PROTOCOL EP0057

A MULTICENTER, OPEN-LABEL, LONG-TERM STUDY TO INVESTIGATE THE SAFETY OF CONVERSION TO LACOSAMIDE AT DOSES UP TO 600MG/DAY AS MONOTHERAPY IN JAPANESE ADULTS WITH PARTIAL-ONSET SEIZURES WITH OR WITHOUT SECONDARY GENERALIZATION

PHASE 3

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Protocol/Amendment number	Date	Type of amendment
Final Protocol	09 Oct 2013	Not applicable

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.

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AE	adverse event
AED	antiepileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AV	atrioventricular
CDMS	clinical data management system
CLcr	creatinine clearance
CNS	central nervous system
CPM	Clinical Project Manager
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
CV	coefficient of variation
DS	Drug Safety
ECG	electrocardiogram
eCRF	electronic Case Report form
EEG	electroencephalogram
EMA	European Medicines Agency
FAS	Full Analysis Set
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
ILAE	International League Against Epilepsy
IMP	investigational medicinal product
IRB	Institutional Review Board
LCM	lacosamide
LFT	liver function test
LOE	lack of efficacy
LOQ	lower limit of quantification
MRI	magnetic resonance imaging
N/A	not applicable
PK	pharmacokinetics

PMDA	Pharmaceutical and Medical Devices Agency in Japan
SAE	serious adverse event
SD	standard deviation
SOP	standard operating procedure
SS	Safety Set
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VNS	vagus nerve stimulation
WHO	World Health Organization

1 SUMMARY

EP0057 is a Phase 3, multicenter, open-label, study designed to evaluate the safety, tolerability, and efficacy of long-term administration of lacosamide (LCM; VIMPAT®; SPM 927; previously referred to as harkoseride; (R)-2-acetamido-N-benzyl-3-methoxypropionamide, ADD 234037) in Japanese adults with partial-onset seizures with or without secondary generalization who are not controlled by an antiepileptic drug (AED) with marketing approval in Japan taken in monotherapy. In this study, LCM will be administered as a monotherapy at doses from 200mg/day up to 600mg/day.

Enrollment of at least 10 subjects is planned for this study. EP0057 will continue until the marketing approval of LCM for the indication of partial-onset seizure monotherapy in Japan is obtained or until the time when the sponsor decides to discontinue the development of LCM for the same indication. The expected duration of subject participation is approximately 2.5 years. EP0057 consists of 1-week Screening Period and an approximately 2.5-year Treatment Period. The Treatment Period consists of the following: a 4-week forced titration up to LCM 400mg/day (referred to as the Titration Period), a maximum of 12 weeks of tapering off baseline AED (referred to as the AED Withdrawal Period), and a 52-week Evaluation Period where subjects continue with the optimal dose of LCM monotherapy achieved during the periods prior plus a Follow-Up Period (referred to as the Monotherapy Period). The Treatment Period is followed by a 5-week Taper Period.

At the beginning of the Titration Period, subjects will start with LCM 100mg/day. During the 4-week Titration Period, LCM will be titrated in increments of 100mg/day per week up to LCM 400mg/day. Subjects who complete the Titration Period will enter an AED Withdrawal Period. During this period, concomitant AEDs will be carefully tapered and discontinued within a period of 4 to 12 weeks. Subjects who complete the AED Withdrawal Period will enter the Monotherapy Period. During the AED Withdrawal and the Monotherapy Period, the investigator may increase or decrease the dose of LCM to optimize tolerability and seizure control. The LCM dose may be decreased to a minimum daily dose of 200mg and increased to a maximum daily dose of 600mg in weekly increments of a maximum of 100mg/day. Subjects who prematurely withdraw from the study will be required to enter the Taper Period. Subjects not prematurely withdrawn from the study will continue in the study until LCM is available commercially as a monotherapy. If LCM is not commercially available in Japan at the time the study closes, access to LCM will be provided according to local laws.

The primary safety variables include adverse events (AEs) reported spontaneously by the subjects or observed by the investigator and subject withdrawals due to AEs. Other variables to be assessed include safety (Section 4.1), efficacy (Section 4.2), and pharmacokinetic (PK) measurements (Section 4.3).

2 INTRODUCTION

Epilepsy remains the second most prevalent neurological disorder in the world that affects people of all ages. According to the World Health Organization (WHO), it is estimated that as of 2012, epilepsy was diagnosed in approximately 50 million people worldwide (WHO, 2012).

In Japan, the number of patients with epilepsy is estimated to be approximately 216,000 (Ministry of Health, Labour and Welfare, Patient Survey, 2011). In addition, epidemiologically,

epilepsy affects 0.5% to 1% of the population (Inoue, 2005). There is also a report that suggests the total number of patients with epilepsy in Japan is approximately 1 million people (Ueda, 2007).

Most patients with epilepsy require an appropriate pharmacological therapy (Perucca, 1996). Several options for the treatment of epilepsy have been introduced, including novel AEDs, vagus nerve stimulation (VNS), and surgical intervention. The newer AEDs differ from older agents in several important ways, including mechanism of action, spectrum of activity, and PK characteristics (Herman and Pedley, 1998). However, more than 30% of patients have inadequate seizure control with the currently available AEDs or experience significant adverse drug effects (Beghi and Sander, 2008). Therefore, a need remains for AEDs with improved effectiveness and tolerability (Shorvon et al, 2009).

Lacosamide belongs to a novel class of functionalized amino acids. It was first approved by the European Medicines Agency (EMA) in 2008 and is indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients with epilepsy aged 16 years and older. Lacosamide has also been approved as adjunctive therapy for patients with uncontrolled partial-onset seizures in other countries. The specific indication statement and approved formulation(s) for LCM slightly differ based on the country; thus, local labels should be consulted for further information.

In the clinical development program for LCM, safety and tolerability of multiple doses of up to LCM 800mg/day were evaluated in Phase 1 studies. Lacosamide is rapidly and completely absorbed after oral administration and has minimal protein-binding properties; thus, there is a low risk of displacement drug-drug interactions. Peak plasma concentrations occur between 0.5 and 4 hours after dosing. Pharmacokinetic parameters are proportional to dose, with low intra- and inter-subject variability. The terminal half-life of the unchanged drug in plasma is approximately 13 hours, allowing for a twice-daily dose regimen. The O-desmethyl metabolite (referred to as SPM 12809) is excreted in the urine and represents about 30% of the dose. This metabolite has no known pharmacological activity. After single-dose administration in healthy subjects, bioequivalence has been shown between the tablet and solution for infusion as well as between the tablet and oral solution (syrup) formulation.

Three double-blind, placebo-controlled, multicenter studies (SP667, SP754, and SP755), as well as extension study SP756 (Hussain et al, 2012) established the efficacy of oral LCM 200mg/day (SP667 and SP755), LCM 400mg/day, and LCM 600mg/day (SP667, SP754 and SP756) as adjunctive therapy (1 to 3 concomitant AEDs) in subjects with uncontrolled partial-onset seizures. The most frequently reported treatment-emergent adverse events (TEAEs) were central nervous system (CNS) and gastrointestinal-related events. The efficacy and safety of LCM as monotherapy in patients with partial-onset seizures was reported in SP902, a historical-controlled, multicenter, double-blind, randomized, conversion to LCM 400mg/day or 300mg/day monotherapy study in subjects with partial-onset seizures.

Further information on LCM preclinical results, as well as the PK, efficacy, and safety profiles, can be obtained from the current version of the LCM Investigator's Brochure.

The approach for further LCM development is to evaluate the use of LCM monotherapy for the treatment of partial-onset seizures. The goal of AED monotherapy is to achieve complete seizure freedom with no or minimal side effects. Lacosamide has proven to be an effective and safe

adjunctive treatment for partial-onset seizures with or without secondary generalization. In order to further define its role in the clinical armamentarium for the treatment of newly diagnosed subjects, it has been proposed to compare LCM with a standard AED as initial monotherapy, according to EMA guidelines (CHMP/EWP/566/98, 2010). Following this guideline, UCB has already started SP0993, a Phase 3, multicenter, double-blind, double-dummy, randomized, positive-controlled study comparing the efficacy and safety of LCM (target dose levels of 200, 400, or 600mg/day) to controlled release carbamazepine (target dose levels of 400, 800, or 1200mg/day) used as monotherapy in subjects ≥16 years of age newly or recently diagnosed with epilepsy and experiencing partial-onset seizures or generalized tonic-clonic seizures. Japanese subjects are participating in this study. The Pharmaceutical and Medical Devices Agency (PMDA) in Japan agreed that the SP0993 protocol should be the pivotal confirmatory study intended for the registration of LCM in Japan as monotherapy treatment in subjects ≥16 years of age with partial-onset seizures with or without secondary generalization. However, as there is no planned assessment on the PK and safety information for LCM 600mg/day in Japanese subjects in SP0993, therefore PMDA required an additional study to obtain further safety information for LCM 600mg/day monotherapy in Japanese subjects.

To fulfill the PMDA requirement, this study EP0057, is a Phase 3, multicenter, open-label study, designed to evaluate the safety, tolerability, and efficacy of long-term administration of LCM as a monotherapy at doses from 200mg/day up to 600mg/day in Japanese adults with partial-onset seizures with or without secondary generalization who are not controlled by a single AED with marketing approval in Japan taken in monotherapy.

3 STUDY OBJECTIVES

3.1 Primary objective

The primary objective of this study is to evaluate the long-term safety and tolerability of LCM 200mg/day to LCM 600mg/day taken in monotherapy in Japanese subjects who currently have partial-onset seizures with or without secondary generalization and who are treated with a single AED with marketing approval in Japan.

3.2 Secondary objective

The secondary objectives are to evaluate the efficacy of LCM, and the plasma concentrations of LCM at steady state.

4 STUDY VARIABLES

4.1 Safety variables

4.1.1 Primary safety variables

The primary safety variables are the following:

- Adverse events reported spontaneously by the subject or observed by the investigator
- Subject withdrawals due to AEs
- Serious adverse events (SAEs)

4.1.2 Other safety variables

The other safety variables include:

- Laboratory tests (hematology, clinical chemistry, and urinalysis parameters)
- 12-lead electrocardiograms (ECGs)
- Vital sign measurements (ie, blood pressure and pulse rate)
- Body weight

4.2 Efficacy variables

Efficacy evaluations will be based on subject diaries where seizure types, dates, and number of seizures are recorded. The exploratory efficacy variables are:

- Proportion of subjects remaining seizure free for 6 consecutive months during the Monotherapy Period.
- Proportion of subjects remaining seizure free for 12 consecutive months during the Monotherapy Period.
- Time to discontinuation is evaluated as time to withdrawal of treatment due to AE or lack of efficacy (LOE) in the Monotherapy Period.

