PROTOCOL EP0009 AMENDMENT 2

A MULTICENTER, OPEN-LABEL, UNCONTROLLED, LONG-TERM, EXTENSION STUDY TO EVALUATE THE SAFETY AND EFFICACY OF LACOSAMIDE AS ADJUNCTIVE THERAPY IN JAPANESE AND CHINESE 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	06 Mar 2012	Not applicable
Protocol Amendment 1	12 Sep 2012	Nonsubstantial
Protocol Amendment 2	13 Mar 2013	Nonsubstantial

Confidential Material

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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LIST OF ABBREVIATIONS

AE(s)	adverse event(s)
AED(s)	antiepileptic drug(s)
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AV	atrioventricular
CDMS	clinical data management system
CPM	Clinical Project Manager
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
eCRF	Electronic Case Report form
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
IVRS	interactive voice response system
IWRS	interactive web response system
LCM	lacosamide
LFT	liver function test
MedDRA®	Medical Dictionary for Regulatory Activities
PCH	the percent change in seizure frequency per 28 days
PK	pharmacokinetics
PRC	People's Republic of China
SAE	serious adverse event
SD	standard deviation
SOP(s)	Standard Operating Procedure(s)
SS	Safety Set
TEAE(s)	treatment-emergent adverse event(s)
ULN	upper limit of normal
VNS	vagus nerve stimulation

WHO	World Health Organization

1 SUMMARY

EP0009 is a Phase 3, multicenter, open-label, uncontrolled, extension study designed to evaluate the safety, tolerability, and efficacy of long-term administration of lacosamide (LCM; SPM 927; previously referred to as harkoseride; (R)-2-acetamido-N-benzyl-3-methoxypropionamide, ADD 234037) as adjunctive therapy at doses up to LCM 400mg/day in Japanese and Chinese adults with partial-onset seizures with or without secondary generalization who have completed the Treatment and Transition Periods of EP0008 and chose to enroll in EP0009.

The duration of EP0009 will be until the date of approval in each country or until the time when the sponsor decides to discontinue the development of LCM for the partial-onset seizure indication. The expected duration of subject participation is approximately 3 years following Visit 1.

EP0009 consists of a Treatment Period and, if applicable, a Taper Period. Visit 1 of EP0009 is the same as the Final Visit of EP0008. Visits 2 through 4 of EP0009 will occur at 4-week intervals relative to the date of Visit 1. Beginning with Visit 5, each visit will occur at 12-week intervals relative to the date of Visit 1 until the End-of-Study/Withdrawal Visit. At the end of Treatment Period, an End-of-Study Visit will be required. If subjects prematurely withdraw from the study, a Withdrawal Visit will be required. Subjects who complete the Treatment Period and choose not to continue on to commercial LCM treatment or subjects who withdraw during the study will enter the Taper Period and will be required to taper off LCM. These subjects will return 2 weeks after the final LCM dose for a Final Visit. Subjects who complete the Treatment Period and choose to continue on to commercial LCM treatment are not required to enter the Taper Period to taper off LCM or to return for a Final Visit; the End-of-Study Visit will be the last visit for these subjects. If LCM is not commercially available in a subject's country at the time the study closes, access to LCM will be provided according to local laws.

At the completion of EP0008, all subjects who choose to enroll in EP0009 will be taking a dose of LCM 200mg/day. During the EP0009 Treatment Period, the investigator will be allowed to increase or decrease the doses of LCM and/or up to 3 concomitant antiepileptic drugs (AEDs) to optimize tolerability and seizure reduction for each subject. The LCM dose may be decreased to 100mg/day or increased up to 400mg/day. Changes in concomitant AED(s) will be allowed only if the LCM dose has been stable for the previous 4 weeks; LCM dose must remain stable during changes to concomitant AED(s).

The primary safety variables include adverse events (AEs), reported spontaneously by the subject or observed by the investigator, and subject withdrawals due to AEs. Other variables to be assessed include efficacy (Section 4.2) and additional measures of safety (Section 4.1.2).

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

approximately 50 million people worldwide were diagnosed with epilepsy in 2009 (WHO, 2009).

In Japan, the number of patients with epilepsy is estimated to be approximately 219,000 (Ministry of Health, Labour and Welfare, Patient Survey, 2009). In addition, epidemiologically, epilepsy accounts for 0.5% to 1% of the population (Inoue, 2005). There also is a report that the total number of patients with epilepsy in Japan is estimated to be approximately 1 million people (Ueda, 2007). In China, the prevalence of epilepsy is around 700/100,000, with an annual incidence of 28.8/100,000. It is estimated that there are currently around 9,000,000 patients with epilepsy in China, with approximately 400,000 new patients every year (Chinese Medical Association, 2007).

Most patients with epilepsy require appropriate pharmacological therapy (Perucca, 1996). In the past decade, several new 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 pharmacokinetic (PK) characteristics (Herman and Pedley, 1998). However, more than 30% of patients have inadequate seizure control on 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, 2009).

Lacosamide belongs to a novel class of functionalized amino acids. It was first approved by the European Medicines Agency in 2008 and is indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization 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, including the US, Australia, and Canada. 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.

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.

The clinical development program for LCM includes clinical studies that evaluate efficacy and safety of LCM as adjunctive oral (tablet) therapy in adult subjects with partial-onset seizures. This includes 3 completed primary double-blind, placebo-controlled studies (SP667, SP754, and SP755), 1 completed supporting study (SP607), 3 completed long-term safety and efficacy studies (SP615, SP756, and SP774), and 1 completed long-term safety study (SP926).

Three double-blind, placebo-controlled, multicenter studies (SP667, SP754, and SP755) established the efficacy of oral tablet LCM 200mg/day (SP667 and SP755 only),

LCM 400mg/day, and LCM 600mg/day (SP667 and SP754 only) as adjunctive therapy (1 to 3 concomitant AEDs) in subjects with uncontrolled partial-onset seizures. In pooled analyses of these 3 studies, the most frequently reported AEs were central nervous system- and gastrointestinal-related events. The onset of these occurred commonly during the Titration Period, and the frequency of these AEs was dose-related. Comprehensive evaluation of clinical laboratory results and vital signs measurements did not reveal any issues of clinical concern. There was no increase in QTc interval on the ECG, however an important identified risk was a small dose-related increase in PR interval. Thus, LCM should be used with caution in patients with known conduction problems or severe cardiac disease such as a history of myocardial infarction or heart failure. Subjects randomized to LCM 600mg/day were less likely to tolerate this dose (compared with subjects randomized to LCM 400mg/day) because of central nervous system- and gastrointestinal-related AEs.

The pooled analyses of the clinical studies that evaluated the efficacy and safety of LCM as adjunctive oral (tablet) therapy in adult subjects with partial-onset seizures (SP607, SP615, SP667, SP754, SP755, SP756, and SP774) show that LCM is an effective long-term (>12 months) adjunctive treatment for subjects with partial-onset seizures, and no new types of treatment-emergent adverse events (TEAEs), considered related to LCM, emerged with chronic therapy. In addition, the TEAEs associated with LCM decreased in incidence with chronic therapy.

