PROTOCOL EP0065 AMENDMENT 1

A MULTICENTER, OPEN-LABEL STUDY TO EVALUATE THE PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF INTRAVENOUS BRIVARACETAM IN SUBJECTS ≥1 MONTH TO <16 YEARS OF AGE WITH EPILEPSY

PHASE 2

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SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
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LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
bid	twice daily
BP	blood pressure
BRV	brivaracetam
CDMS	clinical data management system
CRF	Case Report form
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DMC	Data Monitoring Committee
ECG	electrocardiogram
GCP	Good Clinical Practice
HLA	human leukocyte antigen
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IIB	Initiating iv BRV
IMP	investigational medicinal product
IOB	Initiating Oral BRV
IRB	Institutional Review Board
IRT	interactive response technology
iv	intravenous
MedDRA®	Medical Dictionary for Regulatory Activities®
OLB	Open-label BRV
PCS	possibly clinically significant
PD	pharmacodynamic(s)
PDILI	potential drug-induced liver injury
PK	pharmacokinetic(s)

PK-PPS	PK Per-protocol Set
POS	partial-onset seizures
PS	Patient Safety
q12h ±2h	every 12 hours ±2 hours
RR	respiratory rate
RxB	Prescribed-BRV
SAE	serious adverse event
SD	standard deviation
SOP	standard operating procedure
SS	Safety Set
SS-iv	Safety Set-iv
SV2A	synaptic vesicle protein 2A
TC	Telephone Contact
ULN	upper limit of normal
VNS	vagus nerve stimulation

1 SUMMARY

EP0065 is a Phase 2, multicenter, open-label study with a primary objective of evaluating the pharmacokinetics (PK), safety, and tolerability of brivaracetam (BRV) administered as a 15-minute intravenous (iv) infusion and an iv bolus (up to 2-minute infusion) in subjects ≥1 month to <16 years of age with epilepsy.

The following subjects will be eligible for enrollment in EP0065:

- Open-label BRV (OLB) subjects: currently receiving oral BRV as participants in a long-term, open-label study
- Prescribed-BRV (RxB) subjects: currently receiving prescribed oral BRV from commercial supply
- Initiating Oral BRV (IOB) subjects: not currently receiving BRV; first dose of BRV in EP0065 will be oral tablet or solution
- Initiating iv BRV (IIB) subjects: not currently receiving BRV; first dose of BRV in EP0065 will be administered intravenously

EP0065 includes the following consecutive periods:

Subjects	**Screening Period** 1 to 10 days	**IOB Treatment Period** 2 to 10 days	**iv PK Period** 1 to 6 days
OLB	Oral BRV	Not applicable	iv BRV
RxB	Oral BRV	Not applicable	iv BRV
IOB	No BRV	Oral BRV	iv BRV
IIB	No BRV	Not applicable	iv BRV

BRV=brivaracetam; IIB=Initiating iv BRV; IOB=Initiating Oral BRV; iv=intravenous; OLB=Open-label BRV; PK=pharmacokinetic RxB=Prescribed-BRV

Note: Oral BRV will be administered as tablets or oral solution. Tablets will be administered orally, and oral solution will be administered either orally or by enteric administration (eg, feeding tube) based on subject need.

During the Screening Period, OLB and RxB subjects will continue to receive oral BRV (tablet or oral solution) in accordance with their long-term, open-label study dosing or prescribed dosing, respectively. The IOB and IIB subjects will not receive BRV during the Screening Period.

Eligible OLB, RxB, and IIB subjects will progress directly from the Screening Period to the iv PK Period, whereas IOB subjects will enter a 2- to 10-day IOB Treatment Period in which they receive oral BRV before progressing to the iv PK Period. The initial oral BRV dose in the IOB Treatment Period is 2mg/kg/day.

During the iv PK Period, iv BRV will be administered every 12 hours ±2 hours (q12h ± 2h). All subjects will receive 1 to 2 consecutive doses of BRV; however, based on medical need, subjects may receive up to 10 consecutive doses of iv BRV. Blood sampling for PK analyses (herein referred to as "PK sampling") will occur with the first iv BRV administration and with 1 other iv BRV administration. For OLB, RxB, and IOB subjects, the first iv BRV dose will be equivalent

(mg-to-mg) to the final dose of oral BRV prior to the first iv dose. For IIB subjects, the first iv BRV dose will be 1mg/kg, not to exceed 50mg for subjects with body weights ≥50kg. For all subjects, iv BRV doses may be adjusted at the Investigator's discretion after PK sampling for 2 iv doses; however, no doses may exceed the maximum doses indicated below. During the iv PK Period, BRV may only be administered by iv infusion.

At the completion of the iv PK Period, subjects who will continue oral BRV treatment should enroll in a long-term, open-label BRV study. Subjects who have received ≥4 doses of BRV and do not plan to continue treatment with BRV after completion of the iv PK Period or who discontinue BRV treatment during the study will have a Down-Titration Period of up to 4 weeks (28 days) for gradual discontinuation of BRV and a Safety (BRV-free) Period of 2 weeks (14 days) after the final dose of BRV. Subjects who have received <4 doses of BRV may have BRV down titrated at the discretion of the Investigator.

For IOB and IIB subjects, the maximum BRV dose is 4mg/kg/day (2mg/kg twice daily [bid]). For OLB and RxB subjects, the maximum BRV dose is 5mg/kg/day (rounded) in recognition of the possibility that some of these subjects may be using this dose when they enter EP0065. **Throughout the study, no subjects may receive a dose greater than BRV 200mg/day.** Oral BRV will be administered in equally divided doses bid.

It is planned for approximately 50 enrolled subjects to receive iv BRV in the following age-based cohorts (approximately 12 subjects/cohort), with approximately half of the subjects in each cohort receiving iv BRV as a 15-minute (±3 minutes) infusion and half receiving iv BRV as a bolus (up to 2-minute infusion).

- Cohort 1: ≥12 to <16 years
- Cohort 2: ≥6 years to <12 years
- Cohort 3: ≥2 to <6 years
- Cohort 4: 1 month to <2 years

Enrollment will be sequential by descending age beginning with Cohort 1. For each cohort, the first half will receive the 15-minute infusion. The Data Monitoring Committee (DMC) will then meet to review safety and PK data, as available. After the DMC safety review, the remaining half in that cohort will receive iv BRV as a bolus (up to 2-minute infusion), and the next cohort may begin the 15-minute infusion. Subjects may receive bolus infusions only after subjects in the preceding cohort have completed bolus infusions.

The DMC will meet no less than approximately every 6 months commensurate with enrollment.

The PK variables are the plasma concentrations of BRV (parent compound only) before, during, and after the first and 1 subsequent administration of iv BRV.

The primary safety variables are adverse events (AEs) and withdrawals due to AEs. Other safety variables are clinical laboratory parameters (hematology, chemistry, and endocrinology), and urinalysis. Clinically significant new or worsened abnormalities discovered during physical and neurological examinations will be recorded as AEs. Other safety variables also include 12-lead electrocardiogram (ECG), and vital signs (blood pressure [BP], pulse rate, respiratory rate [RR],

and temperature), all of which will be assessed with increased frequency during the iv PK Period.

The maximum study duration for an individual subject will be 68 days. Approximately 60 sites in Europe and North America are planned for participation in EP0065.

2 INTRODUCTION

Brivaracetam ((2S)-2-[(4R)-2-oxo-4-propyltetrahydro-1*H*-pyrrol-1-yl]butanamide) 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. In 2016, marketing authorization for the use of oral and iv BRV as adjunctive treatment of partial-onset seizures (POS) in patients was granted in the EU, US, and Australia for patients 16 years of age and older with epilepsy and in Canada for patients 18 years of age and older with epilepsy.

Epilepsy affects all races of both sexes at any age from the first hour of life to extreme old age. The prevalence of epilepsy is 1% to 2% of the population and 4% of pediatric population in those developed countries where they have been studied; this is probably double in resource-poor countries (Banerjee and Hauser, 2008). In the US, the overall incidence of epilepsy ranges from 35.5 to 48 per 100,000 person-years and the prevalence ranges from 4.7 to 6.8 per 1000 population (Theodore et al, 2006). The incidence of new-onset epilepsy in the pediatric population is 44.5 per 100,000 persons per year (Wirrell et al, 2011). Within the pediatric population, the incidence is highest in children <5 years of age (approximately 60 to 100 per 100,000 person-years), decreasing to approximately 25 to 45 per 100,000 person-years in adolescents and young adults (Wirrell et al, 2011; Hauser et al, 1993).

In the US, 57% of newly diagnosed patients were classified as having POS (Zarrelli et al, 1999; Hauser et al, 1993). In the general population, the incidence of pediatric patients with epilepsy with POS is approximately 16 to 80 per 100,000 (Wirrell, et al, 2011; Banerjee and Hauser, 2008; Hauser et al, 1993).

The existing treatment options for POS in the pediatric population generally follow the treatment options for adults with the same disorder; clinical experience demonstrates that children may have results comparable to adults with administration of the conventional antiepileptic drugs (AEDs). More than 25% of pediatric patients have inadequate seizure control on currently available AEDs or experience significant adverse drug effects (Hadjiloizou and Bourgeois, 2007). There remains a need for potent AEDs with a positive benefit-risk profile in this population.

To date, oral formulations of BRV have been studied in the ongoing BRV pediatric development program as follows:

- N01263 is a completed open-label, multicenter, fixed 3-step up-titration, adjunctive therapy study of the PK, safety, and efficacy of BRV in 100 subjects ≥1 month to <16 years of age with epilepsy. Doses of BRV (oral solution) were adjusted by body weight and did not exceed a maximum of 50mg/day, 100mg/day, and 200mg/day for each titration step. A total of 100 subjects enrolled in N01263: 99 subjects received study drug and were included in the Safety Set. Results from N01263 indicate that BRV was generally well tolerated and that the safety profile in pediatric subjects was consistent with the known safety profile in adult

subjects. In general, there were no clinically meaningful changes in laboratory parameters, vital signs, or ECG parameters. Trough plasma BRV concentrations increased proportionally to the dose.