4.3 Pharmacokinetic variable

The PK variable is the following:

- Plasma concentrations of LCM versus time postdose.

5 STUDY DESIGN

5.1 Study description

EP0057 is a Phase 3, multicenter, open-label, study designed to evaluate the safety, tolerability, and efficacy of long-term administration of LCM as monotherapy at doses from 200mg/day to 600mg/day in Japanese adults with partial-onset seizures with or without secondary generalization who are not controlled by monotherapy with an AED with marketing approval in Japan.

The duration of the study per subject is up to 2.5 years, including a 1-week Screening Period and an approximately 2.5-year Treatment Period. The Treatment Period consists of the following: a 4-week forced titration up to LCM 400mg/day (referred to as the Titration Period), a maximum of 12 weeks of tapering off baseline AED (referred to as the AED Withdrawal Period), and a 52-week Evaluation Period where subjects continue with the optimal dose of LCM monotherapy achieved during the periods prior plus a Follow-Up Period (referred to as the Monotherapy Period). The Treatment Period is followed by a 5-week Taper Period.

A Screening Visit (Visit 1) is conducted to evaluate subject suitability for enrollment. This visit can be conducted on more than 1 day but not more than 7 days. Subjects who fulfill all eligibility criteria shall be enrolled.

At the beginning of the 4-week Titration Period, subjects will start with LCM 100mg/day. The dose is increased by 100mg/day each week until the 400mg/day dose is reached at the beginning

of Week 4. Subjects who are unable to tolerate LCM during the Titration Period will be withdrawn from the study.

During the AED Withdrawal Period, concomitant AEDs will be carefully tapered and discontinued within 4 to 12 weeks. To improve tolerability and reduce drug load, tapering of the concomitant AED may be started during the Titration Period. For safety reasons, tapering of the concomitant AED will be at the discretion of the investigator and will be allowed only if the dose of LCM has been stable at 200mg/day or greater for the previous 3 days.

Subjects who complete the AED Withdrawal Period will enter the Evaluation Period. The Evaluation Period lasts for 52-week and continued by a long term Follow-Up Period. The Follow-Up Period will continue until LCM is available on the market as monotherapy in Japan. Both the Evaluation Period and the Follow-Up Period are collectively termed as the Monotherapy Period.

During the AED Withdrawal and Monotherapy Period, the investigator may increase or decrease the dose of LCM to optimize tolerability and seizure control. The LCM dose may be decreased no lower than 200mg/day or increased, no faster than 100mg/day per week, up to 600mg/day.

For subjects receiving LCM at a dose less than 600mg/day at the beginning of the Monotherapy Period who experience a new seizure (first seizure during the Monotherapy Period), the LCM dose will be increased up to 600mg/day by a maximum increment of 100mg/day weekly.

Subjects who are continuing in the Follow-Up Period until LCM is commercially available as monotherapy will complete the End-of-Study Visit assessments. Subjects who prematurely withdraw from the study at any time during the study will complete the Early Withdrawal Visit assessments. All subjects enter the Monotherapy Period and decided to exit will have to enter a Taper Period. During the Taper Period, subjects receiving doses greater than LCM 200mg/day at the Early Withdrawal Visit/End-of-Study Visit should be tapered off gradually at a recommended decrease rate of LCM 200mg/day per week, unless the investigator feels that a more rapid withdrawal of LCM is required due to safety concerns. UCB (or designee) should be contacted if a more rapid withdrawal is required. A slower taper (eg, LCM 100mg/day per week) is permitted, if medically necessary. Subjects receiving doses of LCM 200mg/day or lower at the Early Withdrawal Visit/End-of-Study Visit are not required to taper off LCM. A Final Visit will be required 2 weeks after the last LCM dose is administered. Subjects who continue in the Monotherapy Period until LCM is commercially available as monotherapy in Japan, and decided to continue on commercial LCM are not required to enter the Taper Period, the End-of-Study Visit will be the last visit for these subjects. If LCM is not commercially available in Japan at the time the study closes, access to LCM will be provided according to the laws.

5.1.1 Study duration per subject

EP0057 will continue until the date of the market approval of LCM for the monotherapy indication in Japan or until the time when the sponsor decides to discontinue the development of LCM for the partial-onset seizure monotherapy indication. The expected maximum duration of subject participation is approximately 2.5 years.

5.1.2 Dates of the planned study duration

The study duration is planned from Jan 2014 to the approval date of monotherapy indication in Japan. For subjects who are still participating at the end of the study, LCM will be provided by

UCB until it is commercially available unless UCB has determined that the clinical development program for the monotherapy indication will be formally discontinued.

5.1.3 Planned number of subjects

No formal sample size determination has been performed. A minimum of 10 subjects are anticipated to participate in this study within the enrollment period from Jan 2014 to Dec 2014.

5.1.4 Anticipated regions and countries

All sites will be in Japan.

5.2 Schedule of study assessments

The schedule of study assessments is provided in Table 5–1.

Table 5–1: Schedule of study assessments

	Screening Period	Titration Period (4 wk)		AED Withdrawal Period (4 to 12 wk)		Monotherapy Period						Taper Period		
						Evaluation (52 wk)					Follow Up			
Visit	**1**	**2**	**3**	**4**	**5, 6[a]**	**MPV 1[b]**	**MPV 2**	**MPV 3**	**MPV 4**	**MPV ≥5**	**ESV[c] /EWV[c]**	**ETV**	**Final Visit[d]**	**Unscheduled Visit[e]**
Visit window (days)	±3	-	±3	±7	±7	±14	±14	±14	±14	±14	-	-	-	-
Informed consent	X													
Demographic and epilepsy information	X													
Inclusion/ exclusion criteria	X	X												
Concomitant AED	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication(s)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medical procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical/ procedure history	X													
Complete physical examination	X					X				X[f]	X			

Table 5–1: Schedule of study assessments

	Screening Period	Titration Period (4 wk)		AED Withdrawal Period (4 to 12 wk)		Monotherapy Period						Taper Period		
						Evaluation (52 wk)					Follow Up			
Visit	**1**	**2**	**3**	**4**	**5, 6[a]**	**MPV 1[b]**	**MPV 2**	**MPV 3**	**MPV 4**	**MPV ≥5**	**ESV[c] /EWV[c]**	**ETV**	**Final Visit[d]**	**Unscheduled Visit[e]**
Brief physical examination				X				X		X[f]				X
Vital signs (BP, PR)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight and height[g]	X			X		X		X		X	X			X
Complete neurological examination	X					X				X[h]	X			
Brief neurological examination				X				X		X[h]				X
EEG[i]	X													
MRI/CT[i]	X													
ECG (12-lead)[j]	X		X	X		X		X		X	X		X	X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests	X		X	X	X	X	X	X	X	X	X		X	X
Pregnancy test[k]	X		X	X	X	X	X	X	X	X	X		X	X

Table 5–1: Schedule of study assessments

	Screening Period	Titration Period (4 wk)		AED Withdrawal Period (4 to 12 wk)		Monotherapy Period						Taper Period		
						Evaluation (52 wk)					Follow Up			
Visit	**1**	**2**	**3**	**4**	**5, 6[a]**	**MPV 1[b]**	**MPV 2**	**MPV 3**	**MPV 4**	**MPV ≥5**	**ESV[c] /EWV[c]**	**ETV**	**Final Visit[d]**	**Unscheduled Visit[e]**
LCM plasma concentration			X	X	X	X	X	X	X	X	X			X
Registration	X	X												
Dispense IMP		X	X	X	X	X	X	X	X	X	X[l]			X
IMP return/review			X	X	X	X	X	X	X	X	X	X		X
Dispense subject diary	X	X	X	X	X	X	X	X	X	X	X[l]	X		
Subject diary return/review		X	X	X	X	X	X	X	X	X	X	X	X	X
AE reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AE=adverse event; AED=antiepileptic drug; BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; CT=computed tomography; ECG=electrocardiogram; EEG=electroencephalogram; ESV=End-of-Study Visit; ETV=End-of-Taper Visit; EWV=Early Withdrawal Visit; IMP= investigational medicinal product; LCM=lacosamide; MPV=Monotherapy Period Visit; MRI=magnetic resonance imaging; PR=pulse rate; wk=weeks

[a] At the beginning of AED Withdrawal Period, the baseline AED will be carefully tapered and discontinued within a period of 4 to 12 weeks. For safety reasons, tapering of the baseline AED will be at the discretion of the investigator and will be allowed only if the dose of LCM has been stable at 200mg/day or greater for the previous 3 days.

[b] MPVs will be performed at 13-week intervals.