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

To support the development of LCM for the adult partial-onset seizure indication in Japan and China, EP0009 is being conducted to evaluate long-term safety, tolerability, and efficacy of LCM in Japanese and Chinese subjects. In addition, this study will provide the subjects who previously participated in EP0008, a Phase 3, multicenter, double-blind placebo-controlled study, the opportunity to continue to receive LCM treatment.

3 STUDY OBJECTIVE(S)

3.1 Primary objectives

The primary objectives of this study are the following:

- To evaluate the safety and tolerability of long-term administration of LCM at doses up to 400mg/day in Japanese and Chinese adults with epilepsy who have completed the Treatment and Transition Period of EP0008
- To allow subjects who had completed the Treatment and Transition Periods of EP0008 to receive LCM

3.2 Secondary objective

The secondary objective of this study is the following:

- To evaluate the efficacy of long-term administration of LCM at doses up to 400mg/day in Japanese and Chinese adults with epilepsy who have completed the Treatment and Transition Periods of EP0008.

4 STUDY VARIABLES

4.1 Safety variables

4.1.1 Primary safety variables

The primary safety variables are the following:

- AEs reported spontaneously by the subject or observed by the investigator
- Subject withdrawals due to AEs

4.1.2 Other safety variables

The other safety variables are the following:

- Changes in hematology, clinical chemistry, and urinalysis parameters
- Changes in 12-lead ECGs
- Changes in vital sign measurements (ie, blood pressure, pulse rate)
- Changes in body weight

4.2 Efficacy variables

4.2.1 Primary efficacy variables

No primary efficacy variables are defined for EP0009.

4.2.2 Secondary efficacy variables

The secondary efficacy variables are the following:

- Percent change from Baseline in partial-onset seizure frequency per 28 days, where Baseline is defined as the Baseline Period of EP0008
- 50% response, where a responder is a subject experiencing a ≥50% reduction from Baseline in partial-onset seizure frequency per 28 days, and Baseline is defined as the Baseline Period of EP0008

4.2.3 Other efficacy variables

Other efficacy variables are the following:

- 75% response, where a responder is a subject experiencing a ≥75% reduction from Baseline in partial-onset seizure frequency per 28 days and Baseline is defined as the Baseline Period of EP0008
- Subjects who achieved "seizure-free" status (yes/no)
- Percentage of seizure-free days
- Subjects who are changed to LCM monotherapy for at least 6 months
- Subjects who are changed to LCM monotherapy for at least 12 months

5 STUDY DESIGN

5.1 Study description

EP0009 is a Phase 3, multicenter, open-label, uncontrolled, extension study designed to evaluate the safety, tolerability, and efficacy of long-term administration of LCM as adjunctive therapy at doses up to 400mg/day in Japanese and Chinese adults with partial-onset seizures with or without secondary generalization who have completed the Treatment and Transition Periods of EP0008 and chose to enroll in EP0009.

EP0009 consists of a Treatment Period and, if applicable, a Taper Period.

Visit 1 of EP0009 is the same as the Final Visit of EP0008. Visits 2 through 4 of EP0009 will occur at 4-week intervals relative to the date of Visit 1. Beginning with Visit 5, each visit will occur at 12-week intervals relative to the date of Visit 1 until the End-of-Study/Withdrawal Visit.

At the completion of EP0008, all subjects who choose to enroll in EP0009 will be taking a dose of LCM 200mg/day. During the EP0009 Treatment Period, the investigator will be allowed to increase or decrease the doses of LCM and/or up to 3 concomitant AEDs to optimize tolerability and seizure reduction for each subject. The LCM dose may be decreased to 100mg/day or increased, no faster than 100mg/day per week, up to 400mg/day. Changes in concomitant AED(s) will be allowed only if the LCM dose has been stable for the previous 4 weeks; LCM dose must remain stable during changes to concomitant AED(s). Subjects may take no more than 3 concomitant AEDs except when temporary (≤12 weeks) use of an additional AED is required to switch to a new AED (ie, taper from old AED during titration of a new AED). New AED(s) may be added only when the subject has not optimally or adequately responded to a maximum tolerated dose of LCM. The concomitant AED(s) can be carefully tapered or discontinued at the discretion of the investigator. Monotherapy with LCM is permitted. Increasing the dose of LCM and/or concomitant AED(s), as well as the addition of a new AED, should be done at a visit (scheduled or unscheduled).

At the end of the Treatment Period, an End-of-Study Visit will be required. If subjects prematurely withdraw from the study, a Withdrawal Visit will be required. Subjects who complete the Treatment Period and choose not to continue on to commercial LCM treatment, and subjects who prematurely withdraw from the study, will enter a Taper Period. During the Taper Period, subjects receiving doses greater than LCM 200mg/day at the End-of-Study/Withdrawal Visit 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. 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/Withdrawal Visit are not required to taper off LCM. A Final Visit will be required 2 weeks after final LCM dose. Subjects who complete the Treatment Period and choose to continue on to commercial LCM treatment are not required to enter the Taper Period to taper off LCM or to return for a Final Visit; the End-of-Study Visit will be the last visit for these subjects. If LCM is not commercially available in a subject's country at the time the study closes, access to LCM will be provided according to local laws.

The Schedule of study assessments and the schematic diagram of the study are provided in Section 5.2 (Table 5-1) and Section 5.3 (Figure 5–1), respectively.

5.1.1 Study duration per subject

EP0009 will continue until the date of the market approval of LCM in each participating country or until the time when the sponsor decides to discontinue the development of LCM for the partial-onset seizure indication. The expected duration of subject participation is approximately 3 years following Visit 1.

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

5.1.2 Dates of the planned study duration

The study duration is planned from third quarter of 2012 to second quarter of 2017.

5.1.3 Planned number of subjects

No formal sample size determination has been performed because EP0009 is an extension study. Approximately 378 subjects, ie, 70% of subjects who are randomized in EP0008, are anticipated to participate in this extension study.

5.1.4 Anticipated regions and countries

All sites will be in Japan and China.

