PROTOCOL SP1042 AMENDMENT 1

A MULTICENTER, OPEN-LABEL, FOLLOW-UP STUDY TO ASSESS THE LONG-TERM USE OF LACOSAMIDE (FLEXIBLE DOSE FROM 200 TO 600MG/DAY) USED AS MONOTHERAPY IN SUBJECTS WHO COMPLETED SP0994 AND RECEIVED LACOSAMIDE MONOTHERAPY TREATMENT

PHASE 3B

EudraCT Number: 2015-001549-96

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Protocol/Amendment number	Date	Type of amendment
Final Protocol	12 May 2015	Not applicable
Protocol Amendment 1	01 Jul 2015	Nonsubstantial

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SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
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LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AV	atrioventricular
CBZ-CR	carbamazepine (controlled release)
CDMS	clinical data management system
CPM	Clinical Project Manager
CPMP	Committee for Proprietary Medicinal Products
CHMP	Committee for Medicinal Products for Human Use
CRF	Case Report form
CRO	contract research organization
DS	Drug Safety
ECG	electrocardiogram
EDC	electronic data capture
EMA/EMEA	European Medicines Agency
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
iv	intravenous
IXRS	interactive voice/web response system
LCM	lacosamide
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic(s)
SAE	serious adverse event
SOP	Standard Operating Procedure
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

1 SUMMARY

SP1042 is a Phase 3B, multicenter, open-label, follow-up study evaluating the safety and tolerability of long-term use of lacosamide (LCM; Vimpat®, SPM 927; previously referred to as harkoseride; [R]-2-acetamido-N-benzyl-3-methoxypropionamide, ADD 234037) (flexible doses from 200 to 600mg/day), used as monotherapy in subjects ≥16 years of age with partial-onset seizures or generalized tonic-clonic seizures who have completed SP0994.

Subjects treated with LCM in SP0994 will be allowed to continue the same treatment in SP1042 until marketing application for LCM is approved and LCM is commercially available for monotherapy in the subject's country, or UCB has determined that the clinical development program for the monotherapy indication will be formally discontinued, or up to a maximum period of 3 years, whichever is earlier.

SP0994 is a double-blind, follow-up study to SP0993 evaluating the long-term safety and tolerability of LCM as compared to carbamazepine (controlled release) (CBZ-CR) and was designed to assess the long-term effects of LCM in accordance with European Medicines Agency (EMA) guidelines (CHMP/EWP/566/98, 2010). Following the database lock and unblinding of SP0993, SP0994 will be unblinded. The individual subject treatment (ie, LCM or CBZ-CR) will be made known to both the subject and the investigator. Once the program for follow-up access to LCM monotherapy is established, a Termination Visit will be scheduled as soon as possible.

SP1042 is an open-label, follow-up study evaluating the long-term safety and tolerability of LCM in patients receiving LCM in SP0994, and would commence after the SP0994 Termination Visit. SP1042 will enable collection of additional LCM monotherapy safety data in a controlled manner and will also facilitate access to treatment with LCM for subjects receiving LCM in SP0994 until commercial availability of LCM for monotherapy use.

The study will be conducted at approximately 70 sites in Europe, Latin America, Asia, and other regions. It is anticipated that approximately 150 subjects who receive LCM in SP0994 will participate in this follow-up study.

Subjects in SP0994 who were receiving LCM will have the opportunity to participate in SP1042. Subjects who were receiving CBZ-CR or who were in LCM taper in SP0994 at the time of unblinding will not be allowed to participate in SP1042 and can continue to receive commercially available CBZ therapy or other commercially available treatment options (which will not be provided by UCB). SP1042 consists of a Treatment Phase of up to 156 weeks and an End-of-Study Phase of up to 8 weeks. Visit 1 for SP1042 will be the same as the Termination Visit of SP0994. Beginning with SP1042 Visit 1, study visits will occur at approximately 26-week intervals through the Early Termination/Termination Visit. The Termination Visit for subjects in the SP1042 Treatment Phase will be performed at the time that the marketing application for LCM is approved and LCM is commercially available for monotherapy in the subject's country, or UCB has determined that the clinical development program for the monotherapy indication will be formally discontinued, or up to a maximum period of 3 years, whichever is earlier. Subjects may be immediately prescribed commercially available LCM. Subjects who do not wish to continue LCM at the end of the study will be tapered off LCM. A Final Visit will occur 2 weeks after the final dose of LCM.

The individual starting dose in SP1042 for each subject will be the same dose reached at the end of SP0994 (LCM 200mg/day, 300mg/day, 400mg/day, 500mg/day, or 600mg/day). During SP1042, investigators will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction for each subject based upon individual subject response. The investigator may maintain the subject's LCM dose, decrease the dose in decrements of 100mg/day per week to a minimum dose of LCM 200mg/day, or increase the dose in increments of 100mg/day per week up to a maximum dose of LCM 600mg/day. Lacosamide doses administered in this study must be from 200mg/day to 600mg/day, must comply with doses that can be administered with LCM 50mg tablets, and should be a dose that can be administered in equal divided doses twice daily.

The primary safety variables include reported adverse events (AEs), subject withdrawals due to AEs, and serious AEs (SAEs).