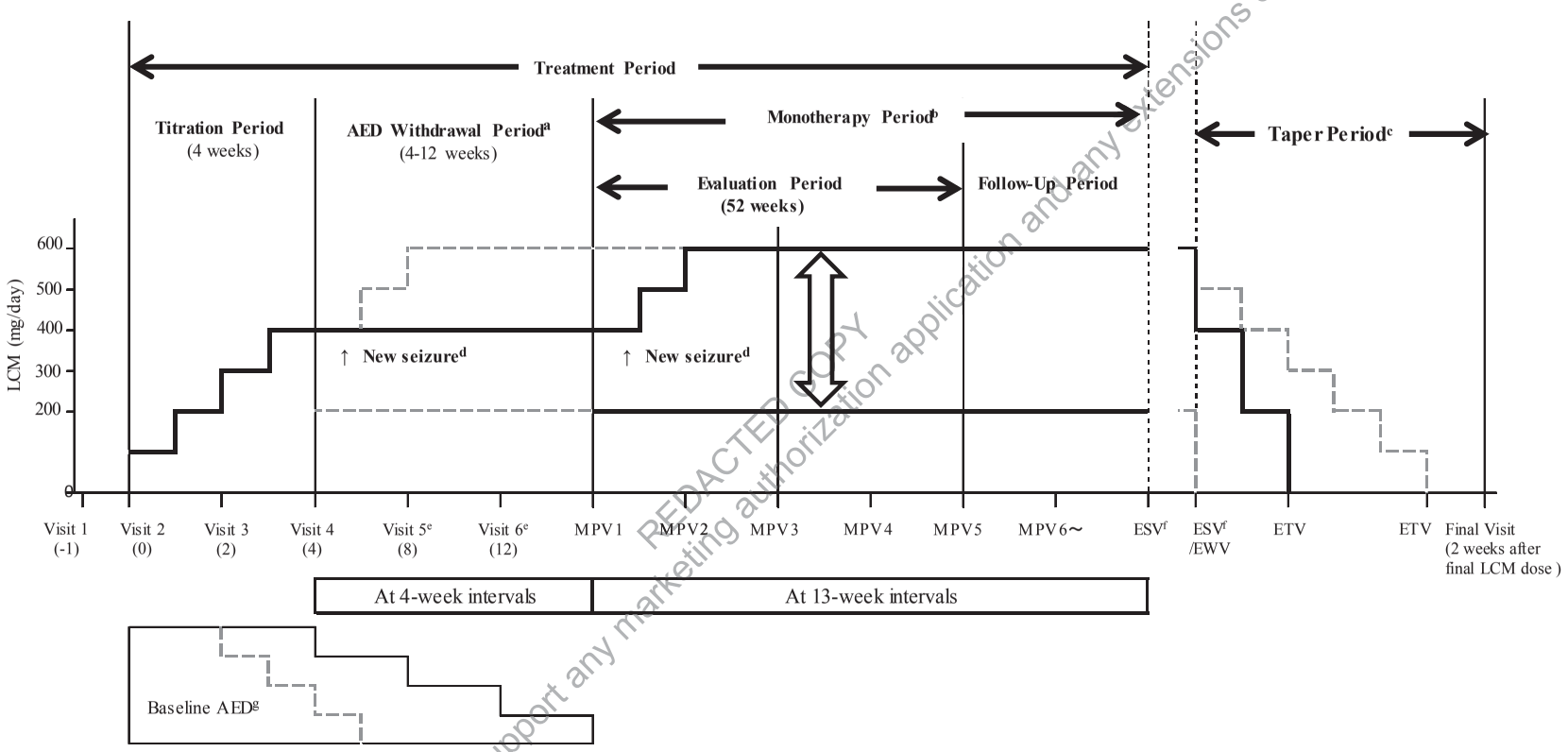
[c] At the time of study completion, or if subjects discontinue the study prematurely, an ESV/EWV will be performed. The ESV is the last visit for subjects who choose to continue on to commercial LCM treatment. Subjects receiving doses greater than LCM 200mg/day at the ESV/EWV should be tapered off gradually at a recommended rate of LCM 200mg/day per week, unless a more rapid withdrawal of LCM due to safety concerns is required. The sponsor should be contacted if the more rapid withdrawal is required. A slower taper (eg, LCM 100mg/day per week) is permitted, if medically necessary.

[d] A Final Visit will be, completed 2 weeks after the last dose of LCM.

[e] The investigator may use an Unscheduled Visit to increase LCM dose if a new seizure occurs, to adjust a subject's LCM dose, to repeat laboratory tests or ECG findings, to follow up on AEs. Additional assessments can be completed as needed at the investigator's discretion.
[f] The complete physical examination will be performed every 52 weeks after MPV 5. The brief physical examination will be performed every 52 weeks after MPV 3.
[g] Height will be recorded at Visit 1 only.
[h] The complete neurological examination will be performed every 52 weeks after MPV 5. The brief neurological examination will be performed every 52 weeks after MPV 3.
[i] Required on Visit 1 if no previous EEG and/or CT/MRI has been performed during the last 24 months prior to Visit 1.
[j] Electrocardiogram (12-lead) examination will be performed Visit 1, Visit 3, Visit 4, and MPV 1, MPV 3, MPV 5 and every 26 weeks after MPV 5, and at the ESV/EWV. If an ECG abnormality is detected at the EWV, an ECG will be performed in the following visit of the Taper Period for safety follow up. If an ECG abnormality is found at the ESV, it will be followed up by postmarketing surveillance.
[k] A serum pregnancy test will be performed at Visit 1. A urine pregnancy test will be performed at each visit where the laboratory assessments are performed.
[l] At ESV, IMP and subject diary will not be dispensed for subjects who complete the Monotherapy Period and choose to continue on to commercial LCM treatment.

5.3 Schematic diagram

Figure 5–1: Schematic diagram



( )= weeks; AED=antiepileptic drug; ESV= End-of-Study Visit; ETV= End-of-Taper Visit; EWV= Early Withdrawal Visit; LCM=lacosaminde; MPV= Monotherapy Period Visit

[a] At the beginning of the AED Withdrawal Period, the baseline AED will be carefully tapered and discontinued during a period of a maximum of 12 weeks. For safety reasons, tapering of the baseline AED will be at the discretion of the investigator and will be allowed only if the dose of LCM has been stable at 200mg/day or greater for the previous 3 days.

[b] In the LCM Monotherapy Period, a flexible dose ranging between 200 and 600mg/day will be used depending on the conditions of individual subjects. During this period, visits will be performed at 13-week intervals.

[c] Subjects receiving doses greater than LCM 200mg/day at the ESV/EWV should be tapered off gradually at a recommended decrease rate of LCM 200mg/day per week, unless the investigator feels that safety concerns require more rapid withdrawal of LCM. A slower taper (eg, LCM 100mg/day per week) is permitted, if medically necessary. Subjects receiving LCM 200mg/day at the ESV/EWV are not required to taper off LCM.

[d] When the subjects receiving LCM at a dose less than 600mg/day at the beginning of the Monotherapy Period/AED Withdrawal Period have a new seizure during the Monotherapy Period/AED Withdrawal Period, the LCM dose will be increased up to 600mg/day. In other cases, the investigator will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure control. The LCM dose may be decreased to a minimum dose of 200mg/day or increased to a maximum dose of 600mg/day in weekly steps of no faster than 100mg/day per week.

[e] During the AED Withdrawal Period, if the concomitant AED withdrawal is reached at the 4th week after Visit 4, Visit 5 and Visit 6 will be canceled. If the concomitant AED is withdrawn within 8 weeks, Visit 6 will be canceled.

[f] The ESV is the last visit for subjects who complete the Monotherapy Period and choose to continue taking commercial LCM. Subjects who complete the Monotherapy Period and choose not to continue taking commercial LCM will complete the ESV and enter a Taper Period.

[g] To improve tolerability and reduce drug load, tapering of the baseline AED may be started during the Titration Period. For safety reasons, tapering of the baseline AED will be at the discretion of the investigator, and will be allowed only if the dose of LCM has been stable at 200mg/day or greater for the previous 3 days.

5.4 Rationale for study design and selection of dose

EP0057 is designed to evaluate the safety, tolerability, and efficacy of long-term administration of LCM as a monotherapy at doses from 200mg/day to 600mg/day in Japanese adults with partial-onset seizures with or without secondary generalization who are not fully controlled by monotherapy with other approved AEDs.

The PMDA in Japan agreed that the SP0993 protocol should be the pivotal confirmatory study intended for the registration of LCM in Japan as monotherapy treatment in subjects ≥16 years of age with partial-onset seizures with or without secondary generalization. However, as there is no planned assessment on the PK and safety information for LCM 600mg/day in Japanese subjects in SP0993, therefore PMDA required an additional study to obtain further safety information for LCM 600mg/day monotherapy in Japanese subjects. In EP0057, LCM will be force-titrated to dose up to 400mg/day. Increasing the dose up to LCM 600mg/day will be at the discretion of the investigator if a new seizure occurs during the AED Withdrawal Period and the Monotherapy Period.

The selection of the LCM dose and regimen for this study, from 200mg/day (100mg twice daily) to 600mg/day (300mg twice daily), is based on SP0993.

The approved dose of LCM as an adjunctive therapy for adult partial epilepsy patients is 200 to 400mg/day in overseas countries, based on the results of 3 major placebo-controlled double-blind comparative studies (SP667, SP754, and SP755). These studies were conducted with forced up-titration in patients taking 2 or 3 concomitant AEDs. LCM 600mg/day was as effective as 400mg/day; 600mg/day was effective but was less well-tolerated due to AEs related to the CNS and gastrointestinal tract with the majority of subjects being treated in parallel with sodium channel blocking antiepileptic drugs causing additive effects on CNS-related side effects. Based on these results, 600mg/day was not deemed to be a recommended dose in adjunctive therapy for partial-onset seizures. Although efficacy was similar for the primary efficacy endpoints in the global partial-onset seizure adjunctive studies, there was evidence of additional benefit of LCM 600mg/day over LCM 400mg/day based on some secondary efficacy endpoints (ie, percentage of seizure-free days and the proportion of subjects becoming seizure free). The median change in percentage of seizure-free days was dose-related with an increase in the median percentage of seizure-free days of 7.4%, 9.3%, and 12.1% in the LCM 200, 400, and 600mg/day groups, compared with 5.4% in the placebo group. These results suggest that compared to placebo, the LCM 400 and 600mg/day doses may provide an additional 33.9 and 44.2 seizure-free days, respectively, over a year of treatment. In addition, among subjects who completed the 12-week Maintenance Phase, a total of 12 subjects (3.3%) and 6 subjects (4.8%) randomized to LCM 400mg/day and LCM 600mg/day, respectively, were seizure free throughout the Maintenance Phase compared with 3 subjects (0.9%) randomized to placebo. It is therefore expected that the 600mg/day dose of LCM as monotherapy will add additional benefit for some of the subjects who need a higher dose than LCM 400mg/day.

The long term safety and efficacy of LCM was reported in SP756, a multicenter, open-label extension study of LCM as adjunctive therapy in subjects with partial-onset seizures who had completed the double-blind study SP754. Lacosamide up to 800mg/day is generally well tolerated over up to a 5-year treatment period when added to up to 3 concomitant AEDs. Eight of 9 subjects maintained on LCM monotherapy for more than 6 months experienced median percent reductions in seizure frequency ranging from 53.6 to100% compared to baseline.

Subsequently, 7 of the 8 subjects on LCM monotherapy for more than 12 months were deemed 50% responders over the entire treatment period. The type of AEs reported were similar to those reported in the previous double-blind LCM adjunctive therapy studies.