5.2 Schedule of study assessments

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

Table 5-1 Schedule of study assessments

Study Period	Treatment Period																	Taper Period	
Visit	**1**	**2**	**3**	**4**	**5[a]**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**≥16**	**ESV[b] /WV[b]**	**Final Visit**	**Unscheduled Visit[c]**
Weeks in study	**0**	**4**	**8**	**12**	**24**	**36**	**48**	**60**	**72**	**84**	**96**	**108**	**120**	**132**	**144**	**≥156**	**-**	**2 weeks after final LCM dose**	**-**
Visit window (days)[d]	**-**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**-**	**-**	**-**
Informed Consent[e]	X																		
Inclusion/exclusion Criteria	X																		
Concomitant AED(s)	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication(s)/ medical procedure(s)	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete physical examination[f]	X[e]				X		X				X				X	X[f]	X	X	X[g]
Brief neurological examination[f]	X[e]				X		X				X				X	X[f]	X	X	X[g]
Vital signs and weight	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS (the "Since Last Visit" version)	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[g]
Laboratory tests[h]:																			
Clinical chemistry/ hematology	X[e]	X	X	X	X	X	X	X	X	X	X	X		X		X[h]	X	X	X
Urinalysis	X[e]	X	X	X	X	X	X	X	X	X	X	X		X		X[h]	X	X	X

Table 5-1 Schedule of study assessments

Study Period	Treatment Period																	Taper Period	
Visit	**1**	**2**	**3**	**4**	**5[a]**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**≥16**	**ESV[b] /WV[b]**	**Final Visit**	**Unscheduled Visit[c]**
Weeks in study	**0**	**4**	**8**	**12**	**24**	**36**	**48**	**60**	**72**	**84**	**96**	**108**	**120**	**132**	**144**	**≥156**	**-**	**2 weeks after final LCM dose**	**-**
Visit window (days)[d]	-	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	-	-	-
Pregnancy test[i]	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[i]	X[i]	X[g]
12-lead ECG[j]	X[e]			X		X		X		X		X		X		X[j]	X	X	X[g]
Contact IVRS/IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[g]
Dispense IMP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[k]		X[g]
IMP return/review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[l]
Dispense subject diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[k]		
Subject diary return/review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[l]
AE assessment	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Withdrawal criteria	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

AE=adverse event; AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ESV=End-of-Study Visit; IMP=investigational medicinal product; IVRS=Interactive Voice Response System; IWRS=Interactive Web Response System; LCM=lacosamide; WV=Withdrawal Visit

[a] Beginning with Visit 5, visits will be performed at 12-week intervals.

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

[c] An Unscheduled Visit may be performed at the investigator's discretion. The investigator should use an Unscheduled Visit to increase a subject's LCM /concomitant AED(s) dose(s) or to add a new AED.

[d] A visit window ±7 day relative to Visit 1 is applicable.

[e] The Informed Consent form must be signed and dated at any time between Visit 7 and Visit 8 of EP0008. Visit 1 of EP0009 is the same as the Final Visit of EP0008. All other assessments marked "e" should be completed during the Final Visit of EP0008.

[f] After Week 48, physical and neurological (brief) examinations will be performed every 48 weeks until ESV/WV.

[g] These assessments may be performed as needed at the discretion of the investigator.

[h] After Week 108, the laboratory assessments will be performed every 24 weeks until ESV/WV.

[i] Serum pregnancy tests should be performed at Visit 1, ESV and Final Visit. Urine pregnancy tests will be performed for all other designated study visits.

[j] After Visit 4, a 12-lead ECG will subsequently be performed every 24 weeks until ESV/WV.

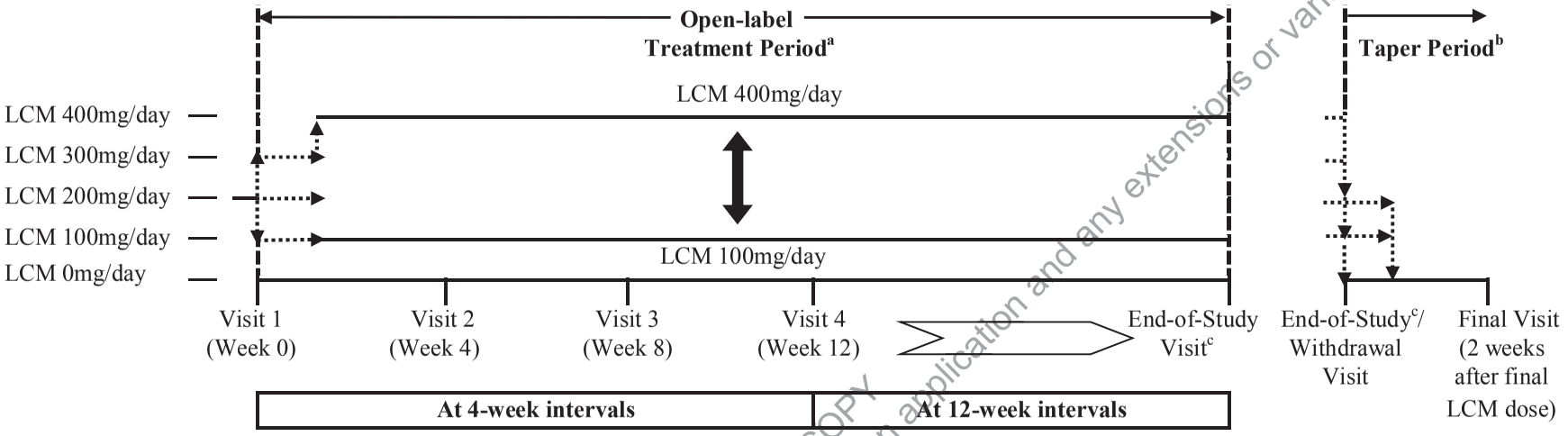
[k] At an ESV, the subject diary and IMP will not be dispensed for subjects who complete the Treatment Period and choose to continue on to commercial LCM treatment. If LCM is not commercially available in a subject's country at the time, access to LCM will be provided according to local laws.

[l] Subjects should bring the subject diary and IMP to the clinic for review.

5.3 Schematic diagram

The schematic diagram for EP0009 is provided in Figure 5–1.

Figure 5–1: Schematic diagram



LCM=lacosamide

[a] At the completion of EP0008, all subjects will be taking LCM 200mg/day. During the Treatment Period of EP0009, the LCM dose may be decreased to 100mg/day or increased, no faster than 100mg/day per week, up to 400mg/day.

[b] Subjects receiving doses greater than LCM 200mg/day at the End-of-Study/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 safety concerns require more rapid withdrawal of LCM. 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/Withdrawal Visit are not required to taper off LCM.

[c] The End-of-Study Visit is the last visit for the subjects who choose to continue on to commercial LCM treatment. The subjects who complete the Treatment Period and choose not to continue on to commercial LCM treatment will enter a Taper Period.

5.4 Rationale for study design and selection of dose

EP0009 is designed to evaluate the safety, tolerability, and efficacy of long-term administration of LCM as adjunctive therapy in Japanese and Chinese adults with partial-onset seizures with or without secondary generalization who have completed the Treatment and Transition Periods of EP0008. This design will allow the subjects who completed the Treatment and Transition Periods of EP0008 to continue with the treatment of LCM.

The doses in this study were selected to obtain long-term safety information of LCM within the approved doses and to give investigators the flexibility to optimize seizure control and tolerability in study subjects..

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Inclusion criteria

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

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent 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 (Japanese subjects under 20 years of age and Chinese subjects under 18 years of age).
2. Subject has completed the Treatment and Transition Periods of EP0008.
3. Subject is expected to benefit from participation, in the opinion of the investigator.
4. Subject is willing and able to comply with all study requirements.