2 INTRODUCTION

Epilepsy is the second most prevalent neurological disorder in the world. More than 40 million people suffer from epilepsy – about 1% of the world's population (Dichek, 1999). Although some forms of epilepsy may respond to surgical treatment and others may not require any treatment at all, most patients with epilepsy require appropriate pharmacological therapy (Perucca, 1996). In the past decade, several new options for the medical treatment of epilepsy have been introduced, including novel antiepileptic drugs (AEDs) and vagus nerve stimulation.

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. Lacosamide has proven to be an effective and [redacted] adjunctive treatment for partial-onset seizures, with or without secondary generalization, based on 3 double-blind, placebo-controlled, multicenter studies (SP667, SP754, and SP755) in subjects with difficult-to-control partial-onset seizures. Lacosamide has also been shown to be an effective and [redacted] adjunctive treatment over the long term (up to 9 years) for subjects with partial-onset seizures. Lacosamide has been approved in the EU as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients 16 years of age and older (oral tablets, syrup, and solution for intravenous [iv] infusion). Lacosamide has also been approved in the US as adjunctive therapy in the treatment of partial-onset seizures in patients 17 years of age and older (oral tablets, oral solution, and solution for iv infusion). In addition, LCM has been approved for a similar epilepsy indication in other countries. Use of a loading dose for initiation of adjunctive LCM treatment (single loading dose of LCM 200mg, followed approximately 12 hours later by LCM 100mg twice daily [200mg/day] maintenance dose regimen) is approved in the EU, US, and other countries.

The efficacy and safety of LCM as monotherapy in partial-onset seizures were established in SP902, a Phase 3, historical-controlled, multicenter, double-blind, randomized, conversion to monotherapy study in 425 adult subjects. The results of the efficacy analyses demonstrate that the LCM 400mg/day dose was efficacious as withdrawal to monotherapy in subjects with

partial-onset seizures. Lacosamide, at doses of 400mg/day and 300mg/day, was [redacted] and well tolerated when administered as monotherapy to subjects with partial-onset seizures, with an AE profile similar to that reported for LCM as adjunctive therapy.

Based on these results, LCM as monotherapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older was approved on 29 Aug 2014 in the US. Use of a LCM 200mg loading dose for initiation of LCM monotherapy or conversion to LCM monotherapy is also approved in the US.

In the clinical development program for LCM, safety and tolerability of multiple doses of up to LCM 400mg given twice daily (LCM 800mg/day) were evaluated in approximately 700 unique healthy subjects who received LCM in Phase 1 studies. Lacosamide is rapidly and completely absorbed after oral administration and has minimal protein-binding properties, thus a low risk of displacement drug-drug interactions. Lacosamide is neither a strong inhibitor nor a known inducer of the CYP450 enzymes and hence has a low potential for drug-drug interactions. Food does not affect the rate and extent of absorption. Peak plasma concentrations occur between 0.5 and 4 hours after dosing. The PK properties of LCM are proportional to dose, with low intrasubject and intersubject 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, represents about 30% of the dose, and has no known pharmacological activity. After single dose administration in healthy subjects, bioequivalence has been shown between the tablet and solution for iv infusion as well as between the tablet and oral solution (syrup) formulations.

The efficacy and safety of LCM have also been evaluated in Phase 2/3 studies as adjunctive oral therapy in over 1300 adult subjects with partial-onset seizures and as oral monotherapy in over 2400 adult subjects in other indications (eg, neuropathic pain, osteoarthritis). The development programs for osteoarthritis and diabetic neuropathic pain were discontinued and LCM is not approved for these indications. Further information on LCM preclinical results, as well as the PK, efficacy, and safety profiles, can be obtained from the current version of the LCM Investigator's Brochure.

SP0993 was designed to compare the efficacy and safety of LCM to CBZ-CR when used as monotherapy in subjects ≥16 years of age newly or recently diagnosed with epilepsy and experiencing partial-onset seizures or generalized tonic-clonic seizures and employed a noninferiority design in accordance with EMA guidelines (CHMP/EWP/566/98, 2010). Subjects were randomized to receive either CBZ-CR (400mg/day to 1200mg/day) or LCM (200mg/day to 600mg/day). The dose ranges for CBZ-CR and LCM used in SP0994 are anticipated to be clinically [redacted] and effective for monotherapy treatment (Gilliam et al, 1998; Faught et al, 1993; Sachdeo et al, 1992).

SP0994 was designed as a follow-up study for SP0993 allowing collection of long-term safety and tolerability data in a controlled and blinded manner and also allowed subjects who completed SP0993 to continue with the same treatment regime they had been randomized to in SP0993 while also maintaining the study blind for SP0993 until SP0993 database lock.

Following the database lock and unblinding of SP0993, SP0994 will be unblinded. The individual subject treatment (ie, LCM or CBZ-CR) will be made known to both the subject and the investigator. Once the program for follow-up access to LCM monotherapy is established and

the SP0993 database is locked, a Termination Visit will be scheduled as soon as possible. For subjects who were receiving LCM in SP0994, continued access to open-label follow-up treatment with LCM will be provided by UCB within SP1042 for use as monotherapy until marketing application for LCM is approved and LCM is commercially available for monotherapy in the subject's country, or UCB has determined that the clinical development program for the monotherapy indication will be formally discontinued, or up to a maximum period of 3 years, whichever is earlier. Subjects who were receiving CBZ-CR in SP0994, and who wish to continue treatment after the close of SP0994, may be prescribed CBZ by their physician (ie, not supplied by UCB) if medically appropriate and will not be required to taper CBZ. Subjects receiving CBZ-CR will not be allowed to participate in SP1042. Subjects who do not continue treatment with LCM or CBZ-CR should be tapered off study medication.