The efficacy and safety of LCM as monotherapy in patients with partial-onset seizures was reported in SP902, a historical-controlled, multicenter, double-blind, randomized, conversion to LCM 400mg/day or 300mg/day monotherapy study in subjects with partial-onset seizures. Lacosamide 400mg/day was effective as monotherapy, and LCM 400mg/day and 300mg/day were generally well-tolerated. Based on an exploratory analysis, results for the LCM 300mg/day dose were similar to those for the LCM 400mg/day dose. The type of AEs reported were similar to those reported in the previous LCM adjunctive therapy studies.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Inclusion criteria

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

1. An Institutional Review Board (IRB) approved written Informed Consent form is signed and dated by the subject or by the parent(s) or legal representative. The Informed Consent form or a specific Assent form, where required, will be signed and dated by minors.
2. Subject/legal representative is considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, and medication intake according to the judgment of the investigator.
3. Subject is male or female and ≥16 years of age.
4. Subject has a diagnosis of epilepsy, having experienced unprovoked partial-onset seizures (IA, IB, or IC with clear focal origin) that are classifiable according to the International League Against Epilepsy (ILAE) Classification of Epileptic Seizures, 1981.
5. Subject experiences partial-onset seizures despite appropriately chosen and adequately tried treatment with 1 AED.
6. Subject has been treated for epilepsy with a stable dose of 1 marketed AED. The use of benzodiazepines is permitted as rescue therapy for epilepsy. Benzodiazepines may have been used as needed but not more frequently than once per week.
7. Subject has had an electroencephalogram (EEG) and a brain computed tomography (CT) scan or magnetic resonance imaging (MRI) exam of the brain within the past 24 months. If the EEG and brain CT scan or MRI exam were not performed prior to Visit 1, they need to be completed and results must be available prior to registration at Visit 2.

6.2 Exclusion criteria

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

1. Subject has previously participated in this study or subject has previously been taken LCM in a study.
2. Subject is currently or has in the last 60 days participated in another study of an investigational drug or experimental device.

3. Subject has a history or presence of seizures of other types than partial onset (IA, IB, or IC with clear focal origin).
4. Subject has a history or presence of seizures occurring in clustered patterns, defined as repeated seizures occurring over a short period of time (ie, <20 minutes) with or without function regained between 2 ictal events.
5. Subject has an implanted VNS, deep brain stimulation, or other neurostimulation for epilepsy, device implanted or activated less than 1 year prior to Visit 1, or stimulation parameters that have been stable for less than 3 months, or battery life of unit not anticipated to extend for duration of study.
6. Subject has current or previous diagnosis of pseudoseizures, conversion disorders, or other nonepileptic ictal events that could be confused with seizures based on expert opinion and/or EEG evidence.
7. Subject is taking benzodiazepines for a nonepilepsy indication. (Exception: Concomitant use of benzodiazepines is allowed if the subject is taking them on a regular basis, has been on a stable dose for at least 1 month prior to Visit 1, and does not require changes in the dosage and administration throughout the study period. However, concomitant use of benzodiazepines on an as-needed basis is not permitted.)
8. Subject has a known hypersensitivity to any components of LCM tablets as described in the Investigator's Brochure.
9. Female subject who is pregnant or nursing, and/or a woman of childbearing potential who is not surgically sterile, 2 years postmenopausal or does not practice 1 highly effective method of contraception, unless sexually abstinent, for the duration of the study.

   Female subject of childbearing potential taking enzyme-inducing AEDs (EI-AEDs: CBZ, phenytoin, barbiturates, primidone, topiramate) who is not surgically sterile, 2 years postmenopausal or does not practice 1 highly effective method of contraception according to the WHO recommendation (ie, depot medroxyprogesterone acetate, norethisterone enantate, intrauterine devices, combined injectables, and progestogen implants) with administration of EI-AEDs or does not practice 2 combined methods of contraception (ie, combined hormonal contraception plus barrier method with spermicidal agent), unless sexually abstinent, for the duration of the study.
10. Subject has a medical condition that could reasonably be expected to interfere with drug absorption, distribution, metabolism, or excretion.
11. 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 in this study.
12. Subject has a lifetime history of suicide attempt (including an active attempt, interrupted attempt, or aborted attempt), or has had suicidal ideation in the past 6 months as indicated by a positive response ('Yes') to either Question 4 or Question 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at Screening.
13. Subject has an acute or sub-acutely progressive CNS disease.
14. Subject has a history of alcohol or drug abuse within the last 2 years.

15. Subject has a known history of severe anaphylactic reaction or serious blood dyscrasias.
16. Subject has alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin levels ≥2x the upper limit of normal (ULN) or has alkaline phosphatase levels ≥3xULN at Visit 1.
17. Subject has impaired renal function (ie, creatinine clearance [CLcr] is lower than 30mL/min) at Visit 1. Creatinine clearance will be estimated as follows:

    Adult males: CLcr=(140-age) x weight in kg/(72 x serum creatinine in mg/dL)

    Adult females: CLcr=[(140-age) x weight in kg/(72 x serum creatinine in mg/dL)] x 0.85
18. Subject has sick sinus syndrome without a pacemaker, or a second- or third-degree atrioventricular (AV) block, or subject has any other clinically relevant ECG abnormalities.
19. Subject has a known cardiac sodium channelopathy, such as Brugada syndrome.
20. Subject has experienced a myocardial infarction in the last 3 months.
21. Subject has New York Heart Association Class III or Class IV heart failure (See Table 6–1).

Table 6–1: New York Heart Association Criteria

Class I	Patients with cardiac disease, but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Data source: the Criteria Committee of the New York Heart Association, 1994

22. Subject with concomitant treatment of felbamate for less than 12 months, serious toxicity with prior felbamate, or previous felbamate therapy within the last 6 months prior to study entry.
23. Subject has taken vigabatrin in the preceding 6 months. (Note: A subject with a history of vigabatrin treatment must have had a visual perimetry test at least 6 months following conclusion of treatment. The results of the visual perimetry test must have shown either no damage or a visual field defect associated with 1 of the following 2 conditions: 1) there was no change from a visual field test done at some point while the subject was taking vigabatrin, or 2) there was no change from a visual field test done shortly after stopping vigabatrin administration.

24. Subject has a history of convulsive status epilepticus within the last 12 months prior to Visit 1.

6.3 Withdrawal criteria

Subjects are free to withdraw from the study at any time, without prejudice to their continued care. Investigators should contact the sponsor whenever possible to discuss the withdrawal of a subject in advance. All subjects receiving a dose greater than LCM 200mg/day and discontinuing treatment with LCM for any reason should taper LCM. All subjects who withdraw due to an AE must be followed until resolution of the event or until the event is considered stable.

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

1. Subject develops second- or third-degree AV block, or another clinically relevant change in medical condition (or ECG or laboratory parameter) as determined by the investigator, or if the investigator feels it is in the interest of the subject to withdraw.
2. Request of the sponsor or a regulatory agency.
3. The subject is unwilling or unable to continue and withdraws consent.
4. The subject develops an AE that would interfere with his/her continued participation.
5. In the case of liver function test (LFT) results of transaminases (AST and/or ALT) ≥3xULN to <5xULN and total bilirubin ≥2xULN or transaminases (AST and/or ALT) ≥5xULN, LCM must be immediately discontinued and the subject withdrawn from the study. The LFTs will be repeated as soon as possible, and in no case more than 1 week later.
6. Subject has actual suicidal ideation as indicated by a positive response (Yes) to either Question 4 or Question 5 of the "Since Last Visit" version of the C-SSRS or attempts a suicide. The subject should be referred immediately to a mental healthcare professional.
7. Subject does not discontinue a concomitant AED within ≤ 12 weeks.
8. Subject becomes pregnant as evidenced by a positive pregnancy test.

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

1. The subject requires a medication that is not permitted (see Section 7.8.2).
2. The subject is noncompliant with the study procedures or medications, in the opinion of the investigator.
3. Transaminases (AST, ALT, or both) ≥3xULN to <5xULN, in the presence of normal total bilirubin, will be repeated within a few days. If the repeat testing confirms the abnormality (ie, transaminases are ≥3xULN to <5xULN with normal bilirubin), then weekly monitoring of LFTs should continue until resolved (ie, <3xULN or stable condition). The investigator is to decide whether or not to stop the study medication.
4. Subject is judged as having a LOE at the investigator's discretion.

Investigators should attempt to obtain information on subjects in the case of withdrawal or discontinuation. For subjects considered as lost to follow up, the investigator should make an effort (at least 1 phone call and 1 written message to the subject), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents),

to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the subject, must be recorded in the source documents. The electronic Case Report form (eCRF) must document the primary reason for withdrawal or discontinuation.

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

7 STUDY TREATMENTS

7.1 Description of investigational medicinal product(s)

Lacosamide will be supplied as immediate-release, film-coated tablets at a strength of 50mg (pinkish in color).

7.2 Treatment(s) to be administered

Lacosamide will be orally administered twice daily (once in the morning and once in the evening) in 2 equally divided doses.

At the beginning of the 4-week Titration Period, subjects who meet the eligibility criteria will be started on LCM 100mg/day. The dose is increased by 100mg/day each week until the 400mg/day dose is reached at the beginning of Week 4.

Subjects who are unable to tolerate LCM during the Titration Period will be withdrawn from the study.

At the beginning of the AED Withdrawal Period, the investigator may increase or decrease the dose of LCM to optimize tolerability and seizure control. During the AED Withdrawal Period and Monotherapy Period, the LCM dose may be decreased to a minimum dose of 200mg/day or increased to a maximum dose of 600mg/day in a weekly increment of 100mg/day or less.

For subjects receiving less than LCM 600mg/day at the beginning of the Monotherapy Period who experience new seizure (first seizure during the Monotherapy Period), the LCM dose will be increased up to 600mg/day by a maximum increment of 100mg/day weekly.

Increasing the dose of LCM should be done at a visit (scheduled or unscheduled).

Subjects prematurely withdraw from the study, and subjects complete the study, but decide not to continue on commercial LCM treatment will complete End-of-Study/Early Withdrawal Visit and enter a Taper Period. During the Taper Period, subjects receiving doses greater than LCM 200mg/day at the End-of-Study/Early Withdrawal Visit should be tapered off gradually at a recommended decrease rate of LCM 200mg/day per week (See Table 7–1), unless the investigator feels that more rapid withdrawal of LCM is required due to safety concerns. UCB (or designee) should be contacted if a more rapid withdrawal is required. A slower taper (eg, LCM 100mg/day per week) is permitted, if medically necessary. Subjects receiving doses of LCM 200mg/day or lower at the End-of-Study/Early Withdrawal Visit are not required to taper off LCM. Subjects who do not prematurely withdraw from the study will continue in the study until LCM is commercially available as a monotherapy.

