the excipients for the development formulation.
Section 9.3.1, Pharmacokinetic analyses	Added text: In the case that the CIs for $C_{max,ss}$ and AUC_{tau} are not contained in the range of 0.80 to 1.25, bioequivalence can still be concluded if the following criteria are met: 1) the point estimate of the adjusted GMR (Test/Reference) for $C_{max,ss}$ and AUC_{tau} are contained in the range of 0.90 to 1.11, and 2) in vitro dissolution rates of Test (dry syrup) and Reference (tablet)	Updated to include text that describes the option of dissolution testing that could be used to determine bioequivalence.

Section # and name	Description of change	Brief rationale
	formulations are available and are deemed similar according to the Japanese bioequivalence guideline (PSEHB/PED Notification No. 0319-1, 2020).	
Section 9.8, Determination of sample size	Previous text: In the group sequential design for this study, an interim analysis will be performed for bioequivalence or futility after approximately 60 evaluable participants, which is at 90% power for bioequivalence based on the study assumptions. New text: In the group sequential design for this study, an interim analysis will be performed for bioequivalence or futility after approximately 60 evaluable participants, which is at 90% power for bioequivalence based on the CIs of the adjusted GMR (Test/Reference) with the study assumptions.	Updated for clarity.
Section 11, References	New text: Ministry of Health, Labour and Welfare. PSEHB/PED Notification No. 0319-1 The Partial Amendment to Guideline for Bioequivalence Studies of Generic Products 19 Mar 2020.	Added to provide a reference for the Japanese bioequivalence guideline.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore, have not been summarized.

AUC_{tau}=area under the curve during a dosing interval at steady state; BRV=brivaracetam; CI=confidence interval; $C_{max,ss}$=maximum plasma concentration at steady state; GMR=geometric mean ratio; No=number; PED=Pharmaceutical Evaluation Division; PSEHB=Pharmaceutical Safety and Environmental Health Bureau

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	Europe and rest of world for interventional and non-interventional clinical studies, (except United States and Canada), please dial: +32 2 386 2421
Email	Worldwide for interventional clinical studies, please contact: DS_ICT@ucb.com

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1 PROTOCOL SUMMARY

1.1 Synopsis

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

Short title: A multiple-dose study to assess the bioequivalence between BRV tablet and dry syrup in healthy male Japanese 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 and patients with dysphagia. This study aims to assess the bioequivalence between the BRV 50mg tablet and BRV 50mg as a dry syrup formulation in a multiple-dose setting.

Objectives and endpoints

Objectives	Endpoints
Primary objective	
• To assess bioequivalence between the BRV 50mg tablet and BRV 50mg dry syrup after multiple oral doses in healthy male Japanese participants	Primary PK endpoints from plasma BRV concentrations: • $C_{max,ss}$ • AUC_{tau}
Secondary objective	
• To evaluate the safety and tolerability of multiple oral doses of the BRV 50mg tablet and BRV 50mg dry syrup in healthy male Japanese participants	Secondary safety endpoints: • Incidence of TEAEs • Incidence of treatment-emergent SAEs • Incidence of TEAEs leading to discontinuation
Other objectives	
• To evaluate other PK parameters after multiple oral doses of the BRV 50mg tablet and BRV 50mg dry syrup in healthy male Japanese participants	Other PK endpoints from plasma BRV concentrations: • C_{trough} • CL_{ss}/F • $t_{max,ss}$
• To further evaluate the safety and tolerability after multiple oral doses of the BRV 50mg tablet and BRV 50mg dry syrup in healthy male Japanese participants	Other safety endpoints: • Change from Baseline in clinical laboratory test parameters (ie, hematology, clinical chemistry, and urinalysis) • Change from Baseline in vital signs (SBP, DBP, body temperature, respiratory rate, and heart rate) • 12-lead ECG parameters and findings

	• Physical examinations

AUC_{tau}=area under the curve during a dosing interval at steady state; BRV=brivaracetam; CLss/F=apparent total body clearance at steady state; $C_{max,ss}$=maximum plasma concentration at steady state; C_{trough}=measured concentration at the end of a dosing interval at steady state; DBP=diastolic blood pressure; ECG=electrocardiogram; PK=pharmacokinetics; SAE=serious adverse event; SBP=systolic blood pressure; TEAE=treatment-emergent adverse event; $t_{max,ss}$=time of $C_{max,ss}$

Overall design

EP0231 is a single-center, multiple-dose, open-label, randomized, group sequential design, 2-way cross-over study to assess the bioequivalence of BRV 50mg tablet and BRV 50mg dry syrup in healthy male Japanese participants after oral administration under fasted conditions. In addition, the safety and tolerability of BRV will be evaluated.

Participants will enter a Screening Period (2 to 28 days before administration of investigational medicinal product [IMP]), and eligible participants will start the Dosing Period. The Dosing Period consists of 2 periods (Dosing Period 1 and Dosing Period 2) of 5 days each (Day -1 to Day 4) with a total of 5 administrations of BRV 50mg on Day 1 and Day 2 (morning and evening doses 12 hours apart), and Day 3 (morning dose only).

Participants will receive 1 of the following treatments in each Dosing Period under fasting conditions according to randomly assigned treatment sequences (A-B or B-A):

- Treatment A – multiple doses of BRV 50mg tablets
- Treatment B – multiple doses of BRV 50mg dry syrup (1.25g of granules for oral suspension 4% w/w)

The Dosing Periods will be separated by a Wash-Out Period (minimum of 6 days and preferably no more than 10 days between the final dose in Dosing Period 1 and the first dose in Dosing Period 2 for each participant) and followed by a Safety Follow-Up (SFU) Visit, 7 to 9 days after the last administration of IMP. Participants who prematurely discontinue the IMP/study will be encouraged to return for an SFU Visit, 7 to 9 days after the final IMP administration. Refer to the study schematic in Figure 1-1.

The activities to be performed during the Dosing Periods are presented in the Schedule of Activities (Section 1.3).

Number of participants

Up to approximately 96 participants will be recruited into 2 cohorts to ensure a total of up to approximately 90 evaluable participants. After the first cohort (approximately 60 evaluable participants) has completed both Dosing Periods, an interim analysis will be performed and an internal Data Monitoring Committee (DMC) will determine whether the primary objective is achieved, futility of the study is confirmed, or whether the study should continue with recruitment of the second cohort (approximately 30 evaluable participants).

Treatment groups and duration

The total duration of the study for an individual participant is 21 to 53 days and will include:

- A Screening Period (2 to 28 days before IMP administration)
- Two Dosing Periods (5 days each, with a total of 5 administrations of BRV 50mg on Day 1 and Day 2 (morning and evening doses 12 hours apart), and Day 3 (morning dose only)
- A Wash-Out Period following Dosing Period 1 (minimum of 6 days and preferably no more than 10 days between the final dose in Dosing Period 1 and the first dose in Dosing Period 2 for each participant)
- An SFU Visit 7 to 9 days after the final IMP administration