6.2 Exclusion criteria

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

1. Subject is receiving an investigational medicinal product (IMP) or unapproved medication, or using an experimental medical device in each respective country.
2. Subject who withdrew from EP0008.
3. Female subject who is pregnant or nursing. Female subjects of childbearing potential (without a history of hysterectomy or bilateral oophorectomy) are eligible, if they use a medically accepted contraceptive method for the duration of the study participation. They must understand and accept that pregnancy should be avoided during participation in the study. Female subjects without childbearing potential (who have been surgically sterilized or who are at least 2 years postmenopausal) are eligible.
4. Subject is experiencing an ongoing serious adverse event, unless approved by the sponsor.

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 LCM dose greater than 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 (atrioventricular) block.
2. Confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
3. The subject is unwilling or unable to continue and withdraws consent.
4. Request of the sponsor or a regulatory agency.
5. The subject develops an AE that would interfere with his/her continued participation.
6. In the case of liver function test (LFT) results of transaminases (aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT]) ≥3x upper limit of normal (ULN) 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 (See Section 9.6.3).
7. 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 Columbia-Suicide Severity Rating Scale (C-SSRS). The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

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

8. Subject requires a medication that is not permitted.
9. The subject is noncompliant with the study procedures or medications in the opinion of the investigator.
10. 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 (See Section 9.6.3).
11. Subject develops a clinically relevant change in medical condition (or ECG or laboratory parameter) as determined by the investigator, and the investigator feels it is in the interest of the subject to withdraw.

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 UCB (or designee), whenever possible, to discuss the withdrawal of a subject in advance.

7 STUDY TREATMENT(S)

7.1 Description of investigational medicinal product

Lacosamide will be supplied as immediate-release, film-coated, tablets in strengths of 50mg (pinkish) and 100mg (dark yellow).

7.2 Treatments 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 completion of EP0008, all subjects who choose to enroll in EP0009 will be taking a dose of LCM 200mg/day. At the beginning of EP0009, the investigator may maintain the LCM dose or increase or decrease the dose. During the Treatment Period, the investigator will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction. The LCM dose may be decreased to 100mg/day or increased, no faster than 100mg/day per week, up to 400mg/day. Increasing the dose of LCM should be done at a visit (scheduled or unscheduled). Lacosamide dose must remain stable during changes to concomitant AED(s).

Subjects who complete the Treatment Period and choose not to continue on to commercial LCM treatment, and who withdraw from the study prematurely, will enter a Taper Period. During the Taper Period, subjects receiving doses greater than LCM 200mg/day at the End-of-Study/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 safety concerns require more rapid withdrawal of LCM. 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/Withdrawal Visit are not required to taper off LCM.

The details of concomitant AED(s) to be administered are described in Section 7.8.1.

Table 7-1 Recommended LCM dose reduction (Taper Period)

Dose of LCM at End-of-Study/ Withdrawal Visit	Taper Schedule	
	Week 1	Week 2
LCM 400mg/day	LCM 200mg/day	n/a
LCM 300mg/day	LCM 100mg/day	n/a
LCM 200mg/day	n/a	n/a
LCM 100mg/day	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 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 the IMP is responsible for the safe and proper storage of IMP at the site. Investigational medicinal product stored by the person in charge of the IMP 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 (copy of the temperature log and duration of the out-of-range temperature, if available) to the Drug Supply Coordinator. Based on discussion with a UCB Quality Assurance representative, the Drug 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 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 the IMP is responsible for retaining all used, unused, and partially used containers of IMP until returned or destroyed.

The investigator or the head of the participating study site (Japan only) 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 medications/treatments

7.8.1 Permitted concomitant AED(s)

At the beginning of EP0009, the concomitant AED(s) that were used in EP0008 are permitted. The investigator (or designee) will be allowed to change the type, dosage and administration, or discontinuation/resumption of concomitant AEDs to optimize tolerability and seizure reduction for each subject. Antiepileptic drugs approved for epilepsy in the subject's country (ie, Japan or China) are permitted during the study. Changes in concomitant AED(s) will be allowed only if the dose of LCM has been stable for the previous 4 weeks; LCM dose must remain stable during changes to concomitant AED(s). Subjects may take no more than 3 concomitant AEDs except when temporary (≤12 weeks) use of an additional AED is required to switch to a new AED (ie, taper from old AED during titration of new AED). New AED(s) may be added only when the subject has not optimally or adequately responded to a maximum tolerated dose of LCM. The concomitant AED(s) can be carefully tapered or discontinued at the discretion of the investigator. Monotherapy with LCM is permitted. Increasing the dose of LCM and/or concomitant AED(s), as well as addition of a new AED should be done at a visit (scheduled or unscheduled). There are no restrictions for concomitant AED(s) during the Taper Period, considering subject safety.

7.8.2 Prohibited concomitant treatments (medications and therapies)

The following concomitant medications/treatments are prohibited during the study:

- Antischizophrenic agents
- Monoamine oxidase inhibitors
- Barbiturates (except for an epilepsy indication or a single administration at the time when examinations such as an EEG are performed)
- Narcotic analgesics (except for short-term use for things such as a broken bone, a tooth extraction, etc)
- Psychostimulants
- AEDs given by a route other than oral (except benzodiazepine for rescue medication)
- Herbal medicines approved for epilepsy
- Potassium bromide, sodium bromide, and calcium bromide
- Bemegride
- Pregabalin
- Ketogenic diet

- Brain surgery (minimally invasive brain surgery, such as brain mapping, may be permitted with the approval of the Study Physician)
- VNS, except for the subjects who used VNS in EP0008
- Other investigational medicinal products, and drugs and medical devices that have not been approved in Japan and China
- The drugs which contain the contraindication for epilepsy patients in their package insert

7.8.3 Rescue medication

The use of benzodiazepines, which have the indication for epilepsy for the control of uncountable seizures due to clustering, is restricted to rescue therapy.

7.9 Blinding

EP0009 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. The unique identification number assigned to subjects during EP0008 will be used to identify subjects and to maintain subject confidentiality throughout EP0009. An interactive voice response system (IVRS) or interactive web response system (IWRS) will be used to assign the applicable LCM bottle number(s). Further instructions will be provide in the IVRS/IWRS manual.