The present study, SP1042, is an open-label follow-up study designed to allow the collection of long-term safety data of LCM (200mg/day to 600mg/day) used as monotherapy in subjects who were treated with LCM and completed SP0994 and will allow such subjects to continue with the same treatment until marketing application for LCM is approved and LCM is commercially available for monotherapy in the subject's country, or UCB has determined that the clinical development program for the monotherapy indication will be formally discontinued, or up to a maximum period of 3 years, whichever is earlier.

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), and the applicable regulatory requirements.

3 STUDY OBJECTIVE

The primary objective of the study is to assess the long-term safety and tolerability of LCM dosed at 200mg/day to 600mg/day when used as monotherapy in subjects, with partial-onset seizures or generalized tonic-clonic seizures (without clear focal origin), who completed SP0994 and received LCM.

4 STUDY VARIABLES

4.1 Safety variables

4.1.1 Primary safety variables

The primary safety variables are as follows:

- AEs reported spontaneously by the subject and/or caregiver or observed by the investigator
- Withdrawals due to AEs
- SAEs

5 STUDY DESIGN

5.1 Study description

SP1042 is a long-term, open-label, follow-up study for subjects being treated with LCM monotherapy at the time of unblinding of SP0994. Following the database lock and unblinding of SP0993, SP0994 will be unblinded. Once the program for follow-up access to LCM monotherapy is established and the SP0993 database is locked, a Termination Visit will be

scheduled as soon as possible for subjects in SP0994. Subjects in SP0994 who were receiving LCM will have the opportunity to participate in SP1042 and will have access to open-label follow-up treatment with LCM. Subjects who were receiving CBZ-CR or who were in LCM taper in SP0994 at the time of unblinding will not be allowed to participate in SP1042. Subjects who do not wish to continue LCM therapy after unblinding of SP0994 will be tapered off LCM and will not participate in SP1042.

Visit 1 for SP1042 will be the same as the Termination Visit of SP0994. Prior to or at Visit 1 of SP1042, the subject's informed consent will be signed and eligibility assessed, concomitant medications including AEDs will be recorded, AEs will be assessed, and LCM dispensed (call to interactive voice/web response system [IXRS]). The subject will subsequently enter the Treatment Phase of SP1042. Clinic visits are scheduled approximately every 26 weeks relative to the SP1042 Visit 1 date. Dose modifications required for optimization of seizure control or tolerability issues will be addressed in Unscheduled Visits or regularly scheduled visits. A visit window of ±7 days relative to Visit 1 is applicable for all regularly scheduled visits.

In SP0994, subjects will be receiving a dose of LCM 200mg/day, 300mg/day, 400mg/day, 500mg/day, or 600mg/day and will continue to receive the same dose in SP1042 until further dose adjustments are required.

During SP1042 visits, investigators will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure control for each subject. The investigator may maintain the subject's LCM dose, decrease the dose in decrements of 100mg/day per week to a minimum dose of LCM 200mg/day, or increase the dose in increments of 100mg/day per week up to a maximum dose of LCM 600mg/day. Lacosamide doses administered in this study must be from 200mg/day to 600mg/day, must comply with doses that can be administered with LCM 50mg tablets, and should be a dose that can be administered in equal divided doses twice daily. The IXRS should be called any time there is a dose increase or dose reduction.

In order to continue study participation, subjects must maintain treatment with LCM monotherapy.

Subjects requiring dose escalation

If the subject experiences a seizure at the existing dose levels, and in the opinion of the investigator, dose increase is the best option for the subject, the subject should attend a clinic visit for dose escalation. This dose escalation will be managed via an Unscheduled Visit, or a regularly scheduled clinic visit. The investigator can increase the LCM dose with weekly titration of the dose (as described above) for adequate seizure control up to a maximum dose of LCM 600mg/day.

If this is still not sufficient to control seizures, then the subject must be withdrawn from the study and either:

- Switched from LCM to other AED per investigator's choice (In this case LCM needs to be tapered) or
- Other AEDs must be added to LCM as adjunctive therapy. In this case no LCM taper is necessary, but the LCM dose should be adapted per investigator's judgment.

In case the subject has experienced tolerability issues previously at a higher dose in SP0993/SP0994, then it will be at the investigator's discretion to allow the subject to continue in

the study with appropriate dose escalation for adequate seizure control or to withdraw the subject from the study after appropriate tapering of LCM therapy.