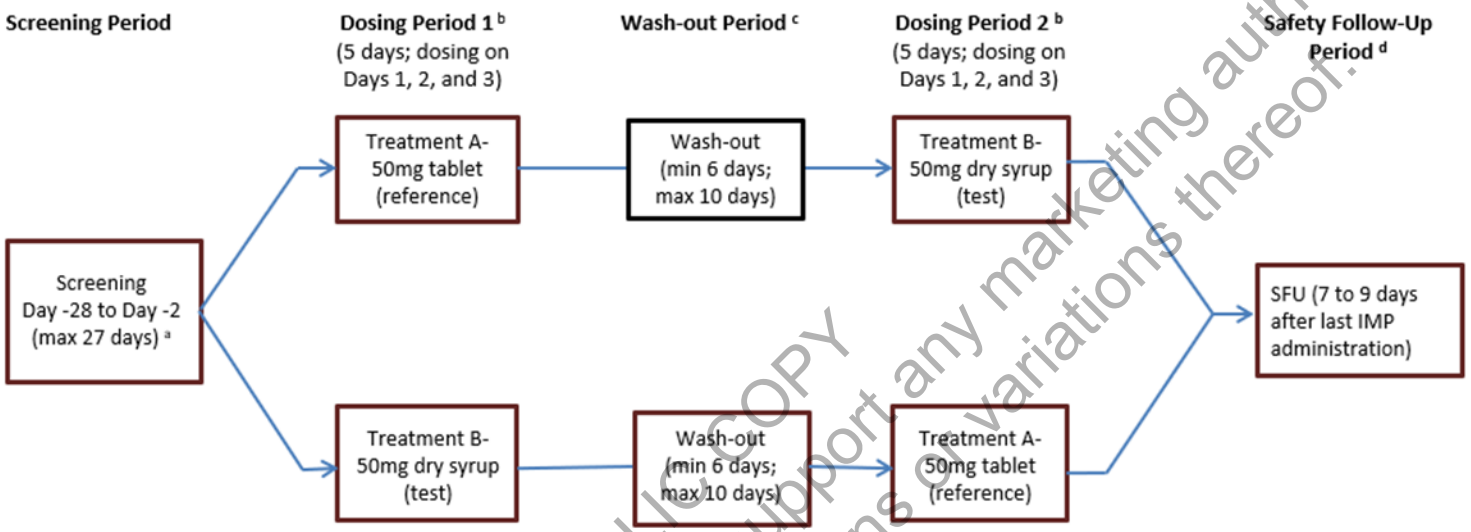
The estimated study duration does not exactly match the length of the study periods as some of study periods can overlap.

Refer to Figure 1-1 for the study design.

1.2 Schema

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

Figure 1-1: Schematic diagram



BRV=brivaracetam; DMC=Data Monitoring Committee; IMP=investigational medicinal product; max=maximum; min=minimum; SFU=Safety Follow-Up; w/w=weight/weight

[a] Following a Screening Period (up to 27 days before the start of Dosing Period 1), eligible participants 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. After the first cohort (approximately 60 evaluable participants) has completed both Dosing Periods, an interim analysis will be performed, and an internal DMC will determine whether the primary objective is achieved, futility of the study is confirmed, or whether the study should continue with recruitment of the second cohort (approximately 30 evaluable participants).

[b] Each Dosing Period is 5 days each (Day -1 to Day 4). Brivaracetam 50mg will be administered twice daily (morning and evening doses 12 hours apart) as 50mg tablets (Treatment A [Reference]) or dry syrup (1.25g of BRV granules for oral suspension 4% w/w; Treatment B [Test]). On Day 1 and Day 2, participants will fast for at least 2 hours before and after IMP administration. On Day 3, only the morning dose will be administered, and the participants will fast for 10 hours before and 4 hours after IMP administration. For each Dosing Period, participants will be admitted to the study site on Day -1 (1 day before dosing) and will be discharged on the morning of Day 4, approximately 24 hours after last administration of IMP in each Dosing Period, at the discretion of the Investigator.

[c] The Dosing Periods will be separated by a Wash-Out Period (minimum of 6 days and preferably no more than 10 days between the final dose in Dosing Period 1 and the first dose in Dosing Period 2) for each participant.

[d] An SFU Visit will occur 7 to 9 days after the final IMP administration. Participants who prematurely discontinue the IMP/study will be encouraged to return for an SFU Visit within 7 to 9 days after the final IMP administration.

1.3 Schedule of Activities

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

Table 1-1: Schedule of Activities

Procedure	Screening Period	Dosing Period 1 or Dosing Period 2 [a]					SFU [b]
	2 to 28 days before administration of IMP	Check in Day -1	Day 1	Day 2	Day 3	Day 4	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					
Verification of withdrawal criteria [c]		X	X	X	X	X	
Medical/surgical history	X	X					
Physical examination	X	X				X	X
Height and weight	X						
Viral serology (HBsAg, HCV, HIV, and syphilis)	X						
Alcohol and drug (including cotinine) testing	X	X					
COVID-19 precautions [d]	X	X					X
Vital signs [e]	X	X	X	X	X	X	X
Clinical laboratory tests (hematology, clinical chemistry, and urinalysis)	X	X				X	X
Randomization [f]		X					
12-lead ECG [g]	X		X			X	X
IMP administration [h]			X	X	X		
Blood sampling for PK [i]			X	X	X		

Table 1-1: Schedule of Activities

Procedure	Screening Period	Dosing Period 1 or Dosing Period 2 [a]					SFU [b]
	2 to 28 days before administration of IMP	Check in Day -1	Day 1	Day 2	Day 3	Day 4	7 to 9 days after the last administration of IMP
Recording of prior and concomitant medication and procedures	X	X	X	X	X	X	X
Recording of AEs	X	X	X	X	X	X	X
Confinement		X	X	X	X	X [j]	

AE=adverse event; BRV=brivaracetam; COVID-19=coronavirus disease 2019; 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; w/w=weight/weight

[a] Each participant will enter 2 Dosing Periods, separated by a Wash-Out Period. Dosing Period 2 will begin after the Wash-Out Period (minimum of 6 days and preferably no more than 10 days between the final IMP administration in Dosing Period 1 and the first IMP administration in Dosing Period 2).

[b] An SFU Visit will occur 7 to 9 days after the last administration of IMP. Participants who prematurely discontinue the IMP/study will be encouraged to undergo an SFU Visit within 7 to 9 days after the last administration of IMP.

[c] Confirmation that participants do not fulfill the withdrawal or stopping criteria (Section 7) will occur on Day -1, before dosing on Days 1, 2, and 3, and prior to discharge on Day 4.

[d] Coronavirus disease 2019 precautions will be performed in alignment with the study site's local requirements (refer to Section 2.3.1 for additional details).

[e] Vital signs (blood pressure [systolic blood pressure and diastolic blood pressure], heart rate, respiratory rate, and body temperature) will be taken at the Screening Visit; for each Dosing Period (on Day -1 check in, Day 1 predose and 12 hours postdose [before the evening dose is administered]), Day 2 [premorning dose] and Day 3 predose, and Day 4 prior to discharge); and at the SFU Visit.

[f] Randomization will occur only for Dosing Period 1; either on Day -1 after all assessments for Day -1 are performed or Day 1 before any assessments for Day 1 are performed. Each participant will be randomly assigned to 1 of 2 treatment sequences (A-B or B-A).

[g] Single 12-lead ECGs will be recorded at Screening, for each Dosing Period (Day 1 predose and Day 4 prior to discharge), and at the SFU Visit.

[h] Investigational medicinal product administration: Brivaracetam 50mg will be administered twice daily (approximately 12 hours apart) as 50mg tablets (Treatment A [Reference]) or dry syrup (1.25g of BRV granules for oral suspension 4% w/w; Treatment B [Test]). On Day 1 and Day 2, participants will fast for at least 2 hours before and after IMP administration. On Day 3, only the morning dose will be administered, and the participants will fast for 10 hours before and 4 hours after IMP administration.

[i] For each Dosing Period, blood samples for PK analysis will be collected on Day 1 (before the morning and evening doses [0 and 12hr]), Day 2 (before the morning and evening doses [24 and 36hr]), and Day 3 (predose [48hr] and 10min, 15min, 20min, 30min, 45min, 60min, 75min, 90min, 2hr, 6hr, 9hr, and 12hr postdose).

Table 1-1: Schedule of Activities

Procedure	Screening Period	Dosing Period 1 or Dosing Period 2 [a]					SFU [b]
	2 to 28 days before administration of IMP	Check in Day -1	Day 1	Day 2	Day 3	Day 4	7 to 9 days after the last administration of IMP

[j] Participants will check out of the clinical unit the morning of Day 4, approximately 24 hours after the final dose of IMP administered, at the discretion of the Investigator.