Table 7–1: Recommended LCM taper schedule (Taper Period)

Dose of LCM at End-of-Study/ Early Withdrawal Visit	Taper schedule		
	First week	Second week	Third week
LCM 600mg/day	LCM 400mg/day	LCM 200mg/day	N/A
LCM 500mg/day	LCM 300mg/day	LCM 100mg/day	N/A
LCM 400mg/day	LCM 200mg/day	N/A	N/A
LCM 300mg/day	LCM 100mg/day	N/A	N/A
LCM 200mg/day	N/A	N/A	N/A

LCM=lacosamide; N/A =not applicable (ie, no investigational medicinal product will be administered.)

7.3 Packaging

Lacosamide is manufactured, packaged, and labeled according to Good Manufacturing Practice guidelines and applicable laws or regulations. The investigational medicinal product (IMP) is suitably packaged in such a way as to protect it from deterioration during transport and storage. The IMP will be packaged in bottles.

7.4 Labeling

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

7.5 Handling and storage requirements

The person in charge of IMP is responsible for the safe and proper storage of IMP at the site. Investigational medicinal product is to be kept in a secured area with limited access.

Investigational medicinal product is to be stored according to the instructions on the label.

In case an out-of-range temperature is noted, it must be immediately communicated to the Clinical Project Manager (CPM) (or designee) before further use of the IMP.

The CPM (or designee) will transmit the out-of-range temperature documentation (copy of the temperature log and duration of the out-of-range temperature, if available) to the Clinical Supply Coordinator. Based on assessment by a UCB Temperature Excursion Team, the Clinical Supply Coordinator will then provide the CPM (or designee) with instructions for the site regarding use of the IMP.

The investigator (or designee) will instruct the subject to store the IMP following the instructions on the label.

7.6 Drug accountability

A Drug Accountability form will be used to record IMP dispensing and return information on a by-subject basis and will serve as source documentation during the course of the study. Details of any IMP lost (due to breakage or wastage), not 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 person in charge of IMP is responsible for retaining all used, unused, and partially used containers of IMP until returned or destroyed.

The head of the participating study site 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) and unused IMP containers must be reconciled and returned to UCB (or designee), preferably in their original package. 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 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.

If a subject is found to be persistently noncompliant (less than 75% or more than 125%), 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)

7.8.1 Permitted concomitant AED treatments

Antiepileptic drugs approved for epilepsy in Japan are permitted. The AED is restricted to the subject's initial background AEDs, except for the Taper Period, when they may be used per the investigator's judgment. Antiepileptic drugs containing more than 1 AED compound (ie, combination product) are prohibited.

At the beginning of the AED Withdrawal Period, the concomitant AED will be carefully tapered and discontinued within a period of 4 to 12 weeks. To improve tolerability and reduce drug load, tapering of the concomitant AED may be started during the Titration Period. For safety reasons, tapering of the concomitant AED will be at the discretion of the investigator and will be allowed only if the dose of LCM has been stable at 200mg/day or greater for the previous 3 days.

There are no restrictions for concomitant AED(s) during the Taper Period, considering subjects safety.

7.8.2 Prohibited concomitant treatments (medications and therapies)

The following concomitant medications are prohibited during the study:

- Felbamate and vigabatrin as clarified in exclusion criteria 22 and 23.
- Investigational products and drugs and medical devices that have not been approved in Japan (see exclusion criterion 2).
- Drugs which contain the contraindication for patients with epilepsy in their package inserts.

7.8.3 Restricted concomitant treatments (medications and therapies)

There is no restricted concomitant treatment in this study.

7.8.4 Rescue medication

The use of benzodiazepines as rescue therapy for epilepsy is allowed if taken at a maximum frequency of once per week prior to Visit 1 and during study participation; more frequent use precludes subjects from study participation.

7.9 Blinding

EP0057 is an open-label study; thus, there will be no blinding.

7.10 Randomization and numbering of subjects

Subjects will not be randomized in this study. Each subject will be identified by a unique 3-digit code indicating the study site and a unique 5-digit code indicating the subject.

8 STUDY PROCEDURES BY VISIT

Allowable windows for scheduling visits are as follows:

- A visit window of ±3 days relative to Visit 2 is applicable for Visit 1 and Visit 3. A visit window of ±7 days is applicable for Visit 4 to Visit 6. For subsequent visits, a visit window of ±14 days relative to Monotherapy Period Visit 1 is applicable.

8.1 Screening Period

8.1.1 Visit 1 (Week -1)

Prior to the conduct of any study-related procedures, a complete explanation (both verbal and written) of the nature and purpose of the study will be given to the subject/legal representative by the investigator (or designee). The subject/legal representative is required to sign and date the IRB-approved informed consent if he/she decides to participate in the study, followed by notification to the registration center by the investigator or designee.

At the Screening Visit (Visit 1), subjects will be evaluated for their suitability for enrollment. Screening Visit assessments will be conducted 1 week prior to the first administration of IMP. This assessment can be conducted on more than 1 day, although, it should not be done over a period longer than 7 days.

The subject's eligibility for the study will be determined on the basis of the inclusion/exclusion criteria, signature of an informed consent prior to any study-related procedures or evaluations, and the results of the following pretreatment assessments (for further details of the assessments and the required procedures and methods, please refer to Section 9, Section 10, and Section 11 in this protocol):

- Informed consent
- Check of inclusion/exclusion criteria
- Demographic information recording

- Epilepsy information recording (diagnosis of epilepsy, etiology of epilepsy, ILAE seizure classification, focus localization [see Section 17.1], classification of epileptic syndrome [see Section 17.2], and treatment history)
- Concomitant AED recording
- Concomitant medication(s) recording
- Concomitant medical procedures recording
- Medical/procedure history recording
- Complete physical examination
- Vital signs (blood pressure and pulse rate) measurement
- Body weight and height measurements
- Complete neurological examination
- EEG examination. If not been performed during the last 24 months prior to Visit 1, EEG must be performed prior to Visit 2.
- CT scan/MRI examination. If a CT scan or MRI has not been performed during the last 24 months prior to Visit 1, it has to be performed prior to Visit 2.
- ECG (12-lead) examination
- C-SSRS assessment
- Collection of blood and urine samples for clinical laboratory values (includes hematology, clinical chemistry, and urinalysis)
- Collection of blood sample for pregnancy test (for woman of childbearing potential)
- Registration for screening
- Dispense subject diary
- AE reporting

8.2 Titration Period

8.2.1 Visit 2 (Week 0)

The following will be performed:

- Check of inclusion/exclusion criteria
- Concomitant AED recording
- Concomitant medication(s) recording
- Concomitant medical procedures recording
- Vital signs (blood pressure and pulse rate) measurement
- C-SSRS assessment
- Registration for evaluation

- IMP dispensing
- Subject diary dispensing
- Subject diary return/review
- AE reporting

The subject will take the first dose of IMP in the clinic. The subject will be instructed to call the investigator if any intolerable AEs and/or SAEs occur. If any change in the IMP is required or AEs necessitate a subject's withdrawal from the study, the subject should come in for a clinic visit as soon as possible after the occurrence of the AE.

8.2.2 Visit 3 (Week 2)

The following will be performed:

- Concomitant AED recording
- Concomitant medication(s) recording
- Concomitant medical procedures recording
- Vital signs (blood pressure and pulse rate) measurement
- ECG (12-lead) examination
- C-SSRS assessment
- Collection of blood and urine samples for clinical laboratory values (includes hematology, clinical chemistry, and urinalysis)
- Urine pregnancy testing (for woman of childbearing potential)
- Collection of blood samples for LCM plasma concentration (refer to Section 11)
- IMP dispensing
- IMP return/review
- Subject diary dispensing
- Subject diary return/review
- AE reporting

8.3 AED Withdrawal Period

Subjects who complete the Titration Period enter the AED Withdrawal Period for up to a maximum of 12 weeks.

8.3.1 Visit 4 (Week 4)

The following will be performed:

- Concomitant AED recording
- Concomitant medication(s) recording
- Concomitant medical procedures recording

- Brief physical examination
- Vital signs (blood pressure and pulse rate) measurement
- Body weight measurement
- Brief neurological examination
- ECG (12-lead) examination
- C-SSRS assessment
- Collection of blood and urine samples for clinical laboratory values (includes hematology, clinical chemistry, and urinalysis)
- Urine pregnancy testing (for woman of childbearing potential)
- Collection of blood sample for LCM plasma concentration
- IMP dispensing
- IMP return/review
- Subject diary dispensing
- Subject diary return/review
- AE reporting

8.3.2 Visit 5 and Visit 6 (Week 8 and Week 12)

If the concomitant AED withdrawal is reached at the 4th week after Visit 4, Visit 5 and Visit 6 will be canceled. If the concomitant AED is withdrawn within 8 weeks, Visit 6 will be canceled.

The following will be performed:

- Concomitant AED recording
- Concomitant medication(s) recording
- Concomitant medical procedures recording
- Vital signs (blood pressure and pulse rate) measurement
- C-SSRS assessment
- Collection of blood and urine samples for clinical laboratory values (includes hematology, clinical chemistry, and urinalysis)
- Urine pregnancy testing (for woman of childbearing potential)
- Collection of blood sample for LCM plasma concentration
- IMP dispensing
- IMP return/review
- Subject diary dispensing
- Subject diary return/review

- AE reporting

8.4 Monotherapy Period

At Monotherapy Period Visit 1, concomitant AED should be discontinued. Monotherapy Period consists of the Evaluation Period (Monotherapy Period Visits 1 to Visit 5) and the Follow-Up Period (subsequent visits after Monotherapy Period Visit 5).