N01266 is an ongoing open-label, multicenter study to evaluate the long-term safety and efficacy of bid administration of BRV oral solution and oral tablets in pediatric subjects with epilepsy who are receiving ≥ 1 AED other than BRV; the maximum allowable BRV dose is 5mg/kg/day not to exceed 200mg/day in subjects with body weights >40kg. N01266 was initially designed as a long-term follow-up to N01263, which enrolled only subjects with either focal epilepsy or generalized epilepsy but was amended to also allow direct enrollment of subjects 4 years to <17 years of age who have focal epilepsy. Over 200 subjects have enrolled in N01266.

In addition to oral formulations, iv formulations of AEDs are particularly helpful as short-term replacements when use of oral formulations is not possible or feasible (eg, pre and postoperative patients, patients with acute gastrointestinal disorders, patients with acute swallowing disorders). Brivaractem injection has been approved for use as adjunctive therapy in the treatment of POS in patients 16 years of age and older with epilepsy and may be used when oral administration of BRV is temporarily not feasible. Treatment with BRV may be initiated with tablets, oral solution, or solution for injection.

The current study, EP0065, is planned to evaluate the PK, safety, and tolerability of iv BRV administered as a 15-minute infusion and bolus (up to 2-minute infusion) in subjects ≥1 month to <16 years of age with epilepsy.

The iv dose for subjects initiating BRV in this study was predicted in N01331, which modeled based on PK data from N01263 and N01256 (BRV adult study) and simulated the BRV iv concentrations in pediatric subjects. Based on the results of N01331, in the pediatric population 1 month to <17 years of age, an iv injection 15-minute infusion or bolus (up to 2-minute infusion) of 4mg/kg/day (2mg/kg bid) regimen (with a maximum of 200mg/day [100mg bid] for subjects with body weights ≥50kg) results in plasma concentrations in the same range as seen in adults receiving 200mg/day (100mg bid), the maximum recommended dose in adults with POS. These data support using a mg-to-mg equivalent to the oral dose for OLB and RxB subjects. As demonstrated in the concentration-effect analysis CL0258 using levetiracetam PK and pharmacodynamic (PD) data from adults and children and BRV PK and PD data in adults (N01358) and PK data in children (N01263), in subjects 4 to 16 years of age, similar weight-normalized doses are needed to achieve the same efficacy as compared with adults, with a maximum response at 4mg/kg/day.

More detailed information regarding the nonclinical and clinical development programs for BRV is provided in the Investigator's Brochure.

3 STUDY OBJECTIVES

The primary objective is to evaluate the PK, safety, and tolerability of BRV administered as a 15-minute iv infusion and iv bolus (up to 2-minute infusion) in subjects ≥1 month to <16 years of age with epilepsy.

4 STUDY VARIABLES

4.1 Pharmacokinetic variables

- Plasma concentration of BRV (parent compound only) before, during, and after iv BRV administration

4.2 Safety variables

4.2.1 Primary safety variables

- Adverse events throughout the study
- Subject withdrawals due to AEs

4.2.2 Other safety variables

- 12-lead ECG values before, during, and after each iv BRV administration
- BP, pulse rate, RR, and temperature values before, during, and after each iv BRV administration
- Clinical laboratory parameters (hematology, chemistry, and endocrinology) pre and posttreatment
- Urinalysis parameters pre and posttreatment

5 STUDY DESIGN

5.1 Study description

EP0065 is a Phase 2 multicenter, open-label study to evaluate the PK, safety, and tolerability of iv BRV administered as a 15-minute iv infusion and an iv bolus (up to 2-minute infusion) in subjects ≥1 month to <16 years of age with epilepsy.

It is planned for approximately 50 enrolled subjects to receive iv BRV in the following age-based cohorts (approximately 12 subjects/cohort):

- Cohort 1: ≥12 to <16 years
- Cohort 2: ≥6 years to <12 years
- Cohort 3: ≥2 to <6 years
- Cohort 4: 1 month to <2 years

The following subjects will be eligible for enrollment in EP0065:

- OLB subjects: currently receiving oral BRV as participants in a long-term, open-label study
- RxB subjects: currently receiving prescribed oral BRV from commercial supply
- IOB subjects: not currently receiving BRV; first dose of BRV in EP0065 will be oral tablet or solution
- IIB subjects: not currently receiving BRV; first dose of BRV in EP0065 will be by iv infusion

For OLB and RxB subjects, the maximum BRV dose is 5mg/kg/day (rounded). For IOB and IIB subjects, the maximum BRV dose is 4mg/kg/day. **Throughout the study, no subject may receive a dose greater than BRV 200mg/day.** Subjects will receive oral BRV (tablets or oral solution) in equally divided doses; BRV oral solution may be given by enteric administration (eg, by feeding tube) based on subject need.

The EP0065 study periods and visits are described below. The PK assessments will be made during the iv PK Period only and safety data will be collected throughout the study, with intensive collection of safety data with each iv BRV dose administered. A Schedule of Study Assessments is provided for the Screening through iv PK Periods in Table 5–1 and for the Down-Titration Period and Safety (BRV-free) Periods (for subjects not continuing BRV) in Table 5–4.

Screening Period (1 to 10 days)

During the Screening Period, the OLB and RxB subjects will continue treatment with oral BRV using their assigned open-label study supply or prescribed commercial supply, respectively. The IOB and IIB subjects will not receive BRV during this period.

The OLB subjects will temporarily discontinue assessments in their long-term, open-label study when they enter EP0065. As such, all assessments for these subjects during the Screening Period (and subsequent periods of EP0065) will be recorded in the EP0065 Case Report form (CRF) until they return to a long-term, open-label study or discontinue BRV treatment.

IOB Treatment Period (2 to 10 days of oral BRV treatment; for IOB subjects only)

Only IOB subjects who meet all eligibility criteria may participate in the IOB Treatment Period. No other subjects may participate in this period.

During the IOB Treatment Period, IOB subjects will initiate treatment with oral BRV 2mg/kg/day not to exceed 100mg/day for subjects with body weights ≥50kg and must have, at minimum, 2 days of treatment with oral BRV before entry into the iv PK Period. Subjects who do not enter the iv PK Period will not be eligible for the long-term, open-label study.

The Investigator is permitted to adjust the oral BRV dose during the IOB Treatment Period in accordance with medical judgment (with a maximum dose of 4mg/kg/day, not to exceed 200mg/day for subjects with body weights ≥50kg); however, subjects must have no change in the oral BRV dose for the 2 days prior to entry into the iv PK Period.

iv PK Period (1 to 6 days, with Day 1 defined as the initial day of iv BRV infusion)

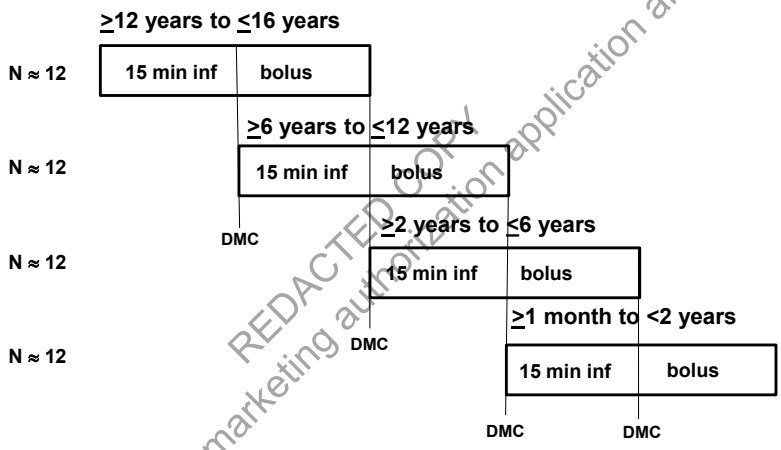
During the iv PK Period, iv BRV will be administered every 12 hours ±2 hours (q12h ± 2h). All subjects are to receive 1 to 2 consecutive doses of BRV; however, based on medical need, subjects may receive up to 10 consecutive doses of iv BRV. The PK sampling will occur with the first iv BRV administration and with 1 other iv BRV administration.

The first dose of iv BRV will be as follows:

- OLB, RxB, and IOB subjects: mg-to-mg equivalent of the oral BRV dose immediately prior to the iv PK Period; administered q12h ±2h after prior oral dose
- IIB subjects: 1mg/kg not to exceed a maximum of 50mg for subjects ≥50kg

After subjects have completed PK sampling with 2 iv BRV infusions, the Investigator may adjust the BRV dose, but the adjusted dose must not exceed 5mg/kg/day (rounded) for OLB and RxB subjects and 4mg/kg/day for IOB and IIB subjects (with the maximums not to exceed 200mg/day). During the iv PK Period, BRV may only be administered intravenously. Enrollment will be sequential by descending age beginning with Cohort 1. For each cohort, the first half will receive the 15-minute infusion. The Data Monitoring Committee (DMC) will then meet to review safety and, as available, PK data (Figure 5–1). After the DMC safety review, the remaining half in that cohort will receive iv BRV as a bolus (up to 2-minute infusion) and the next cohort may begin the 15-minute infusion. Subjects may receive bolus infusions only after subjects in the preceding cohort have completed bolus infusions and the DMC have reviewed these data. The DMC will meet no less than approximately every 6 months commensurate with enrollment.

Figure 5–1: Schematic of sequential cohort enrollment during the iv PK Period



DMC=Data Monitoring Committee; inf=infusion; iv=intravenous; PK=pharmacokinetic

Telephone Contact (TC)-1 will occur 1 to 3 days after completing the final iv BRV dose in the iv PK Period to facilitate reporting of infusion-site related AEs.

The schedules for PK sampling, 12-lead ECGs, and vital sign assessments during the iv PK Period are provided in Table 5–2 (15-minute infusion), and Table 5–3 (bolus [up to 2-minute infusion]).

Down-Titration Period (up to 4 weeks) and Safety (BRV-free) Period (2 weeks)

Subjects who receive ≥4 doses of BRV during either the IOB Treatment Period or the iv PK Period and who do not plan to continue treatment with BRV or who discontinue from the study will enter a Down-Titration Period. Subjects who have received <4 doses of BRV may have BRV down titrated at the discretion of the Investigator. During the Down-Titration Period, subjects will have their BRV dose reduced by a maximum of half the dose every week for a maximum of 4 weeks until a dose of 1mg/kg/day (50mg/day for subjects with body weights ≥50kg) is reached. Subjects not able to receive oral BRV for down titration, may receive iv BRV for down titration. In the latter circumstance, the subjects may receive more than 10 consecutive

doses of iv BRV in accordance with the Investigator's discretion. A 2-week Safety (BRV-free) Period will follow the final dose of BRV.