2 INTRODUCTION

Product description

Brivaracetam ((2S)-2-[(4R)-2-oxo-4-propyltetrahydro-1*H*-pyrrol-1-yl] butanamide) is a 2-pyrrolidone derivative. The current 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.

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 t_{max} is 1hr (range: 0.25 to 3hr) after dosing in fasting participants. The pharmacokinetics (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 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 3hr 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 9hr in healthy adults. More than 95% of the dose, including less than 9% as unchanged BRV, is excreted in the urine within 72hr 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. A combination of these 2 pathways leads to the formation of the hydroxyacid metabolite (ucb-107092-1). These 3 metabolites are not pharmacologically active. There is no evidence of chiral inversion of BRV. In a PK and pharmacodynamic interaction study in healthy participants, BRV increased the effects of alcohol on psychomotor function, attention, and memory, although there was no clinically relevant PK interaction.

Information regarding the bioequivalence between BRV oral tablet and BRV dry syrup from a previous study, EP0110, is presented in Section 2.1.

Safety profile in clinical pharmacology studies

Thirty-two clinical pharmacology studies with BRV have been conducted in healthy participants, with the highest single dose given being BRV 1400mg.

Safety data were pooled (Pool Phase 1) in 2014 for all completed clinical pharmacology studies with the exceptions 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, as well as the 3 formulation studies conducted for BRV (EP0113, EP0115, and EP0131). N01209 and EP0117 studies in healthy male Japanese study participants, were also included in Pool Phase 1. N01069, a Phase 2a study in participants with photosensitive epilepsy, was included in Pool Phase 1 due to its single-dose study design, which was similar to a clinical pharmacology study. Pool Phase 1 includes participants who received BRV oral tablets, capsules, and solution, and participants who received solution for intravenous (iv) injection. Pool Phase 1 included 220 participants in the placebo group and 729 participants in the BRV Overall group. Treatment-emergent adverse events (TEAEs) were reported for 67 participants (30.5%) in the placebo group and 586 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 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 participants with single-dose ranging from BRV 2.5mg to 100mg oral tablets and multiple-doses ranging from BRV 2.5mg twice daily (5mg/day) to 50mg twice daily (100mg/day) oral tablets, a total of 11 adverse events (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 tablets administration in healthy male Japanese participants, the most commonly reported TEAEs were somnolence, dizziness, and nausea.

In EP0110, a single-dose bioequivalence study between BRV 50mg tablet and BRV 50mg as dry syrup formation in healthy male Japanese participants, no notable difference was observed in the overall incidences of TEAEs after administration of the BRV tablet and dry syrup formulations. No major differences in the safety profile were observed between the 2 formulations, and no unexpected safety findings were observed during the study. There were no serious TEAEs, severe TEAEs, or TEAEs leading to discontinuation or death.

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 monotherapy and adjunctive therapy in the treatment of POS with or without secondary generalization in adult and pediatric patients with epilepsy in Japan. In addition to tablets, a dry syrup formulation is being developed specifically for the Japanese market, mainly to allow dose adjustment by body weight in pediatric patients and patients with dysphagia.

As patients may switch from the dry syrup to the tablet, or vice versa, and dry syrup is favorable in pediatric patients and patients with dysphagia, it is important to know whether the dry syrup formulation shows a similar PK profile as the tablet formulation.

A prior study, EP0110, assessed the bioequivalence between the BRV 50mg oral tablet and BRV 50mg dry syrup by employing a standard single-dose, 2-treatment, and 2-period randomized

cross-over design, in alignment with the Japanese bioequivalence guideline (Pharmaceutical Safety and Environmental Health Bureau [PSEHB]/Pharmaceutical Evaluation Division [PED] Notification No. 0319-1, 2020), which recommends a single-dose study with a usual clinical dose. Although all other PK parameters assessed were similar for both formulations (ie, AUC, AUC_{extr}, CL/F, V_Z/F, MRT, t_{max}, $t_{½}$, and λ_z) and $AUC_{(0-t)}$ met the criteria for bioequivalence, the observed C_{max} following administration of the tablet was higher than that observed for the dry syrup; therefore, bioequivalence was not concluded between the 2 formulations (refer to Section 9.8 for additional details).

A subsequent PK simulation based on the data collected in EP0110 showed that in a multiple dose setting, bioequivalence could be established, as the intraparticipant variability for C_{max} seen in EP0110 decreased while the mean ratio for C_{max} increased.

Based upon the outcome of EP0110 and in alignment with the Japanese bioequivalence guideline (PSEHB/PED Notification No. 0319-1, 2020), EP0231 will assess the bioequivalence of the same formulations used in EP0110, employing a group sequential design with twice daily dosing for a total of 5 doses over 3 days.

2.2 Background

Brivaracetam has primarily been studied as oral (tablet) adjunctive therapy in participants with refractory epilepsy, a conversion to monotherapy indication for POS (monotherapy indication was approved in the US by an extrapolation strategy from adjunctive therapy). In addition, an iv formulation of BRV has been studied in participants with epilepsy (N01258) and has also been evaluated as a replacement for oral BRV in adult Japanese 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 indicated for use.

For BRV to be available in a second formulation as a dry syrup in Japan, mainly for pediatric patients and patients with dysphagia, the primary objective of this study is to assess the bioequivalence between the BRV 50mg tablet and BRV 50mg as dry syrup after multiple oral doses in healthy male Japanese participants.

2.3 Benefit/Risk assessment

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

In addition to the most frequently reported AEs from the pooled BRV safety data described in Section 2 (ie, dizziness, somnolence, fatigue, headache, euphoric mood, feeling drunk), the potential risks in the study include:

- Electrocardiogram (ECG) stickers on the participants' chests and limbs may cause some local irritation and may be uncomfortable to remove. 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 participant, and it is possible that bruising, inflammation, and/or hematoma may occur at the site of cannulation.

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

More detailed information about the known and expected risks and reasonably expected AEs of BRV are available in the IB.

Any risks during the study will be minimized by implementation of the following procedures:

- The dose to be administered (50mg twice daily) is 50% of the maximum approved daily dose as per the US and EU labels (200mg/day).
- The participants will reside in the clinical unit from the day prior to administration of the first dose to approximately 24 hours after administration of the final dose of BRV for each Dosing Period.
- All doses will be administered under medical supervision.
- All participants will be closely monitored through the measurement of blood pressure, heart rate, respiratory rate, and body temperature. In addition, physical examinations will be performed on Day -1 and Day 4 of each Dosing Period and 7 to 9 days after the last administration of IMP. Electrocardiograms will be performed on Day 1 and Day 4 of each Dosing Period and 7 to 9 days after the last administration of IMP.

2.3.1 Risk assessment for coronavirus disease 2019

Brivaracetam is a highly selective ligand 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 with a total of 5 administrations of BRV 50mg on Day 1 and Day 2 (morning and evening doses 12 hours apart), and Day 3 (morning dose only) 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 participants.

Therefore, the risk of the 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 participants may have additional contact (eg, commute to the site) and have additional human contact (eg, with site staff and other participants of the clinical study).

Precautions for COVID-19 will be implemented based on local regulations at the study site at the time of study conduct and may include, but are not limited to, screening for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), asking participants about their potential exposure to SARS-CoV-2, monitoring participants for any signs and symptoms of COVID-19, and testing for SARS-CoV-2. Refer to Section 5.3.5 for further details.