8.4.1 Monotherapy Period Visit 1 and Visit 5

The following will be performed:

- Concomitant AED recording
- Concomitant medication(s) recording
- Concomitant medical procedures recording
- Complete physical examination
- Vital signs (blood pressure and pulse rate) measurement
- Body weight measurement
- Complete neurological examination
- ECG (12-lead) examination
- C-SSRS assessment
- Collection of blood and urine samples for clinical laboratory values (includes hematology, clinical chemistry, and urinalysis)
- Urine pregnancy testing (for woman of childbearing potential)
- Collection of blood sample for LCM plasma concentration
- IMP dispensing
- IMP return/review
- Subject diary dispensing
- Subject diary return/review
- AE reporting

8.4.2 Monotherapy Period Visit 2 and Visit 4

The following will be performed:

- Concomitant AED recording
- Concomitant medication(s) recording
- Concomitant medical procedures recording
- Vital signs (blood pressure and pulse rate) measurement
- C-SSRS assessment

- Collection of blood and urine samples for clinical laboratory values (includes hematology, clinical chemistry, and urinalysis)
- Urine pregnancy testing (for woman of childbearing potential)
- Collection of blood sample for LCM plasma concentration
- IMP dispensing
- IMP return/review
- Subject diary dispensing
- Subject diary return/review
- AE reporting

8.4.3 Monotherapy Period Visit 3

The following will be performed:

- Concomitant AED recording
- Concomitant medication(s) recording
- Concomitant medical procedures recording
- Brief physical examination
- Vital signs (blood pressure and pulse rate) measurement
- Body weight measurement
- Brief neurological examination
- ECG (12-lead) examination
- C-SSRS assessment
- Collection of blood and urine samples for clinical laboratory values (includes hematology, clinical chemistry, and urinalysis)
- Urine pregnancy testing (for woman of childbearing potential)
- Collection of blood sample for LCM plasma concentration
- IMP dispensing
- IMP return/review
- Subject diary dispensing
- Subject diary return/review
- AE reporting

8.4.4 Subsequent Visits after Monotherapy Period Visit 5

The following will be performed:

- Concomitant AED recording

- Concomitant medication(s) recording
- Concomitant medical procedures recording
- Complete physical examination (every 52 weeks after Monotherapy Period Visit 5)
- Brief physical examination (every 52 weeks after Monotherapy Period Visit 3)
- Vital signs (blood pressure and pulse rate) measurement
- Body weight measurement
- Complete neurological examination (every 52 weeks after Monotherapy Period Visit 5)
- Brief neurological examination (every 52 weeks after Monotherapy Period Visit 3)
- ECG (12-lead) examination (every 26 weeks after Monotherapy Period Visit 5)
- C-SSRS assessment
- Collection of blood and urine samples for clinical laboratory values (includes hematology, clinical chemistry, and urinalysis)
- Urine pregnancy testing (for woman of childbearing potential)
- Collection of blood sample for LCM plasma concentration
- IMP dispensing
- IMP return/review
- Subject diary dispensing
- Subject diary return/review
- AE reporting

8.4.5 End-of-Study Visit

Subjects continuing LCM monotherapy in the Follow-Up Period, until LCM is commercially available as a monotherapy, will enter End-of-Study Visit. For the subjects who choose to continue on to commercial LCM treatment, the End-of-Study Visit is the last visit. Subjects who choose not to continue on to commercial LCM treatment will enter the Taper Period after the End-of-Study Visit as described in Section 7.2.

The following will be performed:

- Concomitant AED recording
- Concomitant medication(s) recording
- Concomitant medical procedures recording
- Complete physical examination
- Vital signs (blood pressure and pulse rate) measurement
- Body weight measurement
- Complete neurological examination

- ECG (12-lead) examination
- C-SSRS assessment
- Collection of blood and urine samples for clinical laboratory values (includes hematology, clinical chemistry, and urinalysis)
- Urine pregnancy testing (for woman of childbearing potential)
- Collection of blood sample for LCM plasma concentration
- IMP return/review
- Subject diary return/review
- AE reporting

8.5 Early Withdrawal Visit

Subjects who prematurely withdraw at any time during the study must complete the Early Withdrawal Visit. All of these subjects will enter the Taper Period after the Early Withdrawal Visit as described in Section 7.2.

The following will be performed:

- Concomitant AED recording
- Concomitant medication(s) recording
- Concomitant medical procedures recording
- Complete physical examination
- Vital signs (blood pressure and pulse rate) measurement
- Body weight measurement
- Complete neurological examination
- ECG (12-lead) examination
- C-SSRS assessment
- Collection of blood and urine samples for clinical laboratory values (includes hematology, clinical chemistry, and urinalysis)
- Urine pregnancy testing (for woman of childbearing potential)
- Collection of blood sample for LCM plasma concentration
- IMP dispensing (if applicable, refer to Section 7.2)
- IMP return/review
- Subject diary dispensing
- Subject diary return/review
- AE reporting

8.6 Taper Period

For subjects who withdraw prematurely and receive doses greater than LCM 200mg/day, LCM should be tapered off gradually at a recommended decrease rate or 200mg/day per week or according to investigator's discretion (refer to Section 7.2). Subjects who withdraw prematurely and receive doses of LCM 200mg/day or lower are not required to taper LCM.

8.6.1 End-of-Taper Visit

The following will be performed:

- Concomitant AED recording
- Concomitant medication(s) recording
- Concomitant medical procedures recording
- Vital signs (blood pressure and pulse rate) measurement
- C-SSRS assessment
- IMP return/review
- Subject diary dispensing
- Subject diary return/review
- AE reporting

8.6.2 Final Visit (2 weeks after last LCM dose)

For all the subjects entering Taper Period, a Final Visit must be performed 2 weeks after the last LCM dose.

The following will be performed:

- Concomitant AED recording
- Concomitant medication(s) recording
- Concomitant medical procedures recording
- Vital signs (blood pressure and pulse rate) measurement
- ECG (12-lead) examination (only if abnormality is found in Early Withdrawal Visit)
- C-SSRS assessment
- Collection of blood and urine samples for clinical laboratory values (includes hematology, clinical chemistry, and urinalysis)
- Urine pregnancy testing (for woman of childbearing potential)
- Subject diary return/review
- AE reporting

8.7 Unscheduled Visit

An Unscheduled Visit may be performed at the investigator's discretion. Increasing the dose of LCM should be done at a clinic visit.

The following may be performed:

- Concomitant AED(s) recording
- Concomitant medication(s) recording
- Concomitant medical procedures recording
- Brief physical examination
- Vital signs (blood pressure and pulse rate) measurement
- Body weight measurement
- Brief neurological examination
- ECG (12-lead) examination
- C-SSRS assessment
- Collection of blood and urine samples for clinical laboratory values (includes hematology, clinical chemistry, and urinalysis)
- Urine pregnancy testing (for woman of childbearing potential)
- Collection of blood sample for LCM plasma concentration
- IMP dispensing (if applicable; see Section 7.2)
- IMP return/review
- Subject diary return/review
- AE reporting

9 ASSESSMENT OF SAFETY

9.1 Adverse events

9.1.1 Definition of adverse event

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

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the Informed Consent form), including any pretreatment and posttreatment periods required by the protocol, must be reported in the eCRF even if no investigational product 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 investigational product 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.

9.1.2 Procedures for reporting and recording adverse events

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

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

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

9.1.3 Description of adverse events

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

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

9.1.4 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.

If an AE is still 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.

9.1.5 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.

9.1.6 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 Drug Safety (DS) 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 return for an Early Withdrawal Visit.
- The subject should immediately stop the intake of the IMP or the subject's dose should be down-titrated as instructed at the Early Withdrawal Visit.
- A Safety Follow-Up Visit should be scheduled approximately 14 days after the subject has discontinued her IMP.

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 DS 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 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 DS 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 DS department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow-up.

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

9.1.7 Overdose of investigational medicinal product

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

9.1.8 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 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 DS 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.

9.2 Serious adverse events

9.2.1 Definition of serious adverse event

Once it is determined that a subject experienced an AE, the seriousness of the AE must be determined. An 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 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 preexisting 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 preexisting

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.)

9.2.2 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 SAE 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.

9.2.3 Follow up of serious adverse events

An SAE 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.

Information on SAEs obtained after clinical database lock will be captured through the DS database without limitation of time.

9.3 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. The procedure for reporting AEs of special interest is the same as that of SAEs (see Section 9.2.2).

The following are AEs of special interest:

- The following arrhythmias: atrial fibrillation/flutter, ventricular tachycardia or fibrillation, AV block (second-degree, Type I and II, and third-degree), and marked bradycardia (<45 beats/min)
- Syncope or loss of consciousness (other than seizure related)
- Serious suspected multiorgan hypersensitivity reactions
  Serious suspected multiorgan hypersensitivity cases may be identified and reported to the sponsor by the investigator using the following algorithm as agreed with the United States Food and Drug Administration:

  An AE or laboratory value (as defined in the following text) suggestive of internal organ involvement (including but not limited to hepatitis, nephritis, pneumonitis, carditis, colitis, encephalitis, pancreatitis, myositis, arthritis, or hematologic system involvement) combined with at least 1 of the following: fever, rash, lymphadenopathy, or eosinophilia.
  Treatment-emergent abnormal laboratory value criteria suggestive of internal organ involvement or eosinophilia:

  – Eosinophils % ≥10%
  – Eosinophils absolute ≥0.5G/L
  – Neutrophils absolute <1.5G/L
  – Platelets ≤100G/L
  – ALT ≥2xULN
  – AST ≥2xULN

9.4 Immediate reporting of adverse events

The following AEs must be reported immediately:

- SAE: AE that the investigator classifies as serious by the above definitions regardless of causality
- Suspected transmission of an infectious agent via a medicinal product
- AE of special interest (see Section 9.3)

9.5 Anticipated serious adverse events

The following list of Anticipated SAEs has been identified, as these events are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure. This original list will remain in effect for the duration of the protocol.

This list does not change the investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 9.2.2.

Table 9–1: Anticipated serious adverse events for the adult epileptic population

MedDRA SOC	MedDRA PT
Congenital, familial and genetic disorders	Teratogenicity

Table 9–1: Anticipated serious adverse events for the adult epileptic population

MedDRA SOC	MedDRA PT
General disorders and administration site conditions	Sudden unexplained death in epilepsy
Nervous system disorders	Convulsion
	Incontinence
	Status epilepticus
Pregnancy, puerperium and perinatal disorders	Abortion spontaneous
Psychiatric disorders	Psychotic behaviour
	Abnormal behaviour
	Anxiety
	Sleep disorder
Reproductive system and breast disorders	Menstrual disorder
	Impotence

MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class

9.6 Laboratory measurements

Blood and urine specimens for routine assay of hematology, clinical chemistry, and urinalysis testing will be collected according to the tabular schedule of study procedures, see Section 5.2. A central laboratory will perform the routine analysis of blood and urine specimens. The procedures for handling and shipping these specimens will be provided to the sites.