7.11 Allowance for entering an additional study (EP0024)

At selected sites, Japanese subjects may participate in an additional study (EP0024) with an intravenous formulation of LCM without withdrawing from EP0009. The study period of EP0024 will be included in that of EP0009. Subjects will continue to receive their current dose of LCM at the time of entry and remain stable for the duration of EP0024. Subjects who complete or withdraw from EP0024 will be given the opportunity to resume their participation in EP0009 with oral LCM treatment. In the event that a subject withdraws from EP0024 and is required to taper off LCM, the subject will return to EP0009 and taper using LCM tablets. Adverse events and concomitant treatment(s)/medication(s) that occur or administered during EP0024 will be recorded in EP0024. Ongoing AEs and concomitant medication(s)/medical procedure(s) originating from the EP0024 will be followed in EP0009 until resolution or until stable. Where possible, data updates related to the resolution of ongoing AEs and concomitant medication(s)/medical procedure(s) from EP0024 will be reported in the EP0024 database (eg, updates are made in the EP0024 databases until the database is locked). All other data reported for EP0024 will be captured in the EP0024 database. Per the EP0024 protocol, the study (EP0024) will require hospitalization. Hospitalization for study participation does not need to be reported as an SAE as outlined in section 9.4.

8 STUDY PROCEDURES BY VISIT

A window of ±7 days relative to Visit 1 is applicable for all scheduled visits.

A detailed tabular schedule of study procedures is provided in Section 5.2.

8.1 Treatment Period

8.1.1 Visit 1 (Week 0)

For subjects completing the Transition Period of EP0008 and choosing to enroll in EP0009, the Final Visit (Week 18) of EP0008 will serve as Visit 1 of EP0009. Prior to the conduct of any study-related procedures, a complete verbal and written explanation of the nature and purpose of the study will be given to the subject by the investigator (or designee). The subject/legal representative is required to sign and date the IRB/IEC approved Informed Consent if he/she decides to participate in the study.

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 assessments (for further details of the assessments and the required procedures and methods, see Section 9 and Section 10).

The following will be performed prior to the first dose of IMP in EP0009:

- Inclusion/exclusion criteria
- Contact IVRS/IWRS
- Dispense IMP
- Dispense subject diary
- Withdrawal criteria

The following should have already been completed during the previous EP0008 Final Visit:

- Concomitant AED(s)
- Concomitant medication(s)/medical procedure(s)
- Complete physical examination
- Brief neurological examination
- Vital signs and weight
- C-SSRS (the "Since Last Visit" version)
- Blood and urine samples for clinical laboratory values (includes hematology, clinical chemistry, and urinalysis)
- Blood sample for pregnancy test (for women of childbearing potential)
- 12-lead ECG (1 assessment at any time after intake of IMP)
- AE assessment

The following information collected in EP0008 will be used for EP0009: demographic information, medical/procedure history, epilepsy information (diagnosis of epilepsy, etiology of epilepsy, ILAE seizure classification, focus localization, classification of epileptic syndrome [See Section 16.2], treatment history).

8.1.2 Visits 2 through 4 (Weeks 4 through 12)

Visits 2 through 4 will occur at 4-week intervals ±7 days relative to the date of Visit 1.

The following will be performed at every visit:

- Concomitant AED(s)
- Concomitant medication(s)/medical procedure(s)
- Vital signs and weight
- C-SSRS (the "Since Last Visit" version)
- Blood and urine samples for clinical laboratory values (includes hematology, clinical chemistry, and urinalysis
- Urine sample for pregnancy test
- Contact IVRS/IWRS
- Dispense IMP
- IMP return/review
- Dispense subject diary
- Subject diary return/review
- AE assessment
- Withdrawal criteria

The following will be performed at Visit 4 (Week 12) only:

- 12-lead ECG (Visit 4 only)(1 assessment at any time after intake of IMP)

8.1.3 From Visit 5 until End-of-Study/Withdrawal Visit (Week 24 or later)

Beginning with Visit 5, each visit will occur at 12-week intervals ±7 days relative to the date of Visit 1.

The following will be performed at every visit:

- Concomitant AED(s)
- Concomitant medication(s)/medical procedure(s)
- Vital signs and weight
- C-SSRS (the "Since Last Visit" version)
- Urine sample for pregnancy test (for women of childbearing potential)
- Contact IVRS/IWRS
- Dispense IMP
- IMP return/review
- Dispense subject diary

- Subject diary return/review
- AE assessment
- Withdrawal criteria

The following will be performed at Visit 5, Visit 7, and every 48 weeks after Visit 7

- Complete physical examination
- Brief neurological examination

The following will be performed at every 24 weeks after Visit 4:

- 12-lead ECG (1 assessment at any time after intake of IMP)

The following will be performed at every visit through Visit 12 (Week 108) and every 24 weeks after Visit 12.

- Blood and urine samples for clinical laboratory values (includes hematology, clinical chemistry and urinalysis)

8.1.4 End-of-Study Visit

At the end of the Treatment Period, an End-of-Study Visit will be required. 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.

The following will be performed:

- Concomitant AED(s)
- Concomitant medication(s)/medical procedure(s)
- Complete physical examination
- Brief neurological examination
- Vital signs and weight
- C-SSRS (the "Since Last Visit" version)
- Blood and urine samples for clinical laboratory values (includes hematology, clinical chemistry, and urinalysis)
- Blood sample for pregnancy test (for women of childbearing potential)
- 12-lead ECG (1 assessment at any time after intake of IMP)
- Contact IVRS/IWRS
- Dispense IMP for taper (if applicable, See Section 7.2)
- IMP return/review
- Dispense subject diary (if applicable)
- Subject diary return/review

- AE assessment
- Withdrawal criteria

8.1.5 Withdrawal Visit

Subjects who prematurely withdraw from the study must complete a Withdrawal Visit. All those subjects will enter the Taper Period after the Withdrawal Visit.

The following will be performed:

- Concomitant AED(s)
- Concomitant medications(s)/treatment(s)
- Complete physical examination
- Brief neurological examination
- Vital signs and weight
- C-SSRS (the "Since Last Visit" version)
- Blood and urine samples for clinical laboratory values (includes hematology, clinical chemistry, and urinalysis)
- Urine samples for pregnancy test (for women of childbearing potential)
- 12-lead ECG (1 assessment at any time after intake of IMP)
- Contact IVRS/IWRS
- Dispense IMP for taper (if applicable, See Section 7.2)
- IMP return/review
- Dispense subject diary
- Subject diary return/review
- AE assessment
- Withdrawal criteria

8.2 Taper Period

8.2.1 Final Visit (2 weeks after final LCM dose)

For subjects who withdraw during the study and receive doses greater than LCM 200mg/day, and subjects who complete the Treatment Period and choose not to continue on to commercial LCM treatment and receive doses greater than LCM 200mg/day, LCM should be tapered off gradually at a recommended decrease rate or 200mg/day per week (See Section 7.2).

For Subjects who withdraw during the study or complete the Treatment Period and receive doses of LCM 200mg/day or lower are not required to taper LCM.

For all the above subjects, a Final Visit must be performed 2 weeks after the final LCM dose.