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 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 objective	
• To assess bioequivalence between the BRV 50mg tablet and BRV 50mg dry syrup after multiple oral doses in healthy male Japanese participants	Primary PK endpoints from plasma BRV concentrations: • $C_{max,ss}$ • AUC_{tau}
Secondary objective	
• To evaluate the safety and tolerability of multiple oral doses of the BRV 50mg tablet and BRV 50mg dry syrup in healthy male Japanese participants	Secondary safety endpoints: • Incidence of TEAEs • Incidence of treatment-emergent SAEs • Incidence of TEAEs leading to discontinuation
Other objectives	
• To evaluate other PK parameters after multiple oral doses of the BRV 50mg tablet and BRV 50mg dry syrup in healthy male Japanese participants	Other PK endpoints from plasma BRV concentrations: • C_{trough} • CL_{ss}/F • $t_{max,ss}$
• To further evaluate the safety and tolerability after multiple oral doses of the BRV 50mg tablet and BRV 50mg dry syrup in healthy male Japanese participants	Other safety endpoints: • Change from Baseline in clinical laboratory test parameters (ie, hematology, clinical chemistry, and urinalysis) • Change from Baseline in vital signs (SBP, DBP, body temperature, respiratory rate, and heart rate) • 12-lead ECG parameters and findings • Physical examinations

AUC_{tau}=area under the curve during a dosing interval at steady state; BRV=brivaracetam; CLss/F=apparent total body clearance at steady state; $C_{max,ss}$=maximum plasma concentration at steady state; C_{trough}=measured concentration at the end of a dosing interval at steady state; DBP=diastolic blood pressure; ECG=electrocardiogram; PK=pharmacokinetics; SAE=serious adverse event; SBP=systolic blood pressure; TEAE=treatment-emergent adverse event; $t_{max, ss}$=time of $C_{max,ss}$

4 STUDY DESIGN

4.1 Overall design

EP0231 is a single-center, multiple-dose, open-label, randomized, group sequential design, 2-way cross-over study to assess the bioequivalence of BRV 50mg tablet and BRV 50mg dry syrup in healthy male Japanese participants after oral administration under fasted conditions. In addition, the safety and tolerability of BRV will be evaluated.

Participants will enter a Screening Period (2 to 28 days before administration of IMP), and eligible participants will start the Dosing Period. The Dosing Period consists of 2 periods (Dosing Period 1 and Dosing Period 2) of 5 days each (Day -1 to Day 4) with a total of 5 administrations of BRV 50mg on Day 1 and Day 2 (morning and evening doses 12 hours apart), and Day 3 (morning dose only).

Participants will receive 1 of the following treatments in each Dosing Period under fasting conditions according to randomly assigned treatment sequences (A-B or B-A):

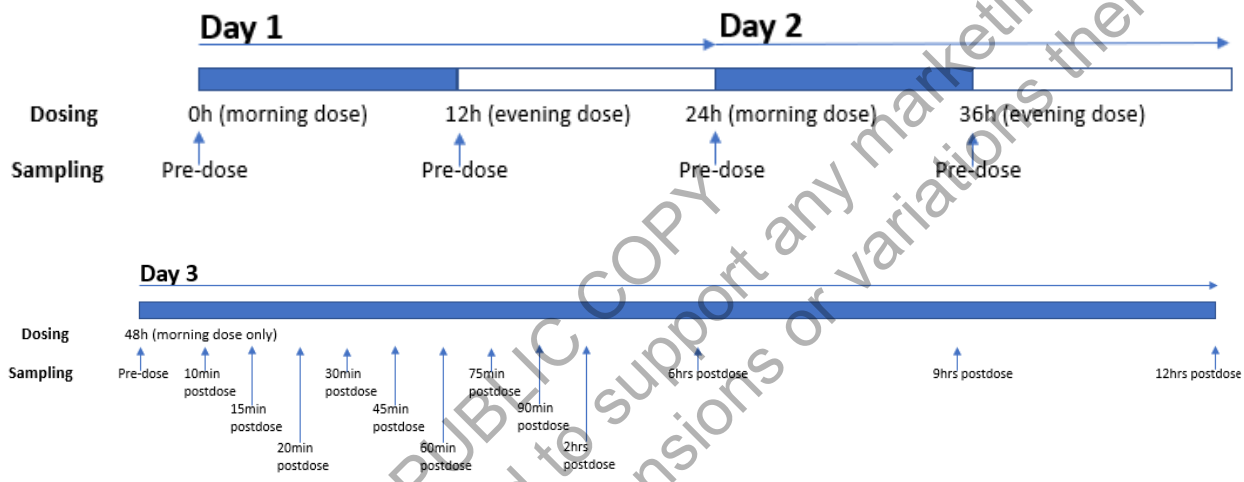
- Treatment A – multiple doses of BRV 50mg tablets
- Treatment B – multiple doses of BRV 50mg dry syrup (1.25g of granules for oral suspension 4% w/w)
- In the treatment sequence A-B, on Day 1 and Day 2 of Dosing Period 1, each participant will receive twice daily (morning and evening 12 hours apart) a dose of BRV tablet formulation (50mg); on Day 3 of Dosing Period 1, each participant will receive a single morning dose of BRV tablet formulation (50mg). On Day 1 and Day 2 of Dosing Period 2, each participant will receive twice daily (morning and evening 12 hours apart) a dose of BRV 50mg dry syrup (1.25g of granules for oral suspension 4% w/w); on Day 3 of Dosing Period 2, each participant will receive a single morning dose of BRV 50mg dry syrup (1.25g of granules for oral suspension 4% w/w).
- In treatment sequence B-A, on Day 1 and Day 2 of Dosing Period 1, each participant will receive twice daily (morning and evening doses 12 hours apart) a dose of BRV 50mg dry syrup (1.25g of granules for oral suspension 4% w/w); on Day 3 of Dosing Period 1, each participant will receive a single morning dose of BRV 50mg dry syrup (1.25g of granules for oral suspension 4% w/w). On Day 1 and Day 2 of Dosing Period 2, each participant will receive twice daily (morning and evening doses 12 hours apart) a dose of BRV tablet formulation (50mg); on Day 3 of Dosing Period 2, each participant will receive a single morning dose of BRV tablet formulation (50mg).

The Dosing Periods will be separated by a Wash-Out Period (minimum of 6 days and preferably no more than 10 days between the final dose in Dosing Period 1 and the first dose in Dosing Period 2 for each participant) and followed by an SFU Visit, 7 to 9 days after the last administration of IMP. Participants who prematurely discontinue the IMP/study will be encouraged to return for an SFU Visit, 7 to 9 days after the final IMP administration.

During each of the 2 Dosing Periods (ie, Dosing Period 1 and Dosing Period 2), participants will be admitted to the clinical study center on Day -1 (1 day before administration of IMP). Participants will fast for at least 2 hours before and 2 hours after each IMP administration on Day 1 and Day 2; on Day 3, participants will fast for 10 hours before and 4 hours after the final IMP administration. Participants will receive standard meals for breakfast, lunch, and dinner during the 5-day in-clinic period. Participants will be discharged on the morning of Day 4 of each Dosing Period, approximately 24 hours after the administration of the final dose of IMP, provided there are no medical objections in the opinion of the Investigator.

The blood sampling scheme for the determination of the plasma concentrations of BRV in each Dosing Period is shown in Figure 4-1.

Figure 4-1: Blood sampling scheme



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 (systolic blood pressure [SBP], diastolic blood pressure [DBP], heart rate, respiratory rate, and body temperature), ECGs, and completion of physical examinations per the Schedule of Activities (Section 1.3).

Within the group sequential design, up to approximately 96 participants will be recruited into 2 cohorts to ensure a total of up to approximately 90 evaluable participants. After the first cohort (approximately 60 evaluable participants) has completed both Dosing Periods, an interim analysis will be performed and an internal DMC will determine whether the primary objective is achieved, futility of the study is confirmed, or whether the study should continue with recruitment of the second cohort (approximately 30 evaluable participants).

4.2 Scientific rationale for study design

The primary objective of this study is to assess the bioequivalence between BRV 50mg tablet and BRV 50mg dry syrup after multiple oral doses.