Subjects requiring dose reduction

If, in the opinion of the investigator, the subject's AEs indicate that the dose is at an intolerable level, the subject's dose can be decreased (in decrements of not more than 100mg/day per week) to a minimum of LCM 200mg/day, provided an optimum seizure control can be achieved at the reduced dose. It will be at the investigator's discretion to withdraw the subject from the study in case a dose reduction for tolerability issues cannot be achieved without compromising optimum seizure control. This dose reduction will be managed via an Unscheduled Visit, phone call, or a regularly scheduled clinic visit. Subjects who enter SP1042 on the lowest dose level (LCM 200mg/day) and who develop intolerance should be withdrawn from the study.

If, in the investigator's opinion, a lower dose of LCM is medically more suitable for a subject, the decision to allow such patients to continue study on a lower dose of LCM will be made based on appropriate medical justification and after prior discussion with the study Medical Monitor.

The overall dosing schedule during the Treatment Phase is summarized in Table 7–1.

Early Termination Visit with tapering of LCM

Subjects who discontinue prematurely from SP1042 and who will not continue further treatment with LCM should gradually taper LCM following an Early Termination Visit. These subjects will perform an Early Termination Visit followed by the visits required for End-of-Study Phase. Subjects should be tapered off LCM at recommended decreasing steps of 200mg/day/week. A slower taper (eg, 100mg/day/week) or faster taper is permitted, if medically necessary; however, the maximum duration of tapering should not exceed 6 weeks. Subjects will attend a Final Visit 2 weeks after the final dose of LCM. In the case of LCM withdrawal and taper, the investigator is allowed to add any other AED during the End-of-Study Phase, following the investigator's medical judgment.

Early Termination Visit without tapering of LCM

Subjects who discontinue from the study as a result of requiring treatment with other AEDs will return for an Early Termination Visit, and may be prescribed LCM by their physician (ie, not supplied by UCB) as adjunctive therapy if LCM is well tolerated by the subject (dose should be adapted as per investigator's judgment). The Early Termination Visit will be the last study visit for these subjects.

Termination Visit

A termination visit will be performed for subjects who are ongoing in the Treatment Phase at the time that the marketing application is approved and LCM is commercially available for monotherapy in the subject's country, or UCB has determined that the clinical development program for the monotherapy indication will be formally discontinued, or up to a maximum period of 3 years, whichever is earlier. Subjects may be immediately prescribed commercially available LCM. In this instance, the Termination Visit will be the last study visit completed by the subject. If subjects do not continue with LCM treatment, following the Termination Visit, subjects will be tapered off LCM. The Final Visit will be conducted 2 weeks after the final dose of LCM.

Dosing schedules during the End-of-Study Phase are described in Table 7–1.

5.1.1 Study duration per subject

Subjects will be allowed to continue treatment in this study until marketing application is approved and LCM is commercially available for monotherapy in the subject's country, or UCB has determined that the clinical development program for the monotherapy indication will be formally discontinued, or up to a maximum period of 3 years, whichever is earlier. The maximum total duration of the study will be 164 weeks, including up to a 156-week Treatment Phase duration and up to an 8-week End-of-Study Phase.

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

5.1.2 Planned number of subjects and sites

Approximately 150 subjects will participate at approximately 70 sites.

5.1.3 Anticipated regions and countries

The countries planned for participation in this study are Bulgaria, Finland, France, Germany, Japan, Latvia, Mexico, Philippines, Poland, Republic of Korea, Russia, Sweden, Switzerland, and Ukraine.

5.2 Schedule of study assessments

Table 5–1 presents the tabular scheme of study assessments.

Table 5–1: Schedule of study assessments

Assessments	Treatment Phase[a]		Early Termination /Termination Visit[b]	End-of-Study Phase[c]	Unscheduled Visit[d]
Visit	**V1[e]**	**V2, V3, V4, V5, V6**		**Final Visit**	
Week	**W0**	**W26, W52, W78, W104, W130**	**NA**	**NA**	**NA**
Written informed consent	X				
Demographic data	X				
Verification of inclusion/exclusion criteria	X				
Concomitant AEDs[f]	X	X	X	X	X
Concomitant medications	X	X	X	X	X
Concomitant medical procedures	X	X	X	X	X
Laboratory tests:					
Chemistry	X[g]	X	X	X	
Hematology	X[g]	X	X	X	
Urinalysis	X[g]	X	X	X	
Pregnancy Test[h]	X[g]	X	X	X	
Call IXRS[i]	X	X	X	X	
Dispense IMP	X	X	X[j]		
Review/return IMP		X	X	X	
Withdrawal criteria		X			X

Table 5–1: Schedule of study assessments

Assessments	Treatment Phase[a]		Early Termination /Termination Visit[b]	End-of-Study Phase[c]	Unscheduled Visit[d]
Visit	**V1[e]**	**V2, V3, V4, V5, V6**		**Final Visit**	
Week	**W0**	**W26, W52, W78, W104, W130**	**NA**	**NA**	**NA**
Recording of adverse events[k]	X	X	X	X	X

AED=antiepileptic drug; ECG=electrocardiogram; IMP=investigational medicinal product; IXRS=Interactive Voice Response System; LCM=lacosamide; NA=not applicable; V=Visit; W=week;

[a] A visit window of ±7 days relative to the Visit 1 is applicable for all regularly scheduled visits. A clinic visit will occur approximately every 26 weeks relative to the SP1042 Visit 1.