Safety assessments will be collected throughout this period (Table 5–4).

5.1.1 Study duration per subject and definition for start/end of study

The maximum possible study duration is 68 days and the maximum period of BRV administration is 44 days including a minimum of 1 dose of iv BRV.

The start of the study is defined as the date the first Informed Consent form (ICF)/Assent form is executed. The end of the study is defined as the date of the last visit of the last subject enrolled.

5.1.2 Planned number of subjects and sites

It is planned for approximately 50 enrolled subjects to receive iv BRV. Approximately 60 sites are planned.

5.1.3 Anticipated regions and countries

Approximately 60 sites in Europe and North America are planned for participation in EP0065.

5.2 Schedule of study assessments

A schedule of study assessments for the Screening Period through the iv PK Period is provided in Table 5–1, with detailed schedules for PK sampling, ECG, and vital sign assessments during the iv PK Period provided in Table 5–2 (15-min infusion) and Table 5–3 (bolus [up to 2-minute infusion]).

A schedule of study assessment for subjects who will not continue BRV is provided in Table 5–4 (Down-Titration and Safety [BRV-free] Periods).

Note, possibly clinically significant (PCS) vital sign values are defined as those PCS values which occur at any time during the study. Only BP to be collected at 2 hours post initiation of infusion. Additional vital sign monitoring, specifically BP is necessary if a low PCS BP value occurs at 2 hours after the start of an infusion. Subjects should not be provided iv BRV if the latest <1-hour pre-initiation measurement of systolic or diastolic BP is a low PCS value. In this case BP measurements should be repeated and the iv BRV infusion be started only after the BP does not meet the low PCS criterion anymore. The criteria for BP values to be low or high PCS values are described in Table 10-6.

Table 5–1: Schedule of Study Assessments (Screening Period through end of iv PK Period)

Period	Screening	IOB Treatment	iv PK		Unsch[a]
Visit	**V1**	**V2**	**V3 to V12**	**TC-1**	
Study Day for					
OLB, RxB, IIB subjects	**-10 to -1**	**N/A**	**1 to 6**	**2 to 9**	**N/A**
IOB subjects	**-20 to -11**	**-10 to -1**			
Assessments					
Informed consent/as applicable, Assent form	X				
Subject identification card dispensing	X				
Inclusion/exclusion criteria	X	X[b]	X[b]		
Demographic data	X				
General medical/procedure history	X				
Historical seizure count	X				
Prior/concomitant medications including AEDs	X	X	X	X	X
Physical examination[c]	X		X[e]		
Tanner staging[d]			X[b]		
Neurological examination[c]	X		X[e]		
Body weight[f]	X	X[b]	X[b]		
Body height	X		X		
Vital signs (BP, pulse rate, RR, temperature)	X	X	X[g]		X
12-lead ECG	X		X[g]		
Clinical chemistry, hematology, and endocrinology	X				

Table 5–1: Schedule of Study Assessments (Screening Period through end of iv PK Period)

Period	Screening	IOB Treatment	iv PK		Unsch[a]
Visit	V1	V2	V3 to V12	TC-1	
Study Day for					
OLB, RxB, IIB subjects	-10 to -1	N/A	1 to 6	2 to 9	N/A
IOB subjects	-20 to -11	-10 to -1			
Urinalysis (for subjects for whom sample collection is feasible)	X				
Pregnancy testing (urine; for females of CB potential)	X	X	X[b]		
AEs[h]	X	X	X	X	X
Withdrawal criteria		X	X	X	X
C-SSRS[i]	X	X	X[j]		X[k]
PK sampling			X[g]		
Dispense/collect oral BRV from EP0065 supply		X	X[l]		
Administration of iv BRV			X		

Table 5–1: Schedule of Study Assessments (Screening Period through end of iv PK Period)

Period	Screening	IOB Treatment	iv PK		Unsch[a]
Visit	V1	V2	V3 to V12	TC-1	
Study Day for					
OLB, RxB, IIB subjects	-10 to -1	N/A	1 to 6	2 to 9	N/A
IOB subjects	-20 to -11	-10 to -1			

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; BRV=brivaracetam; CB=childbearing; CRF=Case Report form; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; IIB=Initiating iv BRV; IOB=Initiating Oral BRV; iv=intravenous; N/A=not applicable; OLB=Open-label BRV; PK=pharmacokinetic; RR=respiratory rate; RxB=Prescribed BRV; TC=Telephone Contact; Unsch=Unscheduled; V=Visit

[a] Additional assessments may be performed at the Investigator's discretion.

[b] To be performed prior to dispensing/administering the initial dose of BRV in this period (for the PK Period, at Visit 3 only).

[c] Complete examinations should be conducted at Visit 1. Brief physical and neurological examinations should be conducted at other designated visits. Clinically new or worsened abnormalities must be reported as AEs.

[d] The Investigator should use clinical judgment in deciding which subjects are selected for evaluation of Tanner Stage (ie, those subjects who are pubescent).

[e] To be performed prior to the initial dose of BRV (Visit 3) and daily thereafter, ideally after the morning dose.

[f] Body weight determinations should be made with subjects wearing light clothing and not wearing shoes.

[g] Detailed timings for these assessments are provided in Table 5–2 (15-minute [±3 minutes] infusion) and Table 5–3 (bolus [up to 2-minute infusion]).

[h] Infusion-site related AEs for subjects who have returned to/entered a long-term, open-label study should continue to be recorded in the EP0065 CRF.

[i] The C-SSRS will be assessed only in subjects ≥6 years of age. The C-SSRS versions to be used are specified in Section 10.3.3.

[j] To be assessed prior to the administration of iv BRV at Visit 3 and after the final iv dose of BRV each day for Visits 4 to 12, as applicable.

[k] The C-SSRS will be assessed only in subjects who attend this visit due to safety reasons.

[l] To be collected as needed for IOB subjects who will enter the long-term, open-label study. To be dispensed, as needed, for subjects continuing into the Down-Titration Period at the final visit of the PK Period.

Table 5–1: Schedule of Study Assessments (Screening Period through end of iv PK Period)

Period	Screening	IOB Treatment	iv PK		Unsch[a]
Visit	V1	V2	V3 to V12	TC-1	
Study Day for					
OLB, RxB, IIB subjects	-10 to -1	N/A	1 to 6	2 to 9	N/A
IOB subjects	-20 to -11	-10 to -1			

Table 5–2: Schedule for iv PK Period ECGs, vital signs, and PK sampling (15-min BRV infusion)

	Time relative to initiation of iv BRV infusion							
	Pre-initiation	Post-initiation						
Assessment	≤ 1hr	5min (±1min)	10min (±1min)	15min[a] (±2min)	30min (±5min)	60min (±10min)	2hr (±15min)	3hr (±15min)
12-lead ECG	X	X	X	X	X	X	X	
Vital signs (BP, pulse rate, RR, temperature)	X	X	X	X	X	X	X[c]	
PK sampling[b]	X			X				X

BP=blood pressure; BRV=brivaracetam; ECG=electrocardiogram; hr=hour(s); min=minute(s); iv=intravenous; PK=pharmacokinetic; PCS=possibly clinically significant; RR=respiratory rate

[a] To be conducted at the end of infusion.
[b] Blood samples for PK analyses will be collected for the initial BRV infusion and 1 subsequent BRV infusion only. Blood samples should be collected after completion of the ECG and the vital sign measurements and from a region of the body not used for iv the BRV administration.
[c] Only BP to be collected at 2 hours post initiation of infusion. Additional vital sign monitoring, specifically BP is necessary if a low PCS BP value occurs at 2 hours after the start of an infusion.

Table 5–3: Schedule for iv PK Period ECGs, vital signs, and PK sampling (bolus [up to 2-min BRV infusion])

Assessment	Time relative to initiation of iv BRV administration							
	Pre-initiation	Post-initiation						
	≤ 1hr	≤ 2min[a]	5min (±1min)	15min (±2min)	30min (±5min)	60min (±10min)	2hr (±15min)	3hr (±15min)
12-lead ECG	X	X	X	X	X	X	X	
Vital signs (BP, pulse rate, RR, temperature)	X	X	X	X	X	X	X[c]	
PK sampling[b]	X			X				X

BP=blood pressure; BRV=brivaracetam; ECG=electrocardiogram; hr=hour(s); min=minute(s); iv=intravenous; PK=pharmacokinetic; PCS=possibly clinically significant; RR=respiratory rate

[a] To be conducted during bolus/infusion, if feasible.

[b] Blood samples for PK analyses will be collected for the initial BRV infusion and 1 subsequent BRV infusion only. Blood samples should be collected after completion of the ECG and the vital sign measurements and from a region of the body not used for the iv BRV administration.

[c] Only BP to be collected at 2 hours post initiation of infusion. Additional vital sign monitoring, specifically BP is necessary if a low PCS BP value occurs at 2 hours after the start of an infusion.

Table 5–4: Schedule of study assessments for Down-Titration and Safety (BRV-free) Periods (subjects not continuing into the Long-Term, Open-Label Study)

	Down-Titration		Safety (BRV-free)
Visit	**TC-2[a]**	**V13**	**TC-3[b]**
Assessments			
Concomitant medications including AEDs	X	X	X
Physical examination (brief)		X	
Neurological examination (brief)		X	
Body height		X	
Vital signs (BP, pulse rate, RR, temperature)		X	
12-lead ECG		X	
Clinical chemistry, hematology, and endocrinology		X	
Urinalysis (for subjects for whom sample collection is feasible)		X	
Pregnancy testing (urine; for females of CB potential)		X	
AEs	X	X	X
Withdrawal criteria	X		
C-SSRS[c]		X	
Collect oral BRV		X	

AEDs=antiepileptic drug; AEs=adverse events; BP=blood pressure; BRV=brivaracetam; CB=childbearing; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; RR=respiratory rate; TC=telephone contact; V=Visit

[a] This TC is only applicable to subjects with a Down-Titration Period of more than 2 weeks. The TC should be conducted approximately half way through the Down-Titration Period.

[b] This TC is only applicable for subjects who have attended Visit 13 and will be conducted approximately 2 weeks after the final dose of BRV.

[c] The C-SSRS will be assessed only in subjects ≥6 years of age. The C-SSRS versions to be used are specified in Section 10.3.3.