EP0231 will include a larger sample size of healthy male Japanese participants (up to approximately 90 evaluable participants) in contrast to a sample size of 24 participants in the

prior bioequivalence study EP0110. This increased sample size in EP0231 is an effort to minimize the impact of intraparticipant variability of the C_{max} and to increase the C_{max} ratio. The larger sample size is based on the results from EP0110 and the multiple dose simulation (refer to Section 9.8 for additional details). An interim analysis to assess bioequivalence will be performed after the first cohort of the group sequential design (approximately 60 evaluable participants) has completed both Dosing Periods. If the interim analysis demonstrates bioequivalence, the study will be stopped.

The group sequential design has been selected to maximize the chances of success while enabling an early stop of the study (ie, after the first cohort) which may help to reduce the number of participants in the study. The study is powered to show bioequivalence in Cohort 1 (Section 9.8).

This study will be conducted in healthy male Japanese participants. A dry syrup formulation for BRV is being developed specifically for the Japanese market.

4.3 Justification for dose

A dose of 50mg, per administration, was specified for this study as it was used in the prior bioequivalence study, EP0110 (refer to Section 2 for additional details). This dose was also proposed as the clinical dose in Japan (bioequivalence guideline in Japan) and is already used in other countries. In this study, a 50mg dose of BRV will be administered twice daily for a total of 5 doses to allow steady state to be reached.

4.4 End of study definition

A 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 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

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

Age

1. Participant must be between 20 to 50 years of age (inclusive) at the time of signing the informed consent form (ICF).

Type of participant and disease characteristics

2. Participant is overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.
3. 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 not be clinically significant for participation in the study (refer to Section 5.2 for exclusion criteria regarding liver function).

4. Participant is of Japanese descent as evidenced by appearance and verbal confirmation of familial heritage (ie, participant has all 4 Japanese grandparents born in Japan).

Weight

5. Participant has a body weight of at least 50kg and body mass index within the range of 18.0 to 30.0kg/m^2 (inclusive) at the Screening Visit.

Sex

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

Informed consent

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

5.2 Exclusion criteria

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

Medical conditions

1. Participant has any medical or psychiatric condition including previous or current episode of suicidal ideation that, in the opinion of the Investigator, could jeopardize or would compromise the participant's ability to participate in this study.
2. 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. Participant has a current history of alcohol or drug use disorder, as defined in Diagnostic and Statistical Manual of Mental Disorders V, or within the previous 6 months.
4. Participant has a known hypersensitivity to any components of the IMP formulations.
5. Participant has alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) ≥1.0x upper limit of normal (ULN).
6. Participant has bilirubin >1.0xULN (isolated bilirubin <1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
7. Participant has 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 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 the ULN, the participant is considered to not meet the exclusion criteria.

Prior/Concomitant therapy

8. Participant has used other drugs, including vaccinations, over-the-counter medications, herbal/traditional medicines, or dietary supplements within 14 days before the first administration of IMP (excluding medicines for external use), with the exception of paracetamol, which is only prohibited during the 5 in-clinic days of each Dosing Period (Section 6.5.1).
9. 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. Participant has participated in another study of an IMP (and/or an investigational device) within the previous 30 days or within 5 times the half-life (whichever is longer) of the first dose of BRV in this study or is currently participating in another study of an IMP (and/or an investigational device).

Diagnostic assessments

11. Participant with clinically relevant abnormalities in a standard 12-lead ECG at Screening Visit as judged by the Investigator.
12. 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. Participant tests positive for alcohol and/or prohibited concomitant drugs (including cotinine) at the Screening Visit or on Day -1.

Other exclusions

14. 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. 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. Participant consumes 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. Participant has consumed grapefruit or grapefruit juice within 7 days before first administration of the IMP.

5.3 Lifestyle restrictions

5.3.1 Meals and dietary restrictions

- Participants must refrain from consumption of grapefruit until completion of the study.

5.3.2 Caffeine, alcohol, and tobacco

- During each Dosing Period, participants will 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 PK sample.
- During each Dosing Period, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK sample.
- During each Dosing Period and the Wash-Out Period, participants will abstain from the use of nicotine-containing products for 30 days before the start of dosing until after collection of the final PK sample.

5.3.3 Activity

- Participants will abstain from strenuous exercise for 96 hours before each blood collection for clinical laboratory tests. 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.

Participants will fast for at least 2 hours before and 2 hours after each IMP administration on Day 1 and Day 2; on Day 3, participants will fast for 10 hours before and 4 hours after the final IMP administration. Participants will receive standard meals for breakfast, lunch, and dinner during the 5-day in-clinic period.

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 tap 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

Even though the COVID-19 pandemic is no longer a global health emergency, 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 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.

The study site will adhere to common practices of monitoring participants for any sign 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.

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

5.4 Screen failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened after Sponsor approval is given for rescreening. Rescreened participants should be assigned a new participant number.

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 the ULN, the participant will be considered 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

ARM name	Treatment A (Reference)	Treatment B (Test)
Intervention name	Brivaracetam	Brivaracetam
Type	Drug	Drug
Dose formulation	Tablet	Dry syrup
Unit dose strength(s)	1 tablet of 50mg	1.25g of granules for oral suspension 4% w/w
Dosage level(s)	Multiple doses (5 in total; twice daily on Day 1 and Day 2 and morning dose only on Day 3)	Multiple doses (5 in total; twice daily on Day 1 and Day 2 and morning dose only on Day 3)
Route of administration	Oral	Oral
Dosing instructions	Tablet will be administered with 200mL water.	Dry syrup will be mixed with 50mL of tap water immediately prior to dosing; 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 with polypropylene caps. Each bottle will be labeled as required per country requirements.	Dry syrup will be provided in high-density polyethylene bottles with polypropylene caps. Each bottle will be labeled as required per country requirements.
Excipients	Croscarmellose sodium Lactose monohydrate Betadex (ß-cylcodextrin) Lactose anhydrous Magnesium stearate Hypromellose Titanium dioxide (E171) Macrogol 3350 Saccharin sodium Talc	[redacted]

Abbreviations: IMP=investigational medicinal product; w/w=weight/weight

6.2 Preparation, handling, storage, and accountability requirements

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

Only participants enrolled in the study may receive IMP, and only authorized site staff may supply or administer IMP. All IMP 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 participant to store the IMP following the instructions on the label.

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

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

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

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

Periodically, and/or after completion of the clinical phase 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 participants to the treatment sequence as per the cross-over design, treatment sequences A-B or B-A.

The study site will generate the randomization list for the treatment sequences (A-B or B-A) allocation. The randomization list will be reviewed by the Clinical Trial Statistician at UCB to ensure that the code meets the study requirements.

6.3.1 Procedures for maintaining and breaking the treatment blind

Not applicable; this is an open-label study.

6.4 Treatment compliance

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)

The following concomitant medications are permitted during the study:

- Paracetamol (acetaminophen) for the treatment of mild symptoms (eg, headache or pain relief) is permitted during the study at a maximum dose of 2g/day, **except during the participant's 5 in-clinic days** (ie, from check-in [Day -1] through discharge [Day 4]) for each Dosing Period.
- Participants are allowed vaccinations up to 14 days prior to the initiation of IMP administration. Vaccine administration will be entered as a prior medication in the eCRF.

No other concomitant medications are allowed during this study.

6.5.2 Prohibited concomitant treatments (medications and therapies)

With the exception of paracetamol (Section 6.5.1), all prescription or over-the-counter 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. Vaccinations are prohibited within the 14 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 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 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 participants; therefore, no treatment will be provided after the end of the study.