[b] The Termination Visit will be performed at Week 156 or earlier, ie, in countries where marketing application is approved and LCM is commercially available for monotherapy prior to Week 156, or UCB has determined that the clinical development program for the monotherapy indication will be formally discontinued prior to Week 156. An Early Termination Visit must be completed for all subjects who prematurely discontinue from the study, followed by a Final Visit (End-of-Study Phase). The Final Visit will occur 2 weeks after the final dose of LCM.

[c] The End-of-Study Phase starts after the Early Termination Visit or Termination Visit. In case of LCM withdrawal and taper, the investigator is allowed to add any other AED during the End-of-Study Phase, following the investigator's medical judgment. A Final Visit will be completed 2 weeks after the final dose of LCM.

[d] An Unscheduled Visit may be performed at the discretion of the investigator. Such visits may be necessary if the dosage of LCM is to be adjusted. If an Unscheduled Visit is needed, then the assessments noted will be performed. Additional assessments may be performed at the investigator's discretion.

[e] Visit 1 for SP1042 will be the same as the Termination Visit of SP0994. Prior to or at Visit 1 of SP1042, the subject's informed consent will be signed and eligibility assessed, concomitant medications including AEDs will be recorded, AEs will be assessed, and LCM dispensed (call to IXRS).

[f] If circumstances obligate the investigator to add an additional AED treatment as a function of safety (eg, seizure control), the subject must be withdrawn from the study but the additional AED may be added prior to the subject's termination from the study if this treatment approach is in the best safety interest of the subject. The use of benzodiazepines as rescue for epilepsy is allowed if taken at a maximum frequency of once per week. The use of benzodiazepines for indications other than epilepsy rescue therapy is permitted.

[g] The designated procedures will serve as the point of data for both the Termination Visit of SP0994 and Visit 1 of SP1042.

[h] Urine pregnancy tests may be performed for all designated study visits.

[i] The IXRS should be called for any cases of dose adjustment.

[j] Dispensing of LCM will be done at the Termination Visit/Early Termination Visit only if tapering of LCM is required.

[k] If the subject reports an AE which could be due to a cardiac condition, an electrocardiogram (ECG) should be performed. Signs and symptoms of depression and/or suicidal ideation or suicidal behavior should be monitored as a part of the AE assessment.

5.3 Rationale for study design and selection of dose

SP1042 is an open-label follow-up study designed to allow the collection of long-term safety and tolerability data of LCM (200mg/day to 600mg/day) used as monotherapy in subjects, having partial-onset or generalized tonic-clonic seizures, treated with LCM as monotherapy and who completed SP0994. The study will allow subjects treated with LCM in SP0994 to continue treatment in SP1042 until marketing application is approved and LCM is commercially available for monotherapy in the subject's country, or UCB has determined that the clinical development program for the monotherapy indication will be formally discontinued, or for a maximum of 3 years duration, whichever is earlier.

Subjects will be receiving LCM in a dose range of 200mg/day to 600mg/day and this dose range is anticipated to be clinically [redacted] and effective for monotherapy treatment.

Subjects will be monitored for seizure control and occurrence of AEs throughout the study.

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 form is signed and dated by the subject or by the parent(s) or legal representative. The Informed Consent form or a specific Assent form, where required, will be signed and dated by minors.
2. Subject/legal representative is considered reliable and capable of adhering to the protocol, visit schedule, and medication intake according to the judgment of the investigator.
3. Subject has completed the Termination Visit of SP0994 and has been treated with LCM monotherapy.

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 any investigational drugs or using any experimental devices in addition to LCM.
2. Subject experienced a seizure at the third target dose (ie, LCM 600 mg/day) during SP0994.
3. Subject requires another AED for the treatment of seizures.
4. Subject meets a "must" withdrawal criterion for the previous study, SP0994.
5. Subject is experiencing an ongoing SAE from the previous study, SP0994.
6. Female subject who is pregnant or nursing, and/or a woman of childbearing potential who is not surgically sterile, 2 year postmenopausal or does not practice one highly effective method of contraception (according to ICH guidance defined as those that result in a failure rate of less than 1% per year when used consistently and correctly), unless sexually abstinent, for the duration of the study.

6.3 Withdrawal criteria

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

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

1. Subject experiences emergence of a seizure type other than partial-onset seizures or generalized tonic-clonic seizures (without clear focal origin), or occurrence of status epilepticus, or for any other safety reason.
2. Subject develops second or third degree atrioventricular (AV) block or if the investigator feels it is in the best interest of the subject to withdraw from the study.
3. Subject experiences a seizure in SP1042 at the highest allowed LCM dose (600mg/day) and requires either an increase in dose or the addition of or change to another AED.
4. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test. Female subjects who plan to become pregnant should inform the investigator and should also be withdrawn from the study.
5. Subject requires another AED for any reason. If circumstances obligate the investigator to add an additional AED treatment as a function of safety (eg, seizure control), the subject must be withdrawn from the study but the additional AED may be added prior to the subject's termination from the study if this treatment approach is in the best safety interest of the subject.
6. Request of the sponsor or regulatory agency.
7. Subject is unwilling or unable to continue and withdraws his/her consent.
8. 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. 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 study medication.
9. Subject experiences AEs related to suicide attempt or severe suicidal ideation.