5.3 Rationale for study design and selection of dose

In 2016, marketing authorization for the use of oral and iv BRV as adjunctive therapy in the treatment of POS was granted in the in the EU, US, and Australia for patients 16 years of age and older and in Canada for patients 18 years of age and older with epilepsy. The recommended starting dosing of BRV is 50mg bid. Based on individual patient tolerability and therapeutic response, the dosage may be adjusted down to 25mg bid (50mg/day) or up to 100mg bid (200mg/day). Brivaracetam injection can be administered intravenously over 2 to 15 minutes when oral administration of BRV is temporarily not feasible. Pharmacokinetic data for BRV administered by the oral route are available over the age range from adults down to 1 month of age and have demonstrated that BRV is completely absorbed and fully bioavailable orally. In adults, BRV iv bolus and oral tablet are bioequivalent.

Brivaracetam injection was evaluated in N01258, an open-label, multicenter study evaluating the safety and tolerability of BRV 200mg/day administered for 4.5 days as a 15-minute iv infusion or a 2-minute iv bolus in subjects ≥16 to 70 years of age with epilepsy. Results from N01258 indicated that iv BRV (as both 15-minute infusion and 2-minute bolus) was well tolerated. The AE profile was similar regardless of whether iv BRV was administered as a 2-minute bolus or a 15-minute infusion. Given these results in older subjects ≥16 years, it is expected that BRV will have similar results in younger subjects aged ≥1 month to <16 years of age.

The PK, safety, and efficacy of BRV in 100 subjects aged ≥1 month to <16 years with epilepsy were evaluated in N01263, an open-label, multicenter, fixed 3-step up-titration, adjunctive therapy study using an oral solution formulation. All doses were adjusted by body weight and did not exceed a maximum of 50mg/day, 100mg/day, and 200mg/day for each titration step. Results from N01263 indicated that BRV was generally well tolerated and that the safety profile in subjects aged ≥1 month to <16 years was consistent with the known safety profile in adults. Trough plasma BRV concentration increased proportionally to BRV dose.

The iv dose for subjects initiating BRV in this study was predicted in N01331, which modeled based on PK data from N01263 and N01256 (BRV adult study) and simulated the BRV iv concentrations in pediatric subjects. Based on the results of N01331, in the pediatric population 1 month to <17 years of age, an iv injection 15-minute infusion or bolus (up to 2-minute infusion) of 4mg/kg/day (2mg/kg bid) regimen with a maximum of 200mg/day (100mg bid) results in plasma concentrations in the same range as seen in adults receiving 200mg/day (100mg bid), the maximum recommended dose in adults with POS. These data support using a mg-to-mg equivalent to the oral dose for OLB and RxB subjects. As demonstrated in the concentration-effect analysis CL0258 using levetiracetam PK and PD data from adults and children and BRV PK and PD data in adults (N01358) and PK data in children (N01263), in subjects 4 to 16 years of age, similar weight-normalized doses are needed to achieve the same efficacy as compared with adults, with a maximum response at 4mg/kg/day.

EP0065 has been designed to evaluate the PK, safety, and tolerability of iv dosing of BRV in subjects 1 month to <16 years of age, as iv formulations are particularly helpful as short-term replacement of oral formulations for patients unable to take oral products (eg, pre and postoperative patients, patients with acute gastrointestinal disorders). For OLB and RxB subjects, the maximum BRV dose is 5mg/kg/day (rounded) to allow for the possibility that these subjects enter EP0065 on this dose. Dose selection for IOB and IIB subjects was based on the results obtained in N01331 and the recommended dose of BRV as adjunctive therapy in the treatment of

POS in patients 16 years of age and older with epilepsy. For IOB and IIB subjects, the starting BRV dose (2mg/kg/day [1mg/kg bid]) and maximum BRV dose (4mg/kg/day [2mg/kg bid]) in subjects with body weights <50kg approximate the 100mg/day (50mg bid) starting dose and 200mg/day (100mg bid) maximum dose recommended for use in adults. **No subjects enrolled in EP0065 are permitted have a dose that exceeds a maximum of 200mg/day (100mg bid) as consistent with the maximum recommended dose.**

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Inclusion criteria

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

1. Subject or the parent(s) or legal representative of the subject has signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written ICF. The ICF or a specific Assent form, where required, will be signed and dated by minors.
2. The Investigator considers the subject/legal representative to be reliable and able to comply with all study requirements.
3. Subject is male or female from ≥1 month to <16 years of age. For subjects who are <1 year from birth and who were preterm infants, the corrected gestational age should be used for this entry requirement. The corrected gestational age is calculated by subtracting the number of weeks born before 37 weeks of gestation from the chronological age.
4. Subject weighs ≥3kg (6.6lbs).
5. Subject has a diagnosis of epilepsy.
6. Subject is an acceptable candidate for venipuncture and iv infusion.
7. Subject being treated with ≥1 AED (including BRV) without a change of dose regimen for at least 7 days prior to Screening.
8. Subject is not being treated with vagus nerve stimulation (VNS), OR the subject is being treated with VNS and the settings have been constant for ≥ 7 days prior to Screening.
9. For female subjects, the subject is

- Not of childbearing potential

  -OR-

- Of childbearing potential, and
  - Is not sexually active
  - Has a negative pregnancy test

  -OR-

- Of childbearing potential, and
  - Is sexually active
  - Has a negative pregnancy test

- Understands the consequences and potential risks of inadequately protected sexual activity, understands and properly uses contraceptive methods, and is willing to inform the Investigator of any contraception changes. Medically acceptable contraceptive methods for the study include, but are not limited to:
  - Oral or depot contraceptive treatment with at least ethinylestradiol 30µg per intake or ethinylestradiol 50µg per intake if also taking one of the following: carbamazepine, phenobarbital, primidone, phenytoin, oxcarbazepine, St. John's Wort, or rifampicin,
  - Barrier contraception: Intra Uterine Device, diaphragm with spermicide, male or female condom with spermicide
  - Abstinence from sexual intercourse

6.2 Exclusion criteria

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

1. Subject has previously received iv BRV in this study.
2. Subject is pregnant or nursing.
3. Subject has any medical, neurological, or psychiatric condition that, in the opinion of the Investigator, could jeopardize the subject's health or compromise the subject's ability to participate.
4. Subject is being treated with BRV at a dose >5mg/kg/day (rounded) or >200mg/day for subjects with body weights >40kg.
5. Subject requires or is likely to require a change in concomitant AED(s), dose of concomitant AED(s), or formulation of AED(s) during the 7 days prior to the iv PK Period.
6. Subject is likely, in the opinion of the Investigator, to require rescue medication during the IOB Treatment or iv PK Periods.
7. Subject is ≥6 years of age and has a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by positive responses ("Yes") to either Question 4 or Question 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at Screening.
8. Subject is participating in a long-term, open-label BRV study and meets any of the must withdraw criteria for that study.
9. Subject has any medical condition that could reasonably be expected to interfere with the absorption, distribution, metabolism, or excretion of BRV.
10. Subject has a clinically relevant ECG abnormality, in the opinion of the Investigator.
11. Subject has experienced generalized convulsive status epilepticus in the 28 days prior to Screening or during the Screening Period.
12. Subject has a known hypersensitivity to a pyrrolidone derivative(s) or any of the components of the oral or iv formulations of BRV.
13. Subject has a history of severe adverse hematologic reaction to any drug.

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

    For randomized subjects with a baseline result >ULN for ALT, AST, ALP, or total bilirubin, a baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the CRF.

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

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

15. Subject has chronic liver disease.

6.3 Withdrawal criteria

Subjects are free to withdraw from the study at any time, without prejudice to their continued care. The following criteria for subject withdrawal from EP0065 are outlined below. Additional discontinuation criteria for potential drug-induced liver injury are presented in Section 6.3.1.

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

1. Subject experiences intolerable AEs and AEs associated with BRV administration that, in the opinion of the Investigator, precludes further participation in this study.
2. Sponsor or a regulatory agency requests withdrawal of the subject.
3. Subject becomes pregnant during the study, as evidenced by a positive pregnancy test.
4. Subject is unwilling or unable to continue, or the parent/legal guardian is unwilling or unable to allow the subject to continue in this study.
5. Investigator decides that withdrawal from further participation would be in the subject's best interest.
6. For subjects ≥6 years of age, subject has active suicidal ideation with a specific plan as indicated by a positive response ("Yes") to Question 5 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and **must** be withdrawn from the study.

Participation in this study **may** be discontinued for any of the following reasons:

7. Subject experiences generalized convulsive status epilepticus.
8. Subject has any clinically relevant change in medical or psychiatric condition (if in the opinion of the Investigator, the change in condition warrants discontinuation from this study).
9. Subject takes prohibited concomitant medications as defined in this protocol (Section 7.8.2).

10. Subject and/or delegated caregiver is noncompliant with study procedures or medication, in the opinion of the Investigator.
11. For subjects ≥6 years of age, subject has active suicidal ideation without a specific plan as indicated by a positive response ("Yes") to Question 4 of the "Since Last Visit" version of C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and *may* be withdrawn from the study based upon the Investigator's judgment of benefit/risk of continuing the subject in the study/on study medication.

- Investigators should attempt to obtain information on subjects in the case of withdrawal; subjects who withdraw from the study without down titration of BRV should complete the Visit 13 (Table 5–4).

For subjects considered lost to follow up, the Investigator should make an effort (at least 1 phone call and 1 written message to the subject), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the subject, must be recorded in the source documents. The CRF must document the primary reason for withdrawal.

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

6.3.1 Potential drug-induced liver injury investigational medicinal product discontinuation criteria

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

The PDILI criteria below require immediate and permanent discontinuation of IMP:

- Subjects with either of the following:
  - ALT or AST ≥5xULN
  - ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN

The PDILI criterion below requires immediate discontinuation of IMP:

- Subjects with ALT or AST ≥3xULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, right upper quadrant pain or tenderness. Hypersensitivity symptoms include fever (without clear alternative cause), rash, or eosinophilia (ie, >5%).

The PDILI criterion below allows for subjects to continue on IMP at the discretion of the Investigator.

- Subjects with ALT or AST ≥3xULN (and ≥2x baseline) and <5xULN, total bilirubin <2xULN, and no eosinophilia (ie, ≤5%), with no fever, rash, or symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness).