The following will be performed:

- Concomitant AED(s)
- Concomitant medication(s)/treatment(s)
- Complete physical examination
- Brief neurological examination
- Vital signs and weight
- C-SSRS (the "Since Last Visit" version)
- Blood and urine samples for clinical laboratory values (includes hematology, clinical chemistry, and urinalysis)
- Blood samples for pregnancy test (for women of childbearing potential)
- 12-lead ECG (1 assessment at any time)
- IMP return/review
- Subject diary return/review
- AE assessment

8.3 Unscheduled Visit

An Unscheduled Visit may be performed at the investigator's discretion. Increasing the dose of LCM and/or concomitant AED(s), as well as addition of a new AED should be done at an Unscheduled Visit.

The following will be performed:

- Concomitant AED(s)
- Concomitant medication(s)/treatment(s)
- Vital signs and weight
- Blood and urine samples for clinical laboratory values (includes hematology, clinical chemistry, and urinalysis)
- IMP review
- Subject diary review
- AE assessment
- Withdrawal criteria

Further assessments/procedures may be performed as needed at the discretion of the investigator (See Section 5.2).

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, including any posttreatment period required by the protocol must be reported in the eCRF even if no IMP was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs that recurred or worsened after the initial visit.

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

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. If necessary, UCB may request that the investigators perform examinations to obtain supplementary measurements and/or evaluations.

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

Should a subject become pregnant after the first intake of any IMP, UCB (or designee) department should be informed immediately. The subject should be withdrawn from the study as soon as pregnancy is known, and the following should be completed:

- The subject should return for a Withdrawal Visit.
- The subject should immediately stop the intake of the IMP or be down-titrated as instructed at the Withdrawal Visit.
- A Safety Follow-Up Visit should be scheduled 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.

In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, UCB (or designee) will ask the investigator or designee to contact the subject and his partner to request consent via the Partner Pregnancy Consent form. If the partner agrees to provide additional information, the Pregnancy Report and Outcome form will be forwarded to the subject's partner for completion.

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. The health of the child must be followed for 30 days after birth for any significant medical issues.

In certain circumstances, UCB (or designee) may request that follow up is continued for a period longer than 30 days.

A pregnancy becomes a serious adverse event (SAE) in the following circumstances: miscarriage, abortion, or anomaly/birth defect of the child. 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 Study Drug Dosing 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/IECs will be informed appropriately and as early as possible.

The Study Physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the Drug Safety 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 pre-existing condition that has not worsened or manifested in an unusual or uncharacteristic manner] do not qualify for reporting. For example, if a

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

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

An Investigator SAE report form will be provided to the investigator.

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 Drug Safety database without limitation of time.

9.3 Adverse events of special interest

An AE of special interest is any AE that the US Food and Drug Administration 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 (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 US 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 ≥2×ULN
  - AST ≥2×ULN

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 SAEs for the adult epileptic population

MedDRA® SOC	MedDRA® PT
Congenital, Familial and Genetic disorders	Teratogenicity
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 behavior
	Abnormal behavior
	Anxiety
	Sleep disorder
Reproductive System and Breast Disorders	Menstrual disorder
	Impotence

MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SAE=serious adverse event; SOC=system organ class

9.6 Other safety assessments

9.6.1 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 and Chinese 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.

9.6.2 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 laboratory tests to be performed are presented in Table 9-2.

Table 9-2 Laboratory measurements

Hematology	Clinical Chemistry	Urinalysis
Hematocrit Hemoglobin Platelet count RBC WBC 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

9.6.3 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.

9.6.4 Pregnancy testing

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.

9.6.5 Vital signs and body weight

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. Body weight will be assessed according to the tabular schedule of study procedures, Section 5.2.

9.6.6 Complete physical examination

The complete 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. The complete physical examination includes cardiac and respiratory function via auscultation, temperature, and review of all body systems. Clinically significant physical examination findings are to be reported as AEs.

9.6.7 Brief neurological examination

Brief neurological examination should 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.

The brief neurological examination will include assessment of consciousness and mental status, muscle strength, reflexes (knee jerk and biceps only), and coordination/cerebellar function. Clinically significant neurological examination findings are to be reported as AEs.

9.6.8 12-lead ECG

A standard 12-lead ECG will be recorded according to the tabular schedule of study procedures, Section 5.2.

9.6.8.1 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 9.6.8.2) 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.

9.6.8.2 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 who is blinded to the treatment. 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.

10 ASSESSMENT OF EFFICACY

10.1 Methods for assessing efficacy variables

The efficacy variables will be measured based on Seizure Records.

Seizure Records

Diagnosis of partial-onset seizures will be based on the International Classification of Epileptic Seizures of the International League Against Epilepsy (See Section 16.1). Each subject will keep a diary to note the daily seizure activity from Visit 1 until the last visit will record the following information:

- Seizure type
- Seizure frequency
- Any AEs, including physical injury that occurred and any concomitant medication(s)/medical procedure(s) that was applied, if applicable.

Appropriate subject diaries will be provided to the subject for this purpose.

Medication Records

Each subject will be asked to record in their diary their daily intake of IMP and concomitant AED(s) from Visit 1 until the last visit. The following information should be completed on a daily basis:

- Record whether IMP tablet was taken
- Record any concomitant AED(s) taken

Any changes in concomitant AED(s) and other medication(s) must be recorded in the diary.

Assessment of Compliance

Subjects must bring their diary containing the seizure and medication records to each visit. The investigator or designee should check the medication record against the returned IMP and packaging. The investigator or designee should record the quantity of IMP returned in the appropriate logs and discrepancies should be addressed. Subject's noncompliance is defined as less than 75% or more than 125% compliant with the dosage schedule, according to tablet counts.

The seizure records will be checked by the investigator or designee with regards to correct and thorough daily completion by the subject. The investigator must be confident that the subject is able to manage seizure records completion.

11 STUDY MANAGEMENT AND ADMINISTRATION

11.1 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/IEC in writing regarding the type of emergency and the course of action taken.

11.2 Monitoring

UCB (or designee) will monitor the study to meet the monitoring Standard Operating Procedures (SOPs), ICH-GCP guideline(s), 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 contract research organization (CRO) or a contract monitor.

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

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

11.2.1 Definition of source data

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes). Photocopies 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 record), subject diaries, laboratory results, pharmacy records, or ECGs, for example. Source documents should be kept in a secure, limited access area.

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

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

11.2.2 Source data verification

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

11.3 Data handling

11.3.1 Case Report form completion

In the event that 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 Instructions.

11.3.2 Database entry and reconciliation

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

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

11.3.3 Subject Screening and Enrollment log/Subject Identification Code list

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

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

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

11.4 Termination of the study

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

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

11.5 Archiving and data retention

The record retainer at the study site and the IRB/IEC will retain the GCP defined essential document until at least 10 years after the discontinuation or completion of the study conduct. If UCB requires retention of these documents for longer period, the duration and method of retention will be decided upon discussion between UCB and study site.

It is responsibility of UCB (or designee) to inform the record retainer as to when the documents should no longer to be retained.

11.6 Audit and inspection

The investigator and head of the participating study site (Japan only) will permit study-related audits mandated by UCB, after reasonable notice, and inspections by domestic or foreign regulatory authorities.