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

1. Subject requires a medication that is not permitted. Benzodiazepines as rescue therapy for epilepsy may be used as needed but not more frequently than once per week. The use of benzodiazepines for a nonepilepsy indication is permitted.
2. Subject is noncompliant with the study procedures or medications, in the opinion of the investigator.
3. Transaminases (AST, ALT, or both) ≥3xULN to <5xULN, in the presence of normal total bilirubin, will be repeated within a few days. If the repeat testing confirms the abnormality

(ie, transaminases are ≥3xULN to <5xULN with normal bilirubin), then weekly monitoring of LFTs should continue until resolved (ie, <3xULN or stable condition). The investigator is to decide whether or not to stop the study medication.

4. Subject develops an illness that would interfere with his/her continued participation.
5. Subject requires a LCM dose level below 200mg/day. In the investigator's opinion, if a lower dose of LCM is medically appropriate for a subject, a decision to continue such subjects in the study will be made after prior consultation with the Medical Monitor and with appropriate medical justification.

Subjects meeting "**must**" Withdrawal Criteria must return for the Early Termination Visit and complete all Early Termination assessments. Subjects who require taper will enter the End-of-Study Phase and should complete a Final Visit 2 weeks after the final dose of IMP.

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 Case Report form (CRF) must document the primary reason for withdrawal or discontinuation.

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

7 STUDY TREATMENT

7.1 Description of investigational medicinal product

Investigational medicinal product (IMP) is LCM oral tablets. This product will be supplied by the UCB Clinical Supply Unit. Drug supplies will consist of commercially available LCM formulation (VIMPAT® - pinkish, oval film-coated tablets debossed with "SP" on one side and "50" on the other side) and will be distributed in study-specific labeled packages at a strength of 50mg.

7.2 Treatment to be administered

Lacosamide will be administered orally twice daily (at approximately 12 hour intervals in the morning and in the evening) in 2 divided doses (see Table 7–1). Medication must not be chewed and must be swallowed with a sufficient amount of fluid.

The dosing schedules during the Treatment Phase and End-of-Study Phase are presented in Table 7–1. Subjects stopping LCM should be tapered off LCM at recommended decreasing steps of 200mg/day/week. A slower taper (eg, 100mg/day/week) or faster taper is permitted, if medically necessary; however, the maximum duration of tapering should not exceed 6 weeks.

Table 7–1: LCM dosing schedule for Treatment Phase and End-of-Study Phase (if tapering is required)

Daily dose	Treatment Phase		End-of-Study Phase									
			First week		Second week		Third week		Fourth week		Fifth week	
	AM dose (mg)	PM dose (mg)	AM dose (mg)	PM dose (mg)	AM dose (mg)	PM dose (mg)	AM dose (mg)	PM dose (mg)	AM dose (mg)	PM dose (mg)	AM dose (mg)	PM dose (mg)
LCM 200mg/day (100mg bid)	100	100	-	-	-	-	Subject has exited study					
Number of LCM tablets	2	2	-	-	-	-						
LCM 300mg/day (150mg bid)	150	150	50	50	-	-	-	-	Subject has exited study			
Number of LCM tablets	3	3	1	1	-	-	-	-				
LCM 400mg/day (200mg bid)	200	200	100	100	-	-	-	-	Subject has exited study			
Number of LCM tablets	4	4	2	2	-	-	-	-				
LCM 500mg/day (250mg bid)	250	250	150	150	50	50	-	-	-	-	Subject has exited study	
Number of LCM tablets	5	5	3	3	1	1	-	-	-	-		
LCM 600mg/day (300mg bid)	300	300	200	200	100	100	-	-	-	-	Subject has exited study	
Number of LCM tablets	6	6	4	4	2	2	-	-	-	-		

-=no tablet; AM=morning; bid=twice daily; LCM=lacosamide; PM=evening

7.3 Packaging

Lacosamide tablets are manufactured, packaged, and labeled according to Good Manufacturing Practice (GMP) guidelines and applicable laws or regulations. The IMP is suitably packaged in such a way as to protect the IMP from deterioration during transport and storage.

The IMP will be packaged in clinical high-density polyethylene bottles with study-specific labels. The sites' supplies will be controlled by the IXRS. All the bottles will be uniquely numbered.

7.4 Labeling

Clinical drug supplies will be labeled in accordance with the current ICH guidelines on GCP and GMP and will include any locally required statements. If necessary, labels will be translated into the local language.

7.5 Handling and storage requirements

The investigator (or designee) is responsible for the safe and proper storage of IMP at the site. Investigational medicinal product stored by the investigator is to be kept in a secured area with limited access.

Appropriate storage conditions must be ensured either by controlled room temperature or by completion of a temperature log in accordance with local requirements on a regular basis (daily to weekly), showing minimum and maximum temperatures reached over the time interval.

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 Clinical Supply Associate or designee. Based on discussion with a UCB Quality Assurance representative, the Clinical Supply Associate or designee will then provide the CPM (or designee) with instructions for the site regarding use of the IMP.