7 DISCONTINUATION OF IMP AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

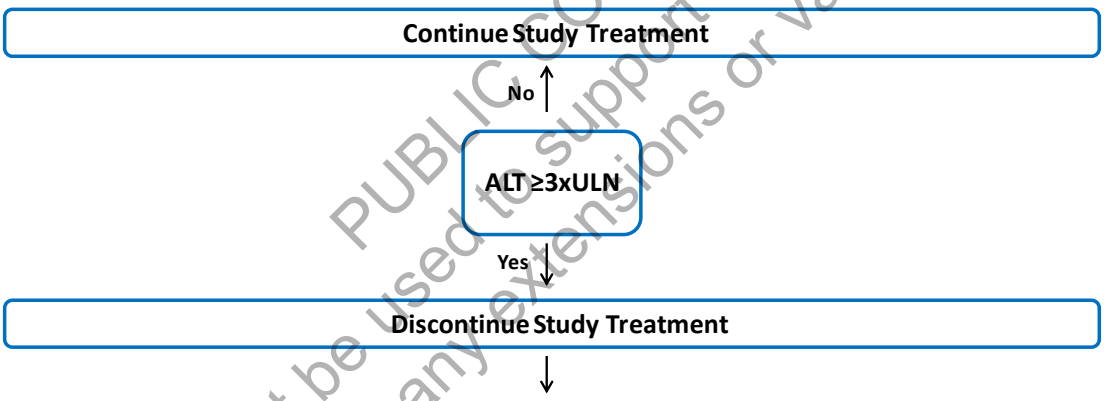
7.1 Discontinuation of IMP

7.1.1 Liver chemistry stopping criteria

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

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

Figure 7-1: Liver chemistry stopping algorithm



ALT=alanine aminotransferase; ULN=upper limit of normal

Evaluation of potential drug-induced liver injury (PDILI) must be initiated as described in this protocol. If 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 Participant discontinuation/withdrawal from the study

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

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

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

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

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

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

1. Participant withdraws his consent.
2. Participant develops an illness that would interfere with his continued participation.
3. Participant is noncompliant with the study procedures or IMP in the opinion of the Investigator.
4. Participant takes prohibited concomitant medications as defined in this protocol.
5. The Sponsor or a regulatory agency requests withdrawal of the 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 (refer to Section 2.3.1 for additional details).

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

7.3 Lost to follow up

A 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 participant fails to return to the clinic for Dosing Period 2 or the SFU Visit.

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

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

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue 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 participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for Screening failure, as applicable.

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

8.1 Efficacy assessments

Not applicable.

8.2 Safety assessments

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

8.2.1 Physical examination

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.

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.

8.2.2 Vital signs

Systolic blood pressure, DBP, heart rate, respiratory rate, and 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, heart rate, 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 ECGs will be obtained at Screening, each Dosing Period (Day 1 predose and Day 4 prior to discharge), and the SFU Visit using an ECG machine that automatically calculates

the heart rate and measures PR, QRS, QT intervals, and QT interval corrected for heart rate with Fridericia's formula (QTcF).

All ECG recordings should be taken with the study participant resting in the supine position for at least 5 minutes before the recording.

8.2.4 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 (Section 1.3).

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE Section of the eCRF. The laboratory reports must be filed with the source documents. 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 final dose of IMP should be repeated until the values return to normal/Baseline, are stabilized, are no longer considered clinically significant by the Investigator or UCB Study Physician, or the participant is lost to follow up (as defined in Section 7.3).

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 (Section 1.3).

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

8.3 Adverse events and serious adverse events

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

Adverse event will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the 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 participant to discontinue the IMP (Section 7).

Confirmed COVID-19 cases will be recorded as AEs.

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

8.3.1 Time period and frequency for collecting AE and SAE information

All SAEs will be collected from the signing of the ICF until the SFU Visit at the time points specified in the Schedule of Activities (Section 1.3).

All AEs will be collected from the signing of the ICF until the SFU Visit at the time points specified in the Schedule of Activities (Section 1.3).

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the ICF), including any pretreatment and posttreatment periods required by the protocol, must be reported in the eCRF even if no 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 participant, and to also inform participants of the need to inform the Investigator of any SAE within this period. Serious AEs that the Investigator thinks may be associated with the 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 nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow up of AEs and SAEs

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

8.3.4 Regulatory reporting requirements for SAEs

Prompt notification of an SAE by the Investigator to the Sponsor is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of 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 (IRBs), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions 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 participants will be collected after the start of IMP and until the end of the study.

If a pregnancy is reported, the Investigator must immediately inform the Sponsor within 1 working day 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 participant.

8.4 Safety signal detection

Not applicable.

8.5 Treatment of overdose

Overdoses are unlikely as all doses will be administered by study staff. There is no specific antidote for a BRV overdose.

However, in the unlikely event, in acute, significant overdose, the stomach may be emptied by gastric lavage, and forced diuresis or hemodialysis might be attempted. Treatment for any signs of overdose will be symptomatic. The participant should be kept under medical surveillance, and blood pressure, heart rate, ECG, and respiratory rate should be monitored.

8.6 Pharmacokinetics

Blood samples of approximately 4mL will be collected for measurement of plasma concentrations of BRV as specified in the Schedule of Activities (Section 1.3) Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24hr 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 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_{tau} area under the curve during a dosing interval at steady state
- CL_{ss}/F apparent total body clearance at steady state
- $C_{max,ss}$ maximum plasma concentration at steady state
- C_{trough} measured concentration at the end of a dosing interval at steady state
- $t_{max,ss}$ time of $C_{max, ss}$

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 International Council for Harmonisation (ICH) guideline M10 on bioanalytical method validation and study sample analysis, January 2023.

Blood sampling time for PK analysis is provided below, and a blood sampling scheme is provided in Figure 4-1.

- Day 1 (before the morning and evening doses [0 and 12hr post the initial dose])
- Day 2 (before the morning and evening doses [24 and 36hr post the initial dose])
- Day 3 (before the morning [only] dose [48hr post the initial dose] and 10min, 15min, 20min, 30min, 45min, 60min, 75min, 90min, 2hr, 6hr, 9hr, and 12hr postdose)

Study sites should aim to collect PK samples at the nominal time points to the extent possible. However, the maximum deviations from scheduled sampling times considered irrelevant for PK are defined in Table 8-1.

Table 8-1: Irrelevant time deviations for PK sampling

PK blood sampling times	Deviation from scheduled time considered irrelevant
Day 1 predose	-30 to 0min
Day 2 predose	-5 to 0min
Day 3 predose	-5 to 0min
Day 3 postdose 10min-1.5hr	±2min
Day 3 postdose 2-9hr	±5min
Day 3 postdose 12hr	0 to +5min

PK=pharmacokinetic

Pharmacokinetic blood samples should be collected within the allowable range described in Table 8-1, and dosing of the IMP should commence at the scheduled time. The time at which the administration of IMP begins must be documented. Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files, but will not constitute a protocol amendment. The IRB will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.7 Biomarkers

Not applicable.

8.8 Immunogenicity assessments

Not applicable.

8.9 Health economics

Not applicable.

9 STATISTICAL CONSIDERATIONS

A description of statistical methods follows and will be described in more detail in the SAP.

9.1 Definition of analysis sets

The following analysis sets will be defined. The reasons for exclusion of participants from any of the below analysis sets will be listed.

Enrolled Set

All participants who have signed the ICF will be included in the Enrolled Set.

Randomized Set

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

Safety Set

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

Pharmacokinetic Set

All participants who are randomized, receive at least 1 dose of active IMP, and have at least 1 quantifiable post-Baseline PK measurement will be included in the Pharmacokinetic Set (PKS).

9.2 General statistical considerations

Statistical analysis and generation of tables, figures, and data listings will be performed using SAS Version 9.4 or higher.

A complete set of listings containing both all documented data and all calculated data will be generated. Missing data will not be imputed.

For categorical endpoints, the number and percentage of participants in each category will be presented. The denominator for percentages will be based on the number of participants appropriate for the purpose of the analysis. For continuous endpoints, descriptive statistics will include number of participants, mean, standard deviation (SD), 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.