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

Investigators should attempt to obtain information on subjects in the case of IMP discontinuation to complete the final evaluation. Subjects with PDILI should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for IMP discontinuation and subject withdrawal (if applicable), must be recorded in the source documents. The CRF must document the primary reason for IMP discontinuation.

7 STUDY TREATMENT(S)

7.1 Description of investigational medicinal products

Information pertaining to excipients and tablet coatings for the IMP used in this study is provided in the Investigator's Brochure.

7.1.1 Film-coated tablets for oral administration

Tablet strengths: BRV 10mg, 25mg, 50mg, 75mg, and 100mg

7.1.2 Oral solution

Concentration: BRV 10mg/mL

7.1.3 Solution for iv injection

Concentration: BRV 10mg/mL

7.2 Treatments to be administered

For BRV tablets, the mg dosage for the oral tablet treatment should be calculated to match as closely as possible the mg/kg based dosage. Tablets of BRV 10mg, 25mg, 50mg, 75mg, and 100mg are supplied and may be combined, as needed, to achieve the calculated mg/kg dose. Tablets and solution must not be used together to comprise an individual dose.

The dose of oral solution will be measured using the appropriate syringes (1mL, 3mL, and/or 10mL) with an adaptor able to fit the bottle sizes. Oral solution should not be mixed with other liquids prior to administration.

For 15-min iv infusions, a calibrated infusion pump should be used for delivering the iv BRV dose at a constant rate over the target duration assigned. A previously unused vial must be administered for each dose. Dilution is not required prior to administration of iv BRV. The BRV solution for iv injection can be diluted as needed in any of the following diluents:

- 0.9% sodium chloride injection
- Lactated Ringer's injection
- 5% dextrose injection

The total volume of diluent should be calculated not to exceed a total volume of fluid intake/day based on the Holliday-Segar equation as follows:

- For children weighing ≤10kg: 100mL/kg body weight
- For children weighing >10 to ≤20kg: 1000mL + 50mL/kg for each kg body weight ≥10kg

- For children weighing ≥20kg: 1500mL + 20mL/kg for each kg body weight ≥20kg

Brivaracetam will be dispensed using interactive response technology (IRT).

7.2.1 Screening, IOB Treatment, and iv PK Periods

Dosing information for BRV during the Screening, IOB Treatment, and iv PK Periods is provided in Table 7–1.

Table 7–1: BRV dosing during the Screening, IOB Treatment, and iv PK Periods

	Study Period				
	Screening (1-10 days)	**IOB Treatment (2-10 days)[a]**	**iv PK (1-6 days)[b]**		
Subjects	**Dose (oral)**	**Dose (oral)**	**First dose (iv)**	**Subsequent dose(s) (iv)**	**Maximum BRV Dose**
OLB	Per Long-Term, Open-Label study	N/A	mg-to-mg equivalent to last oral dose	Equivalent to first iv dose until PK sampling is completed.	5mg/kg/day (rounded) nte. 200mg/day for body weight ≥40kg
RxB	As prescribed	N/A	mg-to-mg equivalent to last oral dose	Equivalent to first iv dose until PK sampling is completed.	5mg/kg/day (rounded) nte. 200mg/day for body weight ≥40kg
IOB	Not receiving BRV	Subjects <50kg: 2mg/kg/day Subjects ≥50kg: nte. 100mg/day	mg-to-mg equivalent to last oral dose	Equivalent to first iv dose until PK sampling is completed.	4mg/kg/day nte. 200mg/day for body weight ≥50kg
IIB	Not receiving BRV	N/A	Subjects <50kg: 1mg/kg Subjects ≥50kg: 50mg	Equivalent to first iv dose until PK sampling is completed.	4mg/kg/day nte. 200mg/day for body weight ≥50kg

	Study Period				
	Screening (1-10 days)	IOB Treatment (2-10 days)[a]	iv PK (1-6 days)[b]		
Subjects	**Dose (oral)**	**Dose (oral)**	**First dose (iv)**	**Subsequent dose(s) (iv)**	**Maximum BRV Dose**

bid=twice daily; BRV=brivaracetam; IIB=Initiating iv BRV; IOB=Initiating Oral BRV; iv=intravenous; LT=Long-term; N/A=not applicable; nte.=not to exceed; OL=Open-label; OLB=Open-label BRV; PK=pharmacokinetic; q12h=every 12 hours; RxB=Prescribed BRV

Note: Oral BRV will be administered in equally divided doses bid as either tablets or oral solution. Tablets will be administered orally and oral solution will be administered either orally or by enteric administration (eg, feeding tube) based on subject need.

Note: Intravenous BRV will be administered as a 15-minute (±3 minutes) infusion or bolus (up to 2-minute infusion), as assigned and will be administered q12hours ± 2 hours.

[a] Dose adjustment is allowed at the Investigator's discretion provided the adjusted dose does not exceed the maximum dose indicated in the rightmost column of this table and does not occur within 2 days of entry into the iv PK Period.

[b] Dose adjustment is allowed at the Investigator's discretion provided that PK sampling has been completed for 2 doses and the adjusted dose does not exceed the maximum dose indicated in the rightmost column of this table and does not occur within 2 days of entry into the iv PK Period.

7.2.2 Down-Titration Period

All subjects who have received ≥4 doses of BRV during either the IOB Treatment Period or the iv PK Period and who will not continue BRV will have their BRV dose reduced by a maximum of half the dose every week for a maximum of 4 weeks until a dose of 1mg/kg/day (50mg for subjects with body weights ≥50kg) is reached. Subjects who have received <4 doses of BRV may have BRV down titrated at the discretion of the Investigator. Subjects not able to receive oral BRV for down titration, may receive iv BRV for down titration. In the later circumstance, the subjects may receive more than 10 consecutive doses of iv BRV in accordance with the Investigator's discretion.

The OLB subjects who discontinue BRV during the Screening Period will return to the long-term, open-label study for down titration of BRV.

7.3 Packaging

Primary packaging:

- Tablets for oral administration: high-density polyethylene bottles with child-resistant closure containing tablets of BRV 10mg, 25mg, 50mg, 75mg, and 100mg
- Oral solution: 300mL amber glass bottles with child-resistant closure
- Solution for iv injection: 6mL clear Type I glass vials with bromobutyl rubber stopper containing 5mL (50mg) of BRV

7.4 Labeling

Clinical drug supplies will be labeled in accordance with the current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice and will include any locally required statements. If necessary, labels will be translated into the local language.

7.5 Handling and storage requirements

The Investigator (or designee) is responsible for the safe and proper storage of IMP at the site. Investigational medicinal product stored by the Investigator is to be kept in a secured area with limited access according to the storage conditions mentioned on the label. Additional information pertaining to the handling of BRV, a Schedule V drug, is provided in the IMP Handling Manual.

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

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

7.6 Drug accountability

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

The Investigator (or designee) is responsible for retaining all used, unused, and partially used containers of IMP until returned or destroyed, taking into account local laws and regulations.

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 containers must be reconciled and either destroyed at the site according to local laws, regulations, and UCB standard operating procedures (SOPs), or returned to UCB (or designee). Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

7.7 Procedures for monitoring subject compliance

At each visit after IMP is dispensed, subjects/guardians must return all unused IMP and empty IMP containers. Drug accountability must be done in the subject's presence in order to obtain explanations regarding discrepancies in compliance with the dosing regimen. Drug accountability must be recorded on the Drug Accountability form.

Site personnel who are administering iv BRV will record information about all doses administered, including the target dose, actual dose administered, and the dates and times of initiation and completion of each iv administration. If the actual dose is less or more than the target dose, the reason a partial or excessive dose was administered will be recorded.

Intravenous solution will be administered under supervision of the Investigator or his/her designee. The noninjected volume will be recorded in the CRF. Compliance with the

recommended duration of the iv administration will also be assessed by recording the start time and the stop time in the CRF.

Subjects who receive <75% or >125% of the planned BRV dose will be considered noncompliant. If a subject is found to be persistently noncompliant in the Investigator's opinion, the Sponsor, in conjunction with the Investigator, will make a decision as to whether the subject should be withdrawn from the study.

7.8 Concomitant medication(s)/treatment(s)

For any treatment other than the IMP, including over-the-counter products, an accurate record must be kept in the clinic chart (source documentation) and in the CRF. Concomitant medications should be recorded on the concomitant AED page or the concomitant non AED medication page of the CRF, according to the indication. New medications should be recorded in the CRF at only the first visit at which they are reported and subsequently only if there is a change. For any change, the start date corresponding to the date of change in administration should be recorded in the CRF.

7.8.1 Permitted concomitant treatments (medications and therapies)

All treatments are permitted with the exception of those listed in Section 7.8.2.

Vagus nerve stimulation is allowed and will be counted as a concomitant AED. A stable ketogenic diet is allowed.

7.8.2 Prohibited concomitant treatments (medications and therapies)

The following concomitant medication is prohibited during the study:

- Levetiracetam

7.8.3 Rescue medication

Investigators may administer rescue medication in accordance with medical judgment at any time during the study. No rescue medication will be supplied by UCB.

7.9 Blinding

This is an open-label study; no blinding is required.

7.10 Randomization and numbering of subjects

Subjects will not be randomized in EP0065.

For OLB subjects, the unique identification number assigned to them in the open-label study will be used to identify them and maintain subject confidentiality throughout EP0065.

The RxB, IOB, and IIB subjects will be assigned a unique identification number for identification and to maintain subject confidentiality. To enroll these subjects, the Investigator or designee will contact the IRT and provide brief details about the subject to be enrolled. Each subject will receive a 5-digit number assigned at screening that serves as the subject identifier throughout the study. The subject number will be required in all communication between the Investigator or designee and the IRT regarding a particular subject. Subject numbers and kit numbers will be tracked via the IRT.

8 STUDY PROCEDURES BY VISIT

Days are provided relative to Day 1, the first day of the iv PK Period.