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

7.6 Drug accountability

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

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

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

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

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers) 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 (defined as less than 75% or more than 125% compliant with the dosage schedule), 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 treatments (medications and therapies)

The following concomitant medications are permitted during the study:

- The use of benzodiazepines as rescue therapy for epilepsy is allowed if taken at a maximum frequency of once per week during study participation; more frequent use precludes subjects from study participation.
- Benzodiazepines used for nonepileptic conditions will be allowed in the study.

  All medications, that are not included in the section of prohibited medication below, will be allowed for use as a concomitant treatment in case of necessity.

7.8.2 Prohibited concomitant treatments (medications and therapies)

Addition or use of any concomitant AED during the study period is forbidden except if circumstances oblige the investigator to do so as a function of safety. Any additions of concomitant AEDs during the study period constitute a protocol deviation. If this occurs, the investigator will contact the Medical Monitor immediately. In the case of study withdrawal and LCM taper, the investigator is allowed to add any other AED, following the investigator's medical judgment.

7.8.3 Permitted agents to be used with caution

Lacosamide should be used with caution in patients treated with medicinal products known to be associated with PR prolongation and in patients treated with Class I antiarrhythmics (eg, quinidine, procainamide, disopyramide, lidocaine, propafenone).

7.9 Blinding

Not applicable.

7.10 Randomization and numbering of subjects

Subject numbers were assigned at the beginning of SP0993 and will remain the same in SP1042.

8 STUDY PROCEDURES BY VISIT

A visit window of ±7 days relative to Visit 1 is applicable for all regularly scheduled visits. A clinic visit will occur approximately every 26 weeks relative to the SP1042 Visit 1 date.

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

8.1 Visit 1 (Week 0)

Visit 1 of SP1042 will correspond to the last visit of SP0994 which is the Termination Visit.

Prior to or at Visit 1 in SP1042, a complete explanation (both verbal and written) of the nature and purpose of the study will be given to the subject by the investigator (or designee). Before conduct of any study-related procedures, the subject is required to sign and date the IRB/IEC approved informed consent if he/she decides to participate in the study.

Prior to or at Visit 1, the subject's eligibility will be assessed based on the inclusion/exclusion criteria, concomitant medications including AEDs will be recorded, AEs will be assessed, and LCM dispensed (call to IXRS).

The following assessments and procedures will be performed for eligible subjects during Visit 1 of SP1042:

- Written Informed Consent
- Verification of inclusion/exclusion criteria
- Demographic data
- Concomitant AEDs
- Concomitant medications
- Concomitant medical procedures
- Call IXRS (for any dose adjustments)
- Dispense IMP

The following procedures will correspond to both the Termination Visit of SP0994 and Visit 1 of SP1042:

- Blood sample for clinical chemistry and hematology
- Urine sample for urinalysis
- Urine pregnancy test
- Recording of AEs

8.2 Visit 2, 3, 4, 5, 6 (Week 26, 52, 78, 104, 130)-Treatment Visits

The following assessments and procedures will be performed at the visits:

- Concomitant AEDs
- Concomitant medications
- Concomitant medical procedures

- Blood sample for clinical chemistry and hematology
- Urine sample for urinalysis
- Urine pregnancy test
- Recording of AEs
- Call IXRS (for any dose adjustments)
- Dispense IMP
- Review/return IMP
- Withdrawal criteria

8.3 Early Termination Visit/Termination Visit

The following assessments and procedures will be performed at the visit:

- Concomitant AEDs
- Concomitant medications
- Concomitant medical procedures
- Blood sample for clinical chemistry and hematology
- Urine sample for urinalysis
- Urine pregnancy test
- Recording of AEs
- Call IXRS
- Dispense IMP (if LCM tapering is required)
- Review/return IMP

8.4 Final Visit

The following assessments and procedures will be performed at the visit:

- Concomitant AEDs
- Concomitant medications
- Concomitant medical procedures
- Blood sample for clinical chemistry and hematology
- Urine sample for urinalysis
- Urine pregnancy test
- Recording of AEs
- Call IXRS
- Review/return IMP

8.5 Unscheduled Visit

An Unscheduled Visit may be performed at any time after Visit 1, at the discretion of the investigator. In addition to the required assessments listed below, further assessments can be completed as needed. The IXRS should be called if IMP has to be dispensed at this visit.

- Concomitant AEDs
- Concomitant medications
- Concomitant medical procedures
- Withdrawal criteria
- Recording of AEs

9 ASSESSMENT OF SAFETY

9.1 Adverse events

9.1.1 Definition of adverse event

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

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

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

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)?"

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 CRF and source documents should be consistent.

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

9.1.4 Follow up of adverse events

An AE should be followed until it has resolved, has a stable sequelae, the investigator determines that it is no longer clinically significant, or the subject is lost to follow up.

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

9.1.5 Rule for repetition of an adverse event

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

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

9.1.6 Pregnancy

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

- The subject should return for an Early Termination Visit.
- The subject should immediately stop the intake of the IMP or undergo tapering as instructed at the Early Termination Visit.
- A Final Visit should be scheduled 2 weeks after the subject has discontinued the IMP.

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

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

In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, the investigator or designee is asked to contact the subject to request consent of the partner via the Partner Pregnancy Consent form that has been approved by the responsible IRB/IEC and should

be available in the investigator site file. In case of questions about the consent process, the investigator may contact the UCB/contract research organization (CRO) contract monitor for the study. The investigator will complete the Pregnancy Report and Outcome form and send it to UCB's DS department (for contact details see SAE reporting information at the beginning of this protocol) only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form. UCB's DS department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow up.