For PK parameter estimation, a noncompartmental analysis will be performed using Phoenix WinNonlin® Version 8.0 or higher (Certara L.P., Princeton, NJ, USA).

9.3 Planned outcome analyses

9.3.1 Pharmacokinetic analyses

Statistical analyses will be performed on the PKS.

All PKS participants who have a sufficient number of bioanalytical assessments to calculate reliable estimates for the primary PK parameters for both BRV formulations will be included in the statistical analysis.

If a participant's predose concentration is greater than 5% of the corresponding $C_{max,ss}$ value in a Dosing Period, the participant's data from that Dosing Period will be excluded from the statistical analysis. If a participant's predose concentration is greater than 5% of the corresponding $C_{max,ss}$ value for both Dosing Periods, the participant will be excluded from the statistical analysis.

If vomiting occurs at or before 2 times the median t_{max} for the tablet and the dry syrup within a Dosing Period, the participant's data from that period will be excluded from the statistical analysis. If vomiting occurs at or before 2 times the median $t_{max,ss}$ within a Dosing Period, for both Dosing Periods, the participant will be excluded from the statistical analysis.

Descriptive statistics will be used to describe all PK parameters for each BRV formulation. 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 semilogarithmic and linear scales.

The bioavailability of BRV dry syrup (1.25g of granules for oral suspension 4% w/w, corresponding to 50mg of BRV) (Test) will be compared with BRV 50mg tablet (Reference).

The primary PK parameters $C_{max,ss}$ and AUC_{tau} will be evaluated according to a linear mixed model, adapted to cross-over experimental designs. The model will include treatment (BRV formulation), period, and sequence as fixed effects. The participant (nested within the sequence) will be included as a random effect. Since the participant is entered as a random effect in the linear mixed model, the data from the nonaffected Dosing Period (ie, evaluable data) can still be used for the bioequivalence assessment even if the data from the other Dosing Period are excluded from the analysis. The dependent variables will be logarithmically (ln) transformed prior to statistical testing, following the usual recommendations. The CIs of the adjusted geometric mean ratio (GMR) (Test/Reference) will be calculated corresponding to the Lan-DeMets alpha spending function approximating a Pocock boundary (Lan and DeMets, 1983), while maintaining the overall 2-sided significance level of 0.1.

Bioequivalence between the Test (dry syrup) and Reference (tablet) formulations will be concluded if the CIs for $C_{max,ss}$ and AUC_{tau} are contained in the range of 0.80 to 1.25.

In the case that the CIs for $C_{max,ss}$ and AUC_{tau} are not contained in the range of 0.80 to 1.25, bioequivalence can still be concluded if the following criteria are met: 1) the point estimate of the adjusted GMR (Test/Reference) for $C_{max,ss}$ and AUC_{tau} are contained in the range of 0.90 to 1.11, and 2) in vitro dissolution rates of Test (dry syrup) and Reference (tablet) formulations are available and are deemed similar according to the Japanese bioequivalence guideline (PSEHB/PED Notification No. 0319-1, 2020).

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

For $t_{max,ss}$, a distribution-free 90% CI (Hodges-Lehmann's method) will be calculated for the median difference between the tablet and the dry syrup formulations.

9.4 Planned safety and other 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 Secondary 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.

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

9.4.2 Other safety analyses

9.4.2.1 Clinical laboratory assessments

Clinical laboratory assessments (hematology and clinical chemistry) and changes from Baseline will be summarized using descriptive statistics by BRV formulation at each time point, as applicable. Shift tables from Baseline to post-Baseline scheduled time point will be presented by BRV formulation, as applicable. Urinalysis data and laboratory values outside the reference range will be provided in a listing.

9.4.2.2 Vital signs

Vital signs assessments (SBP, DBP, heart 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 assessments (PR, QRS, QT intervals, and QTcF) 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 for each cohort. The purpose of this review meeting will be to examine all protocol deviations, define the PKS (Section 9.1), and to verify the quality of the data. If PK parameters are needed to define the PKS, it will be performed based on the analysis data set of the pharmacokinetic parameters. 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).

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

The study may consist of 2 cohorts. A formal interim analysis is planned at the end of Cohort 1, once approximately 60 evaluable participants have completed the study. If bioequivalence or futility is not established in the interim analysis, the final analysis is planned at the end of Cohort 2, once all participants (approximately 90) have completed the study (Section 9.8). The interim analysis, based on a group sequential design, will be an unblinded analysis performed by an internal statistical team independent from the study team and will focus on the analysis for

primary PK parameters $C_{max,ss}$ and AUC_{tau}. The results will be reviewed by an internal DMC, which is independent from the study team, and the following decisions will be made:

1. Early stopping of the study due to demonstrating bioequivalence at the end of Cohort 1:

   The study will be stopped early, after Cohort 1, if bioequivalence between the Test (dry syrup) and Reference (tablet) formulations is established for $C_{max,ss}$ and AUC_{tau} (Section 9.3.1).

2. Early stopping of the study for futility at the end of Cohort 1:

   The study will be stopped early, after Cohort 1, in the event that bioequivalence is not established and the 1-sided (upper) 95% CI of the adjusted GMR (Test/Reference) is less than 0.8700 for $C_{max,ss}$. This corresponds to the GMR of this study being markedly lower than that of single-dose bioequivalence study (EP0110).

3. Continuing to Cohort 2:

   If bioequivalence or futility is not established, the study will continue to Cohort 2, and the remaining approximately 30 participants will be randomized.

9.8 Determination of sample size

A total of up to approximately 90 participants are planned to be evaluable for the primary endpoint.

As detailed in Section 9.7, this study may consist of 2 cohorts, with a formal interim analysis once Cohort 1 has completed both Dosing Periods.

The BRV single-dose bioequivalence study (EP0110) between tablet (Reference) and dry syrup (Test) provided estimates of the GMR (Test/Reference) of 0.8700 for C_{max} and 0.9890 for $AUC_{(0-t)}$ and the intraparticipant variability (CV%) of 21.9% for C_{max} and 2.7% for $AUC_{(0-t)}$ (Table 9-1). The BRV multiple-dose PK simulation results based on the EP0110 study data provided estimates of the GMR of 0.9054 for $C_{max,ss}$ and 0.9893 for AUC_{tau} and the intraparticipant variability (CV%) of 15.3% for $C_{max,ss}$ and 2.7% for AUC_{tau}.

Table 9-1: EP0110 and simulation results of relative bioavailability of BRV tablet formulation vs dry syrup formulation

Parameter	Statistic	EP0110	MD Simulation
C_{max} (µg/mL) [a]	GMR of dry syrup/tablet (Intraparticipant CV%)	0.8700 (21.9)	0.9054 (15.3)
AUC (h*µg/mL) [b]	GMR of dry syrup/tablet (Intraparticipant CV%)	0.9890 (2.7)	0.9893 (2.7)

AUC=area under the curve; $AUC_{(0-t)}$=area under the curve from time 0 to the time of the last quantifiable concentration; AUC_{tau}=area under the curve during a dosage interval at steady state; BRV=brivaracetam; C_{max}=maximum plasma concentration; $C_{max,ss}$=maximum plasma concentration at steady state; CV=coefficient of variation; GMR=geometric mean ratio; MD=multiple-dose

[a] The $C_{max,ss}$ was used for MD simulation results, estimated based upon the EP0110 study data.

[b] The $AUC_{(0-t)}$ was used for EP0110. The AUC_{tau} was used for MD simulation results, based upon the EP0110 study data.