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

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

11.7 Good Clinical Practice

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

12 STATISTICS

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

12.1 Definition of analysis sets

The 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-related data will be the Full Analysis Set and will include all subjects in the SS having at least 1 day with available seizure diary data in EP0009.

12.2 General statistical considerations

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.

Unless otherwise specified, baseline will be determined from the Baseline values of EP0008. Subjects who prematurely withdraw from the study will be evaluated based on the data collected at each visit attended.

12.3 Planned safety analyses

All safety analyses will be performed on the SS.

12.3.1 Analysis of the primary safety variable

Treatment-emergent AEs will be defined as those events starting on or after the date of first dose of IMP, or whose severity worsen on or after the date of first IMP dosing. Adverse events occurring within 30 days after final IMP dose will be considered treatment-emergent.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) and tabulated by System Organ Class and preferred term.

Summary tables for number and percentage of subjects reporting at least 1 TEAE, tabulated by MedDRA® System Organ Class and preferred term, will be presented. In addition, a summary table of TEAEs by intensity may be generated. Treatment-emergent AEs that lead to early withdrawal from the study as well as treatment-emergent SAEs will also be tabulated.

12.3.2 Other safety analyses

Other variables assessing safety are laboratory parameters, ECGs (12-lead), vital signs, and body weight.

Measurements and changes from Baseline in continuous laboratory parameters in hematology, clinical chemistry, and urinalysis, ECGs (12-lead), vital signs (blood pressures and pulse rate), and body weight will be summarized using descriptive statistics (n, mean, standard deviation, 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.

12.4 Planned efficacy analyses

All efficacy variables are to be evaluated descriptively.

12.4.1 Analysis of primary efficacy variables

No primary efficacy variables are defined for EP0009.

12.4.2 Analysis of secondary efficacy variables

Partial-onset seizure frequency per 28 days will be calculated as ([number of seizures over the specified analysis interval] divided by [number of days in the interval]) multiplied by 28. The

percent change in seizure frequency per 28 days (PCH) from the Baseline Period of EP0008 (B) to the appropriate analysis period (P) is defined as:

$$PCH=[(SF_P-SF_B)/SF_B]x100$$

where SF_P corresponds to the seizure frequency during the analysis period and SF_B corresponds to the Baseline Period seizure frequency.

Descriptive statistics (ie, mean, SD, median, minimum and maximum) for the percent change in partial-onset seizure frequency per 28 days from the Baseline Period of EP0008 will be summarized. The number and percentage of subjects with a ≥50% reduction from Baseline in partial-onset seizure frequency per 28 days will be summarized.

12.4.3 Other efficacy analyses

The number and percentage of subjects with a ≥75% reduction from Baseline in partial-onset seizure frequency per 28 days will be summarized. The number and percentage of subjects achieving a seizure-free status and descriptive statistics for the percentage of seizure-free days will be presented. Additionally, the number and percentage of subjects receiving LCM as monotherapy for at least 6 months and at least 12 months will be presented.

12.5 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, a Data Review Meeting will be held. Important protocol deviations (ie, those considered to have an impact on, eg, primary safety parameters or study conduct) will be identified and reviewed by a panel consisting of the Clinical Project Manager, 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.

12.6 Handling of dropouts or missing data

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

12.7 Planned interim analysis and data monitoring

No formal interim analysis is planned. However, data will be reported prior to the completion of this study to support regulatory submissions. At a minimum, 2 interim reports are planned after all enrolled Japanese subjects complete through Visit 5 (Week 24) and after all enrolled Japanese subjects complete through Visit 7 (Week 48).

12.8 Determination of sample size

No formal sample size determination has been performed because EP0009 is an extension study. Approximately 378 subjects, ie, 70% of subjects who were randomized in EP0008, are anticipated to participate in this extension study.

13 ETHICS AND REGULATORY REQUIREMENTS

13.1 Informed consent

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

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

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

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

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.

13.2 Subject identification cards

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

13.3 Institutional Review Boards and Independent Ethics Committees

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

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

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

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

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

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

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

13.4 Subject privacy

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

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

13.5 Protocol amendments

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

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

14 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

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

14.1 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.

14.2 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.

15 REFERENCES

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16 APPENDICES

16.1 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.

16.2 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.

16.3 Protocol Amendment 1

Rationale for the amendment

The primary purpose of this nonsubstantial protocol amendment is to revise the contact information regarding SAE reporting. In accordance with the contract with the CRO, SAEs will be reported to UCB directly.

The current estimated number of patients with epilepsy in China has been corrected. Dates of the planned study duration are revised.

The remainders of the changes in this amendment are described in detail below.

Modifications and changes

Global changes

The following global changes have been made:

- The version of the C-SSRS at each visit has been stipulated clearly for the site.
- The term "active" used in withdrawal criteria related to suicidality has been changed to "actual" for keeping the consistency with the term which is used in the C-SSRS.
- Contact IVRS/IWRS at the Final Visit has been deleted because there is no drug distribution at the Final Visit.
- Inconsistency between Section 5.2 and Section 8 has been corrected.

Specific changes

This section displays the modifications compared with the previous Protocol dated 06 Mar 2012.

Change #1

Title page

UCB Japan Co. Ltd.

Shinjuku Grand Tower 8-17-1

Nishi-Shinjuku

Shinjuku-Ku

Tokyo 160-0023

JAPAN

Has been changed to:

UCB Japan Co. Ltd.

Shinjuku Grand Tower

8-17-1 Nishi-Shinjuku
Shinjuku-Ku
Tokyo 160-0023
JAPAN

Change #2

SPONSOR DECLARATION

Study Physician

[redacted]**, MD, PhD**

_____
Date/Signature

Clinical Program Director

[redacted]**, PhD**

_____
Date/Signature

Has been changed to:

Study Physician

[redacted] **MD**

_____
Date/Signature

Clinical Program Director

[redacted] **PhD**

_____
Date/Signature

Change #3

STUDY CONTACT INFORMATION

UCB Japan Co. Ltd.
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Medical Expert

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Sponsor Study Physician

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Phone:	[redacted]
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Clinical Trial Biostatistician

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Phone:	[redacted]
Fax:	

Has been changed to:

UCB Japan Co. Ltd.