8.1 Visit 1 (Day -10 to Day-1 for OLB, RxB, and IIB subjects; Day -20 to Day -11 for IOB subjects)

- Signing and dating of written ICF by parent(s)/legal representative(s)
- Signing and dating of Assent form by the subject (if applicable, according to age and local requirements)

The following assessments should be performed only after the ICF and Assent form (if applicable) procedures described immediately above are completed:

- Subject identification card dispensing
- Inclusion/exclusion criteria
- Demographic data
- General medical/procedure history
- Historical seizure count
- Prior and concomitant medications including AEDs
- Physical examination (complete)
- Neurological examination (complete)
- Body weight (before BRV dispensed)
- Body height
- Vital signs (BP, pulse rate, RR, and temperature)
- 12-lead ECG
- Clinical chemistry, hematology, and endocrinology
- Urinalysis for subjects for whom urine sample collection is feasible
- Pregnancy testing for females of childbearing potential (urine test)
- AEs
- C-SSRS (for subjects ≥6 years of age); version per Section 10.3.3

8.2 Visit 2 (Day -10 to Day -1; IOB subjects only)

- Inclusion/exclusion criteria (before BRV dispensed)
- Concomitant medications including AEDs
- Body weight (before BRV dispensed)
- Vital signs BP, pulse rate, RR, and temperature
- Pregnancy testing for females of childbearing potential (urine)

- AEs
- C-SSRS (for subjects ≥6 years of age); version per Section 10.3.3
- Withdrawal criteria
- Dispense oral BRV

8.3 Visit 3 (Day 1) through Visit 12 (Day 6)

- Inclusion/exclusion criteria (Visit 3 only; prior to iv BRV administration)
- Concomitant medications including AEDs
- Physical examination (brief) (at Visit 3 prior to the initial dose of BRV and daily thereafter, ideally after the morning dose of BRV each day)
- Tanner staging at Visit 3 prior to iv BRV administration only. The Investigator should use clinical judgment in deciding which subjects are selected for evaluation of Tanner Stage (ie, those subjects who are pubescent).
- Neurological examination (brief) (at Visit 3 prior to iv BRV administration and daily thereafter, ideally after the morning dose of BRV each day)
- Body weight (Visit 3 only, prior to iv BRV administration)
- Body height
- Vital signs (BP, pulse rate, RR, and temperature) (see Table 5–2 and Table 5–3 for timing relative to initiation of iv BRV administration). The criteria for BP values to be low or high PCS values are described in Table 10-6 .
- 12-lead ECG (see Table 5–2 and Table 5–3 for timing relative to initiation of iv BRV administration)
- Pregnancy testing for females of childbearing potential (urine test) (Visit 3 only, prior to iv BRV administration)
- AEs
- Withdrawal criteria
- C-SSRS (for subjects ≥6 years of age); version per Section 10.3.3 (Visit 3 prior to iv BRV administration and, for subjects who receive ≥2 doses of iv BRV and who will enter the Down-Titration Period, at their final visit of the iv PK Period [Visit 4 to 12, as applicable])
- PK sampling (see Table 5–2 and Table 5–3 for timing relative to initiation of iv BRV administration)
- Collect oral BRV (as needed for IOB subjects who will enter the long-term, open-label study)
- Dispense oral BRV (at final visit of this period and only for subjects who will enter the Down-Titration Period)
- iv BRV administration

Subjects who are continuing into the long-term, open-label study after their final dose of iv BRV, will re-enter (OLB subjects)/enter (RxB, IOB, and IIB subjects) that study at the completion of assessments associated with the final iv dose of iv BRV.

8.4 TC-1 (Day 2 to Day 9) (all subjects who received iv BRV)

Telephone Contact-1 (TC-1) should occur 1 to 3 days after the final dose of iv BRV. The primary purpose of this contact is to collect information pertaining to possible infusion-related AEs. Subjects who report new or worsened infusion-site related AEs should return for an Unscheduled Visit as soon as possible.

- Concomitant medications including AEDs
- AEs
- Withdrawal criteria

8.5 TC-2

Telephone Contact-2 is only applicable to subjects who participate in the Down-Titration Period for more than 2 weeks; TC-2 should be conducted approximately half way through the Down-Titration Period.

- Concomitant medications including AEDs
- AEs
- Withdrawal criteria

8.6 Visit 13

This visit is applicable only to subjects who have participated in the Down-Titration Period or to subjects who need to withdraw from the study and do not need to have BRV down titrated.

- Concomitant medications including AEDs
- Physical examination (brief)
- Neurological examination (brief)
- Body height
- Vital signs (BP, pulse rate, RR, and temperature)
- 12-lead ECG
- Clinical chemistry, hematology, and endocrinology
- Urinalysis for subjects for whom urine sample collection is feasible
- Pregnancy testing for females of childbearing potential (urine test)
- AEs
- C-SSRS (for subjects ≥6 years of age); version per Section 10.3.3
- Collect oral BRV

8.7 TC-3

Telephone Contact-3 is only applicable to subjects who have completed Visit 13 and should be conducted 2 weeks after the final dose of BRV.

- Concomitant medications including AEDs
- AEs

8.8 Unscheduled Visit

If an Unscheduled Visit is needed, then the following assessments will be performed. Additional assessments can be performed at the Investigator's discretion.

- Concomitant medications including AEDs.
- Vital signs (BP, pulse rate, RR, and temperature).
- AEs.
- Withdrawal criteria
- C-SSRS for subjects ≥6 years of age using the version indicated in Section 10.3.3. If an Unscheduled Visit is conducted due to safety reasons, a C-SSRS assessment will be performed with the subject during the visit. If the Unscheduled Visit is conducted for reasons other than safety concerns (eg, replacement of lost medication, repeated collection of a laboratory specimen due to collection or analysis issues), a C-SSRS will not be required at this visit.

9 ASSESSMENT OF PHARMACOKINETIC VARIABLES

The PK sampling will be performed in accordance with the schedule provided in Table 5–2 (15-minute [±3 minutes] infusion) and Table 5–3 (bolus [up to 2-minute infusion]). Additional PK sampling may be performed at the discretion of the Investigator, especially in the event of a relevant treatment-emergent AE.

Blood samples should be collected after completion of the ECG and the vital sign measurements and from a region of the body not used for the iv BRV administration. The date, start, and stop time of each iv administration and the date and time of each PK sampling must be recorded.

Per subject, the maximum amount of blood collected for PK analyses and clinical laboratory assessments will not exceed a maximum of 3% of the subject's total blood volume within 4 weeks.

Details of plasma sample collection and processing, sample labeling, and shipment will be provided in the laboratory manual.

10 ASSESSMENT OF SAFETY

10.1 Adverse events

10.1.1 Definitions

10.1.1.1 Adverse event

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

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

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

10.1.1.2 Serious adverse event

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

- Death
- Life-threatening

  (Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form.)
- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect (including that occurring in a fetus)
- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definition of serious

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

  (A patient admitted to a hospital, even if he/she is released on the same day, meets the criteria for the initial inpatient hospitalization. An emergency room visit that results in

admission to the hospital would also qualify for the initial inpatient hospitalization criteria. However, emergency room visits that do not result in admission to the hospital would not qualify for this criteria and, instead, should be evaluated for 1 of the other criteria in the definition of serious [eg, life-threatening adverse experience, important medical event].

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

10.1.1.2.1 Anticipated serious adverse events

The following Anticipated SAEs are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure.

This list does not change the Investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 10.1.2.3.

Table 10–1: Anticipated serious adverse events for the pediatric epilepsy population

MedDRA SOC	MedDRA PT
Congenital, familial and genetic disorders	Teratogenicity
General disorders and administrative site conditions	Sudden unexpected death in epilepsy
Nervous system disorders	Convulsion[a]
	Status epilepticus
Pregnancy, puerperium and perinatal disorders	Abortion spontaneous
Psychiatric disorders	Psychotic behavior
	Abnormal behavior
	Anxiety
	Sleep disorder

MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class
[a] Convulsion if consistent with the seizure type known for the subject.

10.1.1.3 Adverse events of special interest

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

- Autoimmune nephritis
- Nephritis
- Nephritis allergic
- Tubulointerstitial nephritis
- Tubulointerstitial nephritis and uveitis syndrome
- Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of special interest (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the subject.

10.1.2 Procedures for reporting and recording adverse events

The subject and/or caregiver (including parent/legal guardian) will be given the opportunity to report AEs spontaneously. A general prompt will also be given at each study visit to detect AEs. For example:

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

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

The AEs should be recorded in the CRF at only the first visit at which they are reported and subsequently only if there is a change.

10.1.2.1 Description of adverse events

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

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

10.1.2.2 Rule for repetition of an adverse event

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

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

10.1.2.3 Additional procedures for reporting serious adverse events

If an SAE is reported, UCB must be informed within 24 hours of receipt of this information by the site (see contact information for SAE reporting listed in the Serious Adverse Event Reporting

section at the front of the protocol). The Investigator must forward to UCB (or its representative) a duly completed "Investigator SAE Report Form for Development Drug" (SAE Report form) provided by UCB, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions. Information recorded on this form will be entered into the global safety database.

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

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

Additional information (eg, autopsy or laboratory reports) received by the Investigator must be provided within 24 hours. All documents in the local language must be accompanied by a translation in English, or the relevant information included in the same document must be summarized in the Investigator SAE Report form.

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

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

10.1.3 Follow up of adverse events

An AE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest; further details regarding follow up of PDILI events is provided in Section 10.2.1.4.

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

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

If new or worsened infusion-site related AEs are reported during TC-1, the subject should return for an Unscheduled Visit as soon as possible for further assessment.

10.1.4 Pregnancy

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

- The subject should immediately stop the intake of BRV or be down-titrated as instructed by the Investigator.
- For subjects who have BRV down-titrated:
  - Return for Visit 13.
  - TC-3 should be scheduled 2 weeks after the subject has discontinued BRV.

The Investigator must inform the subject of information currently known about potential risks and about available treatment alternatives.

The pregnancy will be documented on the Pregnancy Report and Outcome form provided to the Investigator. The progression of the pregnancy and the eventual birth (if applicable) must be followed up using the Pregnancy Report and Outcome form in which the Investigator has to report on the health of the mother and of the child. Every reasonable attempt should be made to follow the health of the child for 30 days after birth for any significant medical issues. In certain circumstances, UCB may request that follow up is continued for a period longer than 30 days. If the subject is lost to follow up and/or refuses to give information, written documentation of attempts to contact the subject needs to be provided by the Investigator and filed at the site. UCB's PS department is the primary contact for any questions related to the data collection for the pregnancy, eventual birth, and follow up.