The following laboratory parameters will be measured:

Table 9–2: Laboratory measurements

Hematology	Chemistry	Urinalysis
Hematocrit Hemoglobin Platelet count RBC count WBC count Differential count	Calcium Phosphorus Serum electrolytes (sodium, potassium, chloride, bicarbonate) Glucose Albumin Total serum protein BUN Creatinine Uric acid Alkaline phosphatase AST ALT GGT Total bilirubin	Specific gravity pH Albumin Glucose Ketones Microscopic exam for blood cells or casts/hpf

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT=gamma glutamyltransferase; hpf=high power field; RBC=red blood cell; WBC=white blood cell

9.6.1 Liver function tests

Refer to Section 6.3 for LFT withdrawal criteria.

Transaminases (AST, ALT, or both) ≥3xULN but <5xULN, in the presence of total bilirubin ≥2xULN, or transaminases (AST, ALT, or both) ≥5xULN will result in immediate discontinuation of LCM and withdrawal of the subject from the study. The LFTs will be repeated as soon as possible, and in no case more than 1 week later.

Transaminases (AST, ALT, or both) ≥3xULN to <5xULN, in the presence of normal total bilirubin, will be repeated within a few days. If the repeat testing confirms the abnormality (ie, transaminases are ≥3xULN to <5xULN with normal bilirubin), then weekly monitoring of LFTs should continue until resolved (ie, <3xULN or stable condition). The investigator is to decide whether or not to stop the IMP.

In all cases of transaminases (AST, ALT, or both) ≥3xULN, testing for hepatitis A, B, and C will be done.

Referral to a specialist (ie, hepatologist or gastroenterologist) is at the discretion of the investigator. This is recommended especially if the transaminase abnormalities >3xULN persist after discontinuation of the IMP.

9.6.2 Pregnancy tests

Females of childbearing potential (who have not been surgically sterilized or who are not at least 2 years postmenopausal) will have serum and urine dipstick pregnancy testing performed according to the tabular schedule of study procedures, Section 5.2. Serum pregnancy testing will be performed by the central laboratory, and urine pregnancy testing will be performed at the study site.

9.7 Other safety measurements

9.7.1 Physical examination

The physical examination will be performed by a medically qualified clinician licensed to perform the examination, according to the tabular schedule of study procedures, Section 5.2. Clinically significant physical examination findings are to be reported as AEs.

9.7.1.1 Complete physical examination

The complete physical examination includes cardiac and respiratory function via auscultation, temperature, and review of all body systems.

9.7.1.2 Brief physical examination

The brief physical examination will include review of the following body systems:

- Cardiovascular
- Pulmonary
- Abdominal (hepato-gastrointestinal)
- Dermatologic

9.7.2 Neurological examination

Neurological examinations will be performed by a medically qualified clinician with documented training in the conduct of neurological examinations, according to the tabular schedule of study procedures, Section 5.2. If possible, the same clinician should conduct all neurological examinations for the same subject during the study. Clinically significant neurological examination findings are to be reported as AEs.

9.7.2.1 Complete neurological examination

The complete neurological examination will include selected assessment of: general (level of consciousness, mental status, speech), cranial nerves, reflexes, motor system (general, muscle strength, muscle tone), coordination/cerebellar function, and sensation.

9.7.2.2 Brief neurological examination

The brief neurological examination will include selected assessment of: general, reflexes, muscle strength, and coordination/cerebellar function.

9.7.3 Vital signs, body weight, and height

Noninvasive pulse rate, systolic blood pressure, and diastolic blood pressure will be measured at clinic visits with the subject in a sitting position after at least 3 minutes at rest, according to the tabular schedule of study procedures, Section 5.2. Body weight will be determined without shoes

and wearing light clothing, and height will be measured without shoes. Body weight and height will be assessed according to the tabular schedule of study procedures, Section 5.2.

9.7.4 12-lead ECG

Standard 12-lead ECGs will be performed according to the tabular schedule of study procedures, Section 5.2. At any visits during which EEG recording and blood sample collection also take place, the 12-lead ECG recording should be performed at least 15 minutes after removal of scalp electrodes used for EEG recording and prior to blood sample collection. Care should be taken to assure proper lead placement and quality ECG recordings. Subjects should rest in a supine position at least 5 minutes prior to each recording and should be motionless during the recording.

9.7.4.1 Overall ECG interpretation

Electrocardiograms will be initially reviewed locally by the investigator, subinvestigator, or qualified designated reader. If this reading identifies abnormal ECG findings that are assessed by the investigator or subinvestigator to be clinically significant, then the ECG should be repeated in 1 hour. If the clinically significant abnormality is confirmed by the repeat ECG, then the subject must be withdrawn from the study (Withdrawal Criteria, Section 6.3). The investigator may consult with the cardiologist at the central ECG lab (see Section 9.7.4.2) as needed to confirm the presence of a clinically significant ECG abnormality. It remains the responsibility of the investigator to decide whether an ECG finding is of clinical significance on the basis of the complete clinical picture and whether this finding influences the subject's participation in the study.

9.7.4.2 Central ECG laboratory

All ECGs will be transmitted to and evaluated by a central ECG laboratory. Each ECG will be interpreted and reviewed by a qualified cardiologist. The results of this over-read will be entered into the study database and a report will be transmitted to the study investigator. The cardiologist at the central ECG laboratory will be available to consult with study investigators on the interpretation of individual subject ECG recordings as needed.

9.7.5 Assessment of suicidality

Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2008). This scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. The Japanese translations of the C-SSRS will be listed in a separate document. The C-SSRS will be completed according to the tabular schedule of study procedures; see Section 5.2. Suicidal ideation and behavior are to be reported as AEs.

10 ASSESSMENT OF EFFICACY

10.1 Methods for assessing efficacy variables

The seizure-free days will be measured using data obtained from a subject diary.

Subjects will keep a diary to record the daily seizure activity from Visit 1 until the last visit, recording both seizure type and seizure frequency. The seizure records will be checked by the investigator with regards to correct and thorough daily completion by the subject, and to determine if a dose escalation is required.

11 ASSESSMENT OF PHARMACOKINETIC VARIABLE

Blood specimens for steady state plasma concentrations of LCM will be collected along with hematology samples (if applicable) at any time after intake of LCM according to the schedule of study assessments (See Table 5–1). The exact time the subject took the most recent doses of LCM and the exact time of blood sampling must be recorded in the eCRF.

The procedures for handling and shipping these specimens will be provided to the sites.

12 STUDY MANAGEMENT AND ADMINISTRATION

12.1 Adherence to protocol

The investigator should not deviate from the protocol. In medical emergencies, the investigator may use his/her medical judgment and may remove a study participant from immediate hazard before notifying UCB (or its representative) and the IRB in writing regarding the type of emergency and the course of action taken.

12.2 Monitoring

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

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

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

12.2.1 Definition of source data

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

Source documents are original records in which raw data are first recorded. These may include source data documentation for the eCRF, hospital/clinic/general practitioner records (including a copy of the records), subject diaries, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, completed scales, or quality of life questionnaires, for example. Source documents should be kept in a secure, limited access area.

The following data will be recorded directly in the eCRF and will not appear in a source document as defined above.

- Racial group and ethnicity
- Reasons for discontinuation of previous AED treatment

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

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

12.2.2 Source data verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (eg, subject files, recordings from automated instruments, tracings [ECG], x-ray films, laboratory notes). All data reported on the eCRF should be supported by source documents, unless otherwise specified in Section 12.2.1.

12.3 Data handling

12.3.1 Case Report form completion

The study is performed using electronic data capture. The investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRFs and in all required reports.

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

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

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

Detailed instructions will be provided in the eCRF Completion Guidelines.

12.3.2 Database entry and reconciliation

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

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.

12.3.3 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.

12.4 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 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 study drug and other material in accordance with UCB procedures for the study.

12.5 Archiving and data retention

The investigator will maintain adequate records for the study, including eCRFs, 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 10 years after the formal discontinuation of this study. 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]). It is the responsibility of UCB (or designee) to inform the investigator as to when the documents should no longer be retained. 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.

12.6 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 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).

12.7 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.

13 STATISTICS

A description of statistical methods follows and will be described in more detail in the Statistical Analysis Plan, which will be finalized before the database is locked.

13.1 Definition of analysis sets

The primary analysis set will be the Safety Set (SS) and will include all enrolled subjects who took at least 1 dose of LCM.

The analysis set for the efficacy variables will be the Full Analysis Set (FAS) and will include all subjects in the SS having at least 1 seizure diary assessment.

13.2 General statistical considerations

All tables, listings and figures will be generated using SAS version 9.2 (or higher).

Descriptive statistics will be used to provide an overview of the safety and efficacy results. For categorical parameters, the number and percentages of subjects in each category will be presented. The denominator for percentage will be based on the number of subjects appropriate for the purpose of analysis. For continuous parameters, descriptive statistics will include n, mean, standard deviation (SD), median, minimum, and maximum.

Baseline values for safety and efficacy variables will be based on the Visit 1 and/or Visit 2 assessments or the last nonmissing data collected prior to the first dose of IMP, unless otherwise noted.

Subjects who prematurely withdraw from the study will be evaluated based on the data collected at each visit attended.

13.3 Planned safety analyses

All safety analyses will be performed on the SS.

13.3.1 Analysis of the primary safety variables

Primary safety variables to be assessed are AEs, subject withdrawals due to AEs, and SAEs.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Summary tables for number and percentage of subjects reporting at least 1 treatment-emergent AE (TEAE) by system organ class and preferred term will be presented. A TEAE is defined as the AE that has onset or worsened on or after the date of first dose of LCM and within 30 days of the last dose of LCM. Similar tables may be generated for TEAEs that are considered "drug-related" by the investigator. In addition, a summary table of TEAEs by intensity may be generated.

Treatment-emergent AEs that lead to early withdrawal from the study and treatment-emergent SAEs will be tabulated. Treatment-emergent AEs will be presented separately for the Treatment and Taper Periods.

13.3.2 Other safety variables

Measurements and changes from Baseline in continuous laboratory parameters in hematology, clinical chemistry, and urinalysis, ECGs (12-lead), vital signs (ie, blood pressure and pulse rate), and body weight will be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum). 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-Baseline status when compared to their Baseline status.