In the event that EP0231 will have results similar to those observed in EP0110 without any improvement by the multiple-dose study design, 116 participants will be needed to provide a power of 90% with a fixed design (no interim analysis). However, because this study is conducted as a multiple-dose study, it is expected that the PK profile variability will be smaller. It is assumed that both the GMR and intraparticipant SD will show improvement (higher GMR and smaller intraparticipant SD) compared with the single-dose study (EP0110), closer to those shown in the multiple-dose PK simulation results. The study assumptions for GMR and intraparticipant CV% (for C_{max}) are based on the approximate middle values of those seen in EP0110 and the multiple-dose PK simulations based on the EP0110 study data, assuming a GMR of 0.89 and intraparticipant SD of 0.183 (corresponding to a CV% of 18.5%).

In the group sequential design for this study, an interim analysis will be performed for bioequivalence or futility after approximately 60 evaluable participants, which is at 90% power for bioequivalence based on the CIs of the adjusted GMR (Test/Reference) with the study assumptions. Should the assumption regarding variability and GMR not hold, with the study consequently not being stopped for demonstrating bioequivalence or futility at the interim analysis, this allows the opportunity to enroll a further approximately 30 participants and assess bioequivalence after approximately 90 evaluable participants. While maintaining the two 1-sided significance level of 0.05, this should be sufficient to state that the true GMR is in the range of 0.80 to 1.25. The two 1-sided significance levels currently used are 0.03817 for the interim analysis and 0.02704 for the final analysis according to the Lan-DeMets alpha spending function approximating a Pocock boundary, assuming 60 evaluable participants in Cohort 1 and 30 evaluable participants in Cohort 2 as the number of participants to be included in the analyses. A total of 90 evaluable participants will provide an overall power of >75% even if the GMR and intraparticipant CV% remain as observed in EP0110.

The probability of study stopping for demonstrating bioequivalence for Cohort 1 (power at Cohort 1), futility at Cohort 1, and proceeding to Cohort 2 are approximately 91%, approximately 1%, and approximately 8%, respectively. If the study continues to Cohort 2, the bioequivalence will be assessed after completing Cohort 2.

In order to ensure a total of up to approximately 90 evaluable participants for the primary endpoints, assuming a rate of dropout and nonevaluable participants of approximately 5%, 64 participants for Cohort 1, 32 participants for Cohort 2, and up to 96 participants in total are estimated to be randomized in 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, ICH-Good Clinical Practice (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, ICF, IB, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other participant-related documents to be used for the study to the IRB 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 participants or others, and any protocol deviations, to eliminate immediate hazards to participants.

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

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

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

Prior to participation in the study, the ICF should be signed and personally dated by the participant, or his legal representative, and by the person who conducted the informed consent discussion (Investigator or designee). The participant or his legal representative must receive a copy of the signed and dated ICF. As part of the consent process, each participant must consent to direct access to his 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

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

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

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

The participant must be informed that his 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 Committees structure

As described in Section 9.7, a formal interim analysis is planned at the end of Cohort 1 once approximately 60 evaluable participants have completed the study. The results will be reviewed by an internal DMC, which is independent from the study team. The DMC will make 1 of the following decisions: early stopping of the study if the study demonstrates bioequivalence at the end of Cohort 1, early stopping of the study if the study is futile at the end of Cohort 1, or continuing the study to Cohort 2. Details of the DMC will be provided in the DMC Charters.

10.1.6 Dissemination of clinical study data

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

10.1.7 Data quality assurance

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

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

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 participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH-GCP, and all applicable regulatory requirements.

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

10.1.7.1 Case report form completion

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

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

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

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

Detailed instructions will be provided in the Case Report Form Completion Guidelines.

10.1.7.2 Apps

No apps will be used in the study.

10.1.8 Source documents

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

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

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

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

10.1.9 Study and site start and closure

The start of recruitment

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

Study/site termination

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

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

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

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

10.1.10 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 the 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 participants are detailed in Section 5.1 and Section 5.2.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count		RBC Indices: MCV MCH	WBC Count with Differential (absolute values and percentages): Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	RBC Count			
	WBC Count			
	Hemoglobin			
	Hematocrit			
Clinical Chemistry [a]	Blood Urea Nitrogen (BUN)	Potassium	AST/SGOT	Total and direct bilirubin
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Fasting Glucose	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, leukocyte, nitrite by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Alcohol breath test and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines) • Urine cotinine test • Serology (HIV antibody and antigen, HBsAg, hepatitis C virus antibody, and syphilis) All study-required laboratory assessments will be performed by a local laboratory. The results of each test must be entered into the eCRF.			

ALT=alanine transaminase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eCRF=electronic Case Report Form; HBsAg=hepatitis B surface antigen; HIV=human immunodeficiency virus; INR=international normalized ratio; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; SAE=serious adverse event; SGPT=serum glutamic-pyruvic transaminase; SGOT=serum glutamic-oxaloacetic transaminase; 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

Laboratory Assessments	Parameters

injury (possible Hy's Law), and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

Investigators must document their review of each laboratory safety report.

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

Definition of AE

AE definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of 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 <u>meeting</u> 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 <u>NOT</u> meeting the AE definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the study participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of 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 participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a 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 participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include, but are not limited to, potential Hy's Law, invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and follow up of AE and/or SAE

AE and SAE recording

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

Assessment of intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with 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 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/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which 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/her 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 1 of the criteria used when determining regulatory reporting requirements.

Follow up of AEs and SAEs

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

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

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

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

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

Table 10-1: Highly effective contraceptive methods for female partners [a]

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

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

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

Collection of pregnancy information

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study.
- 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

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

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

Participants with PDILI should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for IMP discontinuation and/or 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 participants who have ALT >5×ULN. The monitoring plan should include any necessary follow-up assessments (until resolution of the abnormal laboratory values).

Phase 1 liver chemistry stopping criteria are designed to assure 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 eCRF, and complete an SAE data collection tool if the event also meets 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:** **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 participants weekly until liver function abnormalities resolve, stabilize, or return to Baseline	• Viral hepatitis serology [c] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain blood sample for PK analysis within 1 hour after the most recent dose [d] • Serum CPK and LDH • Fractionate bilirubin if total bilirubin ≥2xULN • Complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury (eg, fatigue, nausea, vomiting, right upper quadrant pain), or hypersensitivity, on the 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:** • Antinuclear antibody, antismooth muscle antibody, Type 1 antiliver kidney microsomal antibodies, and quantitative total IgG or gamma globulins • Serum acetaminophen protein adducts (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week) will be measured using a validated assay.

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**
	• Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete liver imaging and/or liver biopsy eCRFs

AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase; eCRF=electronic Case Report Form; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HPLC=high performance liquid chromatography; IgG=immunoglobulin G; IgM=immunoglobin M; IMP=investigational medicinal product; INR=international normalized ratio; LDH=lactate dehydrogenase; PK=pharmacokinetic; RNA=ribonucleic acid; SAE=serious adverse event; ULN=upper limit of normal

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

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

[c] 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 AEs, adverse device effects, 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

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BRV	brivaracetam
CI	confidence interval
CRO	contract research organization
CYP	cytochrome P450
COVID-19	coronavirus disease 2019
CV	coefficient of variation
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
GCP	Good Clinical Practice
GMR	geometric mean ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IRB	Institutional Review Board
iv	intravenous
MedDRA®	Medical Dictionary for Regulatory Activities
PDILI	potential drug-induced liver injury
PED	Pharmaceutical Evaluation Division
PK	pharmacokinetics
PKS	Pharmacokinetic Set
POS	partial-onset seizures
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
QTcF	QT interval corrected for heart rate with Fridericia's formula
SAE	serious adverse event

SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
SFU	Safety Follow-Up
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 amendment is located before the Table of Contents.

Amendment 1 (14 Dec 2023)

11 REFERENCES

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Ministry of Health, Labour and Welfare. PSEHB/PED Notification No. 0319-1 The Partial Amendment to Guideline for Bioequivalence Studies of Generic Products 19 Mar 2020.

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

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