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

A pregnancy becomes a SAE in the following circumstances: miscarriage, abortion (elective or spontaneous), unintended pregnancy after hormonal contraceptive failure (if the hormonal contraceptive was correctly used), ectopic pregnancy, fetal demise, or any congenital anomaly/birth defect of the baby. Those SAEs must be additionally reported using the Investigator SAE Report form.

10.1.5 Suspected transmission of an infectious agent via a medicinal product

A suspected transmission of infectious agent is defined as any infection that is temporally related to the administration of the medicinal product with no other likely cause. The medical monitor should be contacted immediately. No further medicinal product from that specific batch should be administered. Infections should be treated according to normal clinical practice.

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

10.1.6 Overdose of investigational medicinal product

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

10.1.7 Safety signal detection

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

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

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

For further details please refer to Section 12.7.

10.2 Laboratory measurements

Laboratory assessments for safety (including hematology, chemistry, and endocrinology for all subjects, and urinalysis for subjects for whom sample collection is feasible) will be conducted using standard methods at a central laboratory. The central laboratory will provide the Investigator with dedicated, standardized sampling supplies (labels, needles, tubes) and a study-specific laboratory manual, which will explain how to use the supplies and how to ship the samples to the central laboratory.

Pregnancy tests (urine) for female subjects of childbearing potential will be performed locally.

Table 10–2 provides a list of laboratory parameters that will be assessed.

Table 10–2: Laboratory parameters

Hematology	Chemistry	Urinalysis[a]	Endocrinology	Pregnancy[b]
WBC	Glucose	Glucose	FSH	β-hCG (urine)
RBC	Sodium	Ketones	LH	
Hemoglobin	Potassium	Occult blood	TSH	
Hematocrit	Calcium	Protein	T_3	
Platelet count	Chloride	Nitrites	T_4	
Lymphocytes (number, %)	Bicarbonate	Leukocytes		
Monocytes (number, %)	Phosphorus (inorganic)	Microscopic examination[c]		
Neutrophils (number, %)	Total protein			
Eosinophils (number, %)	Albumin			
Basophils (number, %)	Total bilirubin			
MCH	ALP			
MCHC	AST			
MCV	ALT			
	GGT			
	Uric acid			
	Urea			
	Creatinine			
	Triglycerides			
	Cholesterol			

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; β-hCG=beta-human chorionic gonadotropin; FSH=follicle-stimulating hormone; GGT=gamma-glutamyltransferase; LH=luteinizing hormone; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV= mean corpuscular volume; RBC=red blood cell; T_3=triiodothyronine; T_4=thyroxine; TSH=thyroid-stimulating hormone; WBC=white blood cell

[a] Urinalysis will be performed in subjects for whom urine sample collection is feasible.

[b] For female subjects of childbearing potential only.

[c] Includes bacteria, cells, casts, and crystals for all samples.

For blood samplings, methods to minimize pain are recommended (eg, topical anesthetic or microsamplings may be used). Per subject, the maximum amount of blood collected for clinical laboratory assessments and PK analyses will not exceed a maximum of 3% of the subject's total blood volume within 4 weeks.

10.2.1 Evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 6.3.1, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and Sponsor within 24 hours of learning

of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 10.1.1.3), and, if applicable, also reported as an SAE (see Section 10.1.2.3).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 10–3 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 10.2.1.1). The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 10.2.1.4).

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

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

If tests are done locally for more rapid results, a concurrent sample should also be sent to the central laboratory whenever possible. Medical care decisions are to be made initially using the most rapidly available results and a conservative approach must be taken if the results from the 2 laboratory tests are significantly different. Data from the local and central laboratory are to be recorded on the applicable CRF pages.

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

Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

The table below summarizes the approach to investigate PDILI.

Table 10–3: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN[b]	NA	Hepatology consult.[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 10.2.1.3); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values.[d]
≥3xULN	NA	Yes		Immediate, temporary or permanent, IMP discontinuation.		
≥5xULN (and ≥2x baseline)	<2xULN	No	Discussion with Medical Monitor required. Hepatology consult required if ALT/AST ≥8x ULN.	Immediate, permanent IMP discontinuation.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 10.2.1.3).	

Table 10–3: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN (and ≥2x baseline) and <5xULN	<2xULN	No	Discussion with Medical Monitor required if the criterion that allows for IMP continuation is met.	Further investigation – immediate IMP discontinuation not required (see Section 10.2.1.2). IMP discontinuation required if any of the following occur: • Subject cannot comply with monitoring schedule. • Liver chemistry values continue to increase • Liver chemistry values remain ≥3xULN (and ≥2x baseline) after 2 weeks of monitoring without stabilization or evidence of resolution.	Not required unless otherwise medically indicated (at discretion of Investigator).	Monitoring of liver chemistry values at least twice per week for 2 weeks.[d] Immediate IMP discontinuation required if : • Liver chemistry values continue to increase • Liver chemistry values remain ≥3xULN (and ≥2x baseline) after 2 weeks of monitoring without stabilization or evidence of resolution Continue to monitor until values normalize, stabilize, or return to within baseline values.[d]

Table 10–3: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**

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

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

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

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

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

10.2.1.1 Consultation with Medical Monitor and local hepatologist

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

10.2.1.2 Immediate action: determination of IMP discontinuation

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

The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and ranges from continuation of IMP (followed by immediate investigation) to immediate and permanent discontinuation (see Section 6.3.1 and Table 10–3 for details).

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

10.2.1.3 Testing: identification/exclusion of alternative etiology

The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are detailed in Table 10–4 (laboratory measurements) and Table 10–5 (additional information). Results of the laboratory measurements and information collected are to be submitted to the Sponsor on the corresponding CRF. If the medical history of the subject indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable.

All blood samples should be stored, if possible. If tests are done locally for more rapid results, a concurrent sample must also be sent to the central laboratory.

The following measurements are to be assessed:

Table 10–4: PDILI laboratory measurements

Virology-related	Hepatitis A IgM antibody
	HBsAg
	Hepatitis E IgM antibody
	HBcAb-IgM
	Hepatitis C RNA
	Cytomegalovirus IgM antibody
	Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophile antibody or monospot testing)
Immunology	Anti-nuclear antibody (qualitative and quantitative)
	Anti-smooth muscle antibody (qualitative and quantitative)
	Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative)
Hematology	Eosinophil count
Urinalysis	Toxicology screen
Chemistry	Amylase
	If total bilirubin ≥2xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
Additional	Prothrombin time/INR[a]
	Serum pregnancy test[b]
	PK sample[c]

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

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

[b] Determined only for female subjects of childbearing potential.

[c] Blood sample for determination of plasma concentrations of BRV.

The following additional information is to be collected:

Table 10–5: PDILI information to be collected

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

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

10.2.1.4 Follow-up evaluation

Potential drug-induced liver injury events will require follow-up monitoring as described in Table 10–4. Monitoring should continue until liver chemistry values normalize, stabilize, or return to baseline. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

10.3 Other safety measurements

All safety assessments are to be conducted at the times specified in the Schedules of Study Assessments (Table 5–1 and Table 10-6). During the iv PK Period, intensive assessments of ECGs and vital signs are to be conducted at the times specified in Table 5–2 (15-minute [±3 minutes] infusion) and Table 5–3 (bolus [up to 2-minute infusion]).

10.3.1 ECG

Standard 12-lead ECGs will be performed.

The Investigator will determine whether the results of the ECG are normal or abnormal and assess the clinical significance of any abnormalities.

The original ECG tracing will be signed or initialed and dated by the Investigator, and retained as part of the source documentation.

10.3.2 Vital signs

Vital signs assessments will include BP (systolic and diastolic), pulse rate, RR, and temperature. Vital sign assessments will be performed after the subject is at rest for at least 3 minutes, when feasible. If subjects have an abnormal vital sign value, the measurement will be repeated at the Investigator's discretion.

Possibly clinically significant (PCS) vital sign values are defined as those PCS values which occur at any time during the study. Additional monitoring of BP is necessary if a low PCS BP value occurs at 2 hours after the start of an infusion (Section 5.2). An overview of PCS abnormality criteria for BP is presented in Table 10-6.

Table 10-6: PCS Abnormality criteria for the measurement of blood pressure

Parameter	Age range	Abnormality criteria
Systolic blood pressure (mmHg)	<6m	<60 >100
	6m - <3y	<70 >120
	3y - <12y	<80 >140
	12y - <17y	<90 >160
	≥17y	≤ 90 and a decrease from Baseline of ≥20 ≥ 180 and an increase from Baseline of ≥20
Diastolic blood pressure (mmHg)	<6m	<40 >65
	6m - <3y	<45 >75
	3y - <12y	<50 >80
	12y - <17y	<50 >105
	≥17y	<50 and a decrease from Baseline of ≥15 >105 and an increase from Baseline of ≥ 15

m=month, PCS=possibly clinically significant; y=year. A month is defined as 30 days; a year is defined as 365.25 days.

10.3.3 Assessment of suicidality

Suicidal ideation and behavior be assessed by trained study personnel using the C-SSRS for subjects ≥6 years of age. This scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be completed according to the tabular schedule of study assessments (Section 5.2).

The Investigator's decision about subject continuation in the study or subject withdrawal from the study if the subject has a positive response to the C-SSRS Question 4, should be based on the benefit/risk balance for continuation or discontinuation of study treatment in view of the individual subject circumstances, condition, attained efficacy, causality, alternative risk management options, etc. Details of the case must be documented by the Investigator (Principal Investigator or other medically qualified staff conducting the C-SSRS) and provided to UCB via the SAE reporting process.

All subjects who are ≥6 years of age will complete the following version of the C-SSRS as indicated:

- OLB subjects:
  - "Since Last Visit" version at all visits
- RxB, IOB, and IIB subjects:
  - "Baseline/Screening" version at Visit 1
  - "Since Last Visit" version at subsequent visits
- Subjects who become 6 years of age during EP0065:
  - "Already Enrolled" version at the first visit at which the subject is 6 years of age
  - "Since Last Visit" version at subsequent visits

The C-SSRS is not validated for subjects <6 years of age and will not be used for this population. Subjects should be monitored for any changes in mood, ideas, or behavior for warning signs of depression. The Investigator should be aware of common warning signs that might be a signal for risk of depression. For common signs and symptoms of depression in children younger than 6 years old, reference should be made to the current version of the Diagnostic and Statistical Manual of Mental Disorders. Parents and caregivers should also be advised accordingly and effort should be made at clinic visits to specifically assess potential depression.