Shinjuku Grand Tower

8-17-1 Nishi-Shinjuku

Shinjuku-Ku

Tokyo 160-0023

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Medical Expert (Japan)

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Phone:	[redacted]
Fax:	

Change #4

STUDY CONTACT INFORMATION

The following study contact information has been added:

National Principal Investigator (China)

Name:	[redacted], MD
Address:	Huashan Hospital Fudan University No.12 Middle Urumqi Road, Shanghai, 200040, PRC
Phone:	[redacted]
Fax:	

Change #5

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h), safety related issues	
Fax	**Japan:** UCB Japan: +81 3 6864 7400 PAREXEL: +81 3 6888 5377 **China:** PAREXEL: +86 10 5879 7674
Phone	**Japan:** UCB Japan: +81 3 6864 7410 (during business hours) +81 80 1100 5372 (outside business hours) PAREXEL: +81 3 3537 5907 **China:** PAREXEL: +65 6221 8582 (Singapore)
Email	**Japan:** UCB Japan: JDSO@ucb.com PAREXEL: +Japan-Medical@parexel.com **China:** PAREXEL: Medical_Beijing@parexel.com

Has been changed to:

Serious adverse event reporting (24h)	
Fax	UCB Japan: +81 3 6864 7400
Email	UCB Japan: UCBJ-Safety@ucb.com

Safety related issues	
Phone	PAREXEL International Inc. : +1 978 805 7613

Change #6

Section 2 INTRODUCTION

Last sentence in paragraph 2

It is estimated that there are currently around 4,000,000 patients with epilepsy in China, with approximately 400,000 new patients every year (Chinese Medical Association, 2007).

Has been changed to:

It is estimated that there are currently around 9,000,000 patients with epilepsy in China, with approximately 400,000 new patients every year (Chinese Medical Association, 2007).

Change #7

Section 5.1.2 Dates of the planned study duration

The study duration is planned from first quarter of 2013 to second quarter of 2017.

Has been changed to:

The study duration is planned from third quarter of 2012 to second quarter of 2017.

Change #8

Section 5.2 Table 5-1: Schedule of study assessments

C-SSRS

Has been changed to:

C-SSRS (the "Since Last Visit" version)

Change #9

Section 5.2 Table 5-1: Schedule of study assessments

Contact IVRS/IWRS at Final Visit has been deleted.

Change #10

Section 5.2 Table 5-1: Schedule of study assessments, footnote i

i Serum pregnancy tests should be performed at Visit 1, ESV and Final Visit. Urine pregnancy tests will be performed for all other designed study visits.

Has been changed to:

i Serum pregnancy tests should be performed at Visit 1, ESV and Final Visit. Urine pregnancy tests will be performed for all other designated study visits.

Change #11

Section 6.3 Withdrawal criteria, criterion 7

7. Subject has active suicidal ideation as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Since Last Visit" version of the Columbia-Suicide Severity Rating Scale (C-SSRS). The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

Has been changed to:

7. 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 Columbia-Suicide Severity Rating Scale (C-SSRS). The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

Change #12

Section 8.1.1 Visit 1 (Week 0), Section 8.1.2 Visits 2 through 4 (Weeks 4 through 12), Section 8.1.3 From Visit 5 until End-of-Study/Withdrawal Visit (Week 24 or later), Section 8.1.4 End-of-Study Visit, Section 8.1.5 Withdrawal Visit, and Section 8.2.1 Final visit (2 weeks after final LCM dose), the following bullet:

- C-SSRS

Has been changed to:

- C-SSRS (the "Since Last Visit" version)

Change #13

Section 8.2.1 Final Visit (2 weeks after final LCM dose), the following bullet:

- Contact IVRS/IWRS

Has been deleted.

Change #14

Section 8.3 Unscheduled Visit, the following bullet:

- Urine samples for pregnancy test (for women of childbearing potential)

Has been deleted.

Change #15

Section 9.2.2 Procedures for reporting serious adverse events

First sentence in paragraph 1

If an SAE is reported, UCB (or designee) must be informed within 24 hours of receipt of this information by the site (see contact information for SAE reporting listed in the Serious Adverse Event Reporting section at the front of the protocol).

Has been changed to:

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

Change #16

Section 9.2.2 Procedures for reporting serious adverse events

Last sentence in paragraph 5

Serious AEs that the investigator thinks may be associated with the IMP must be reported to UCB (or designee) regardless of the time between the event and the end of the study.

Has been changed to:

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.

Change #17

Section 9.3 Adverse events of special interest

The following has been added after the first sentence in paragraph 1.

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

Change #18

Section 9.3 Adverse events of special interest, the following bullet:

- Serious suspected multiorgan hypersensitivity reactions

Serious suspected multiorgan hypersensitivity cases may be identified and reported to the sponsor (or designee) by the investigator using the following algorithm as agreed with the US Food and Drug Administration:

Has been changed to:

- 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 US Food and Drug Administration:

16.4 Protocol Amendment 2

Rationale for the amendment

The primary purpose of this nonsubstantial protocol amendment is to clarify the procedure of pregnancy testing. Urine pregnancy testing will be done at each study site.

Withdrawal criteria have been revised to provide additional clarification based on program medical review. Suicidal ideation and behavior and clinically significant neurological examination findings observed throughout the study period are clarified as findings to be reported as AEs. International classification of epilepsies and epileptic syndromes (1989) has been added as an appendix for reference.

Modifications and changes

Global changes

There are no global changes in this amendment.

Specific changes

This section displays the modifications in this amendment compared with the Protocol Amendment 1 dated 12 Sep 2012.

Change #1

Section 6.3 Withdrawal criteria, criterion 1

1. Subject develops second- or third-degree AV (atrioventricular) 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.

Has been changed to:

1. Subject develops second- or third-degree AV (atrioventricular) block.

Change #2

Section 6.3 Withdrawal criteria, criterion 6 and 10

The following has been added after the last sentence:

(See Section 9.6.3)

Change #3

Section 6.3 Withdrawal criteria

The following criterion has been added as withdrawal criterion 11:

11. Subject develops a clinically relevant change in medical condition (or ECG or laboratory parameter) as determined by the investigator, and the investigator feels it is in the interest of the subject to withdraw.

Change #4

Section 8.1.1 Visit 1 (Week 0)

Last sentence

The following information collected in EP0008 will be used for EP0009: demographic information, medical/procedure history, epilepsy information (diagnosis of epilepsy, etiology of epilepsy, ILAE seizure classification, focus localization, classification of epileptic syndrome, treatment history).

Has been changed to:

The following information collected in EP0008 will be used for EP0009: demographic information, medical/procedure history, epilepsy information (diagnosis of epilepsy, etiology of epilepsy, ILAE seizure classification, focus localization, classification of epileptic syndrome [See Section 16.2], treatment history).

Change #5

Section 9.6.1 Assessment of suicidality

The following sentence has been added after the last sentence:

Suicidal ideation and behavior are to be reported as AEs.

Change #6

Section 9.6.4 Pregnancy testing

The following sentence has been added after the last sentence:

Serum pregnancy testing will be performed by the central laboratory, and urine pregnancy testing will be performed at the study site.

Change #7

Section 9.6.7 Brief neurological examination

The following sentence has been added after the last sentence:

Clinically significant neurological examination findings are to be reported as AEs.

Change #8

Section 16.2 International Classification of Epilepsies and Epileptic Syndromes (1989)

The above section and its content have been added.

17 DECLARATION AND SIGNATURE OF INVESTIGATOR

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

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

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

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

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

Investigator:

_____ _____

Printed name Date/Signature