13.4 Planned efficacy and other analyses

13.4.1 Efficacy analyses

Efficacy analyses will be performed for exploratory purposes. All efficacy analyses will be done for the FAS.

The number and percentages of subjects achieving 6 months and 12 months of continuous seizure freedom in the Monotherapy Period will be presented for the FAS.

Time to withdrawal of treatment due to AEs or LOE will be presented using Kaplan-Meier method for the SS.

13.4.2 Pharmacokinetics analysis

Lacosamide plasma concentrations will be summarized using the SS.

Descriptive statistics of LCM plasma concentrations will be presented by visit and actual dose. The following parameters will be calculated for each of the sampling points: n, nLOQ (number of measurements equal to or above the lower limit of quantification [LOQ]), arithmetic mean, SD, coefficient of variation (CV), median, minimum, and maximum value.

Values below LOQ will be replaced by 0 in calculations of mean, SD, CV(%) and median. Mean, SD and CV(%) will only be calculated if at least 2/3 of the data are above LOQ at the respective time point. In tables showing mean values, where values below LOQ are included in the calculation of mean values, these means will be marked.

A listing of LCM plasma concentration data by subject and visit will include actual doses, date and time of sampling, visit, relative day, and the accession number. Samples that were excluded from the descriptive statistics will be marked in the listing.

13.5 Handling of protocol deviations

After all eCRFs have been retrieved and entered, all queries issued and answered to the extent possible, and prior to the database snapshot/lock, Important protocol deviations (ie, those considered to have an impact on, eg, primary safety parameters or study conduct) will be identified and reviewed at ongoing data cleaning and protocol deviations meetings.

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on either primary efficacy outcome or key safety outcomes for an individual

subject. The criteria for identifying important protocol deviations and the classification of important protocol deviations will be defined within the project Data Cleaning Plan. To the extent feasible, rules for identifying protocol deviations will be defined without review of the data and without consideration of the frequency of occurrence of such deviations. Whenever possible, criteria for identifying important protocol deviations will be implemented algorithmically to ensure consistency in the classification of important protocol deviations across all subjects.

Important protocol deviations will be reviewed as part of the blinded Data Evaluation Meetings prior to database snapshot/lock to confirm exclusion from analysis sets. Data Evaluation Meetings are conducted by a panel consisting of the CPM, the study biostatistician, study physician, a representative of the monitoring team, and other appropriate team members according to the specification of the protocol deviations, which will be defined prior to the database snapshot/lock.

13.6 Handling of dropouts or missing data

Subjects who prematurely withdraw from the study will be evaluated base on the data collected at each visit attended.

Subjects who prematurely withdraw from the study that are not due to AEs or LOE will be censored as of the last dose of LCM in time to withdrawal analysis.

No imputation of missing values is planned for the safety and efficacy analyses, with the exception of partial date information for AEs and concomitant medications in order to determine whether they are treatment emergent.

13.7 Planned interim analysis and data monitoring

No interim analysis is planned.

13.8 Determination of sample size

Inferential analysis is not planned. No formal sample size calculation has been performed.

14 ETHICS AND REGULATORY REQUIREMENTS

14.1 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 review, and regulatory inspection.

If the Informed Consent form is amended during the study, the investigator (or the sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended Informed Consent form by the IRB and use of the amended form.

The subject may withdraw his/her consent to participate in the study at any time. A subject is considered as enrolled in the study when he/she has signed the Informed Consent form. An eCRF must not be started, nor may any study specific procedure be performed for a given subject, without having obtained his/her written consent to participate in the study.

14.2 Subject identification cards

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

14.3 Institutional Review Boards and Independent Ethics Committees

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

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

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

The investigator will also promptly report to the IRB all changes in the study, all unanticipated problems involving risks to 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 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 as allowed.

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

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

14.4 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, 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).

14.5 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, and the regulatory authorities (if required), prior to being implemented.

15 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.

15.1 Insurance

If any study-related injuries occur in a subject, the sponsor assumes responsibility for all the injuries and makes compensation available to the subject, except for the case that has been proved that the injury was caused by intentional tort or serious mistake of the participating investigator(s)/study site(s) in a study or intentional tort or serious mistake of the subject himself/herself. The sponsor should explain this in advance to the investigator(s)/study site(s) as well as taking necessary measures, including joining some insurance to secure the responsibility. The sponsor should also tell the subject to inform the investigator(s) immediately if any study related injuries occur. If the investigators receive a report of study-related injuries from the subject, the investigator(s) should give necessary treatment immediately, as well as informing the sponsor. The compensation/indemnification of the health injuries of the subject will be made in accordance with the provisions of the clinical study contract.

15.2 Publication

The investigators should not disclose unpublished data provided by the sponsor to any third party without prior written consent of the sponsor.

When disclosing any information about the study (method and results of study, etc) or information on the investigational product or development, the investigators should obtain prior approval of the sponsor for the contents of a manuscript to be published and other materials. The sponsor will respond to requests for permitting publication accordingly and will not postpone the permission without any justification.

16 REFERENCES

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17 APPENDICES

17.1 International Classification of Epileptic Seizures (1981)

International Classification of Epileptic Seizures (1981)

I. Partial seizures (focal, local)

A. Simple partial seizures (consciousness not impaired)

1. With motor signs
   a) Focal motor without march
   b) Focal motor with march (Jacksonian)
   c) Versive
   d) Postural
   e) Phonatory (vocalization or arrest of speech)
2. With somatosensory or special sensory symptoms (simple hallucinations, eg, tingling, light flashes, buzzing)
   a) Somatosensory
   b) Visual
   c) Auditory
   d) Olfactory
   e) Gustatory
   f) Vertiginous
3. With autonomic symptoms or signs (including epigastric sensation, pallor, sweating, flushing, piloerection, and pupillary dilatation)
4. With psychic symptoms (disturbance of higher cerebral function). These symptoms rarely occur without impairment of consciousness and are much more commonly experienced as complex partial seizures.
   a) Dysphasic
   b) Dysmnesic (eg, déjà-vu)
   c) Cognitive (eg, dreamy states, distortions of time sense)
   d) Affective (fear, anger, etc.)
   e) Illusions (eg, macropsia)
   f) Structured hallucinations (eg, music, scenes)

B. Complex partial seizures (with impairment of consciousness: may sometimes begin with simple symptomatology)

1. Simple partial onset followed by impairment of consciousness
   a) With simple partial features followed by impaired consciousness (A.1. - A.4.)

b) With automatisms

2. With impairment of consciousness at onset

a) With impairment of consciousness only

b) With automatisms

C. Partial seizures evolving to secondarily generalized seizures (this may be generalized tonic-clonic, tonic, or clonic)

1. Simple partial seizures (A) evolving to generalized seizures
2. Complex partial seizures (B) evolving to generalized seizures
3. Simple partial seizures evolving to complex partial seizures evolving to generalized seizures

II. Generalized seizures (convulsive or non-convulsive)

A. 1. Absence seizures

a) Impairment of consciousness only

b) With mild clonic components

c) With atonic components

d) With tonic components

e) With automatisms

f) With autonomic components

(b through f may be used alone or in combination)

2. Atypical absence

May have:

a) Changes in tone that are more pronounced than in A.1

b) Onset and/or cessation that is not abrupt

B. Myoclonic seizures **- Myoclonic jerks (single or multiple)**

C. Clonic seizures

D. Tonic seizures

E. Tonic-clonic seizures

F. Atonic seizures - (Astatic)

(combinations of the above may occur, eg, B and F, B and D)

III. Unclassified epileptic seizures

Includes all seizures that cannot be classified because of inadequate or incomplete data and some that defy classification in hitherto described categories. This includes some neonatal seizures, eg, rhythmic eye movements, chewing, and swimming movements.

Status epilepticus (prolonged partial or generalized seizures without recovery between attacks)

Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia. 1981;22:489-501.

17.2 International Classification of Epilepsies and Epileptic Syndromes (1989)

International Classification of Epilepsies and Epileptic Syndromes (1989)

1. Localization-related (focal, local, partial) epilepsies and syndromes

1.1 Idiopathic (with age-related onset)

- Benign childhood epilepsy with centrotemporal spike
- Childhood epilepsy with occipital paroxysms
- Primary reading epilepsy

1.2 Symptomatic

- Chronic progressive epilepsia partialis continua of childhood (Rasmussen syndrome)
- Syndromes characterized by seizures with specific modes of precipitation
- Temporal lobe epilepsy
- Frontal lobe epilepsy
- Parietal lobe epilepsy
- Occipital lobe epilepsy

1.3 Cryptogenic

2. Generalized epilepsies and syndromes

2.1 Idiopathic (with age-related onset – listed in order of age)

- Benign neonatal familial convulsions
- Benign neonatal convulsions
- Benign myoclonic epilepsy in infancy
- Childhood absence epilepsy (pyknolepsy)
- Juvenile absence epilepsy
- Juvenile myoclonic epilepsy (impulsive petit mal)
- Epilepsy with grand mal (GTCS) seizures on awakening
- Other generalized idiopathic epilepsies not defined above
- Epilepsies with seizures precipitated by specific modes of activation

2.2 Cryptogenic or symptomatic (in order of age)

- West syndrome (infantile spasms, Blitz-Nick-Salaam Krämpfe)
- Lennox-Gastaut syndrome
- Epilepsy with myoclonic-astatic seizures

- Epilepsy with myoclonic absences

2.3 Symptomatic

2.3.1 Non-specific etiology

- Early myoclonic encephalopathy
- Early infantile epileptic encephalopathy with suppression-burst
- Other symptomatic generalized epilepsies not defined above

2.3.2 Specific syndromes

3. Epilepsies and syndromes undetermined whether focal or generalized

3.1 With both generalized and focal seizures

- Neonatal seizures
- Severe myoclonic epilepsy in infancy
- Epilepsy with continuous spikes-waves during slow wave sleep
- Acquired epileptic aphasia (Landau-Kleffner-syndrome)
- Other undetermined epilepsies not defined above

3.2 Without unequivocal generalized or focal features

4. Special syndromes

4.1 Situation-related seizures (Gelegenheitsanfälle, Occasional seizures)

- Febrile convulsions
- Isolated seizures or isolated status epilepticus
- Seizures occurring only when there is an acute metabolic or toxic event due to factors such as alcohol, drugs, eclampsia, nonketotic hyperglycemia

Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia. 1989;30:389-99.

18 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