11 STUDY MANAGEMENT AND ADMINISTRATION

11.1 Adherence to protocol

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

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

11.2 Monitoring

Monitoring of the study will be delegated by UCB to a CRO. The CRO will monitor the study to meet the Sponsor's monitoring SOPs, ICH-GCP guideline, and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate.

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

The Investigator will allow UCB (or designee) to periodically review all CRFs and corresponding source documents (eg, hospital and laboratory records for each study participant). Monitoring visits will provide UCB (or designee) with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of CRFs, ensure that all protocol

requirements, applicable authorities regulations, and Investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

11.2.1 Definition of source data

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

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

Original laboratory results and ECGs are considered as source documents and should be placed and stored with the subject's study information.

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

Electronic data records must be saved and stored as instructed by UCB (or designee).

11.2.2 Source data verification

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

11.3 Data handling

11.3.1 Case Report form completion

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

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

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

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

Detailed instructions will be provided in the CRF Completion Guidelines.

11.3.2 Database entry and reconciliation

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

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

11.3.3 Subject Screening and Enrollment log/Subject Identification Code list

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

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

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

11.4 Termination of the study

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

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

11.5 Archiving and data retention

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

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

relocate or move the study-related files to a location other than that specified in the Sponsor's study master file.

11.6 Audit and inspection

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

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

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

11.7 Good Clinical Practice

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

12 STATISTICS

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

12.1 Definition of analysis sets

The Safety Set iv (SS-iv) will include subjects who received at least 1 dose of iv BRV. The SS-iv will be the primary analysis set for the analysis of safety data.

The Safety Set (SS) will include subjects who received at least 1 dose of BRV (oral or iv). Selected safety summaries will be presented for the SS.

The PK Per-protocol Set (PK-PPS) will include all subjects in the SS having provided at least 1 measurable postdose plasma sample (with recorded sampling time) during the iv PK Period with documented iv BRV intake times.

12.2 General statistical considerations

All computations for the non-PK analyses will be performed using SAS® version 9.3 or later (SAS Institute, NC, USA).

Selected disposition, exposure, demographic, and baseline summaries will be presented by cohort and infusion duration (15-minute [±3 minutes] infusion and bolus [up to 2-minute infusion]), cohorts overall, and across all subjects. Descriptive statistics will be displayed to provide an overview of the Baseline characteristics, PK, safety, and tolerability results. For categorical variables, these will consist of the number and percentage of subjects in each category. The denominator and percentage will be based on the number of subjects appropriate

for the purpose of analysis. For continuous variables, display of descriptive statistics will generally include n (number of subjects), mean, standard deviation (SD), median, minimum, and maximum.

12.3 Planned PK analyses

Descriptive statistics for BRV plasma concentrations, including but not limited to geometric mean and coefficient of variation percentages, will be computed for pre-bolus/infusion and at the post-bolus/infusion time points on each for iv BRV administration during the iv PK Period.

12.4 Planned safety analyses

Safety data will be reported in epochs that include the pre-bolus/infusion period(s), the bolus/infusion period(s), the period(s) immediately post-bolus/infusion, and period(s) between each subsequent bolus/infusion(s). These data will include vital signs, ECGs, and AE reporting.

12.4.1 Analysis of safety variables

Descriptive statistics for the safety variables will be presented by cohort and infusion duration, cohorts overall, and all subjects overall. Additional summaries will include a summary of the OLB, RXB, IOB, and IIB groups by cohort and infusion duration.

12.4.1.1 Primary safety variables

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). Adverse events will be summarized by MedDRA System Organ Class and Preferred Term.

The primary safety variables will be summarized for the iv PK Period for the SS-iv. Summaries of adverse events will also be presented by study period for the SS and epochs relative to bolus/infusion for the SS-iv.

12.4.1.2 Other safety variables

Inferential statistical tests are not planned for the other safety variables. In general, for continuous safety variables including ECG measurements including corrected QT interval, and vital sign measurements, the descriptive analyses (n, mean, SD, median, minimum, maximum) for the actual measurement and its change from baseline (defined as most recent pre-iv BRV measurement) will be presented by epochs relative to bolus/infusion. When analyzing categorical data, the number and percentage of subjects in each category will be presented. In addition, shift tables may be used to evaluate the number and percentage of subjects having a different post-iv BRV status when compared with their pre-iv BRV status for each bolus/infusion. Changes in vital signs and ECG parameters will be presented graphically for epochs relative to bolus/infusion.

12.5 Handling of protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on the primary safety outcomes for an individual subject. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and data evaluation. All important deviations will be identified and documented prior to database lock to confirm exclusion from analysis sets.

12.6 Handling of dropouts or missing data

No specific procedure is foreseen for handling dropouts or missing data.

12.7 Planned interim analysis and data monitoring

No formal interim analysis is planned for this study.

For the first cohort, after the first half of the subjects receive the 15-minute infusion(s), the DMC will meet to review safety (as indicated in the DMC charter) and, as available, PK data. For subsequent cohorts, the DMC will review data for bolus infusions of the previous cohort and the 15-minute infusions of the current cohort. The DMC will meet no less than approximately every 6 months commensurate with enrollment.

12.8 Determination of sample size

The primary objective of the study is to evaluate the PK, safety, and tolerability of BRV given intravenously. The plan for approximately 50 enrolled subjects (4 cohorts of approximately12 subjects each) to receive iv BRV was deemed clinically appropriate for the evaluation of the PK, safety, and tolerability of iv BRV administration in subjects ≥1 month to <16 years of age with epilepsy. No formal sample size calculation has been performed.

13 ETHICS AND REGULATORY REQUIREMENTS

13.1 Informed consent

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

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

Prior to participation in the study, the written Informed Consent form should be signed and personally dated by the subject, or his/her legal representative, and by the person who conducted the informed consent discussion (Investigator or designee). The subject or his/her legal representative must receive a copy of the signed and dated Informed Consent form. As part of the consent process, each subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection. In addition, a Consent form or a specific Assent form, where required, will be signed and dated by minors. Any subject who becomes 16 years of age during EP0065 must sign and date the Informed Consent form according to local regulations.

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

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

The subject or legal representative may withdraw consent for the subject to participate in the study at any time. A subject is considered as enrolled in the study when the subject or legal representative has signed the ICF form/Assent form. A CRF must not be started, nor may any study specific procedure be performed for a given subject, without having obtained the written consent of the subject or legal guardian for the subject to participate in the study.

13.2 Subject identification cards

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

13.3 Institutional Review Boards and Independent Ethics Committees

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, ICH-GCP, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

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

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

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

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

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

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

Investigators are to provide the Sponsor (or its representative) with evidence of such IRB/IEC notification.

13.4 Subject privacy

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

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

13.5 Protocol amendments

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

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

14 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

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

15 REFERENCES

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Theodore WH, Spencer SS, Wiebe, S, Langfitt JT, Ali A, Shafer PO. Epilepsy in North America: a report prepared under the auspices of the global campaign against epilepsy, the International Bureau for Epilepsy, the International League Against Epilepsy, and the World Health Organization. Epilepsia. 2006;47:1800-22.

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16 APPENDIX

16.1 Protocol Amendment 1

Rationale

This nonsubstantial amendment is based on DMC recommendation, as a precaution additional safety monitoring has been added to the protocol. This precaution was not based on any related AE or reported symptoms. Additional vital sign measurements, specifically blood pressure, and criteria for further iv BRV dose allocation were added to further investigate blood pressure changes and ensure safety. Additionally, height measurements have been collected at various visits since the onset of the study, while these were inadvertently absent from the list of assessments. The protocol has therefore been aligned.

Specific changes

Section # and name	Description of change	Brief rationale
Study contact information	Updated Sponsor Study Physician, Clinical Project Manager, and Clinical Trial Biostatistician	Recent changes in study contacts
Section 5.2 Schedule of study assessments	Added definition of PCS Added cross reference to BP PCS values Table 10-6 Added text regarding additional safety monitoring and criteria for further iv and BRV dose allocation	Absent from previous version To clearly define BP PCS values To further investigate BP and ensure safety
Table 5-1 Schedule of Study Assessments (Screening Period through end of iv PK Period)	Added body height assessment	Added this text that was inadvertently omitted during protocol development
Table 5-2 Schedule for iv PK Period ECGs, vital signs, and PK sampling (15-min BRV infusion)	Added BP assessment along at 2hrs post infusion start and accompanying footnote Added description of when additional BP monitoring is required	To further investigate BP and ensure safety

Section # and name	Description of change	Brief rationale
Table 5-3 Schedule for iv PK Period ECGs, vital signs, and PK sampling (bolus [up to 2-min BRV infusion])	Added BP assessment along at 2hrs post infusion start and accompanying footnote Added description of when additional BP monitoring is required	To further investigate BP and ensure safety
Table 5-4 Schedule of study assessments for Down-Titration and Safety (BRV-free) Periods (subjects not continuing into the Long-Term, Open-Label Study)	Added body height assessment	Added this text that was inadvertently omitted during Protocol development
Section 8.1 Visit 1 (Day -10 to Day -1 for OLB, RxB, and IIB subjects; Day -20 to Day -11 for IOB subjects)	Added body height assessment	Added this text that was inadvertently omitted during Protocol development
Section 8.3 Visit 3 (Day 1) through Visit 12 (Day 6)	Added body height assessment Added a cross reference to BP PCS values Table 10-6	Added this text that was inadvertently omitted during Protocol development To clearly define BP PCS values
Section 8.6 Visit 13	Added body height assessment	Added this text that was inadvertently omitted during Protocol development
Section 10.3.2 Vital signs	Added text regarding additional safety monitoring Added Table 10-6 PCS abnormality criteria for the measurement of BP	To further investigate BP and ensure safety To describe the criteria for systolic and diastolic BP to be low or high PCS

17 DECLARATION AND SIGNATURE OF INVESTIGATOR

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

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

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

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

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

Investigator:

Printed name	Date/Signature

18 SPONSOR DECLARATION

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

Approval Signatures

Name: ep0065-protocol-amendment-1

Version: 1.0

Document Number: CLIN-000135150

Title: EP0065 Protocol-Phase 2-Open-label

Approved Date: 20 Jun 2019

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 19-Jun-2019 11:57:23 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Qualified Person Date of Signature: 19-Jun-2019 12:12:50 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 20-Jun-2019 10:09:09 GMT+0000