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

9.1.7 Overdose of investigational medicinal product

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

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 DS representative.

As appropriate for the stage of development and accumulated experience with the IMP, medically qualified personnel at UCB may identify additional safety measures (eg, AEs, vital signs, laboratory or electrocardiogram [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. The Investigator SAE Report form must be completed in English.

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

Additional information (eg, autopsy or laboratory reports) received by the investigator must be provided within 24 hours. All documents in the local language must be accompanied by a

translation in English, or the relevant information included in the same document must be summarized in the Investigator SAE report form.

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

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

9.2.3 Follow up of serious adverse events

An SAE should be followed until it has resolved, has a stable sequelae, the investigator determines that it is no longer clinically significant, or the subject is lost to follow up.

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

9.3 Adverse events of special interest

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

The following are AEs of special interest:

- The following arrhythmias: atrial fibrillation/flutter, ventricular tachycardia or fibrillation, AV block (2nd degree Type I and II and 3rd degree), and marked bradycardia (<45 beats/min)
- Syncope or loss of consciousness (other than seizure related)
- Serious suspected multiorgan hypersensitivity reactions

  Serious suspected multiorgan hypersensitivity cases may be identified and reported to the sponsor by the investigator using the following algorithm as agreed with the United States Food and Drug Administration:

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

  Treatment-emergent abnormal laboratory value criteria suggestive of internal organ involvement or eosinophilia:

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

- ALT ≥2xULN
- AST ≥2xULN

9.4 Immediate reporting of adverse events

The following AEs must be reported immediately:

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

9.5 Anticipated serious adverse events

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

This list does not change the investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 9.2.2. The following list of anticipated SAEs has been identified as these events are anticipated to occur in the epilepsy population at some frequency that is independent of drug exposure.

Table 9–1: Anticipated SAEs for the adult epileptic population

MedDRA SOC	MedDRA PT
Congenital, familial and genetic disorders	Teratogenicity
General disorders and administrative site conditions	Sudden unexplained death in epilepsy
Nervous system disorders	Convulsion[a]
	Incontinence
	Status epilepticus
Pregancy, puerperium and perinatal disorders	Abortion spontaneous
Psychiatric disorders	Psychotic behaviour
	Abnormal behaviour
	Anxiety
	Sleep disorder
Reproductive system and breast disorders	Menstrual disorder
	Impotence

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

[a] Convulsion if consistent with the seizure type known for the subject

9.6 Laboratory measurements

Blood and urine specimens for routine assay of hematology, clinical chemistry, and urinalysis testing as well as pregnancy testing will be performed according to the tabular schedule of study procedures in Section 5.2 to monitor the safety of subjects. The specimens will be analyzed by the local laboratory affiliated to the site. At a minimum, the laboratory parameters specified below in Table 9–2 will be tested. The individual laboratory parameter result data will not be collected; however, the investigator will report out of range results judged to be clinically significant as an AE, as noted in Section 9.1.1.

The following laboratory parameters will be measured:

Table 9–2: Laboratory measurements

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

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

9.6.1 Liver function tests

Refer to Section 6.3 for LFT withdrawal criteria.

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

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

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 LCM.

9.6.2 Pregnancy testing

Females of childbearing potential (who have not been surgically sterilized or who are not at least 2 years postmenopausal) will have urine dipstick pregnancy testing performed according to the tabular schedule of study procedures in Section 5.2.

10 STUDY MANAGEMENT AND ADMINISTRATION

10.1 Adherence to protocol

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

After implementation of such measure, the investigator must notify the CPM of the sponsor within 24 hours and follow any local regulatory requirements.

10.2 Monitoring

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

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

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

10.2.1 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 CRFs are not considered acceptable source documents.

Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, completed scales, or quality of life questionnaires, 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 Holter monitor records or electroencephalogram records, must be saved and stored as instructed by UCB (or designee).

10.2.2 Source data verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (eg, subject files, recordings from automated instruments, tracings [ECG], x-ray films, laboratory notes). All data reported on the CRF should be supported by source documents, unless otherwise specified in Section 10.2.1.

10.3 Data handling

10.3.1 Case Report form completion

In the event that the study is performed using electronic data capture (EDC), the investigator is responsible for prompt reporting of accurate, complete, and legible data in the electronic CRFs and in all required reports.

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

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

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

Detailed instructions will be provided in the CRF Completion Guidelines.

10.3.2 Database entry and reconciliation

An EDC system will be used for the study. External electronic data will be 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. In the event that the study is performed using EDC, the data are entered into the electronic CRFs once and are subsequently verified.

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

10.3.3 Subject Screening and Enrollment log/Subject Identification Code list

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.

10.4 Termination of the study

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

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

10.5 Archiving and data retention

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

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

10.6 Audit and inspection

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

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

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

10.7 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.

11 STATISTICS

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

11.1 Definition of analysis sets

The primary analysis set will be the Safety Set, which is defined as all subjects who meet the inclusion/exclusion criteria, sign an Informed Consent form, and take at least 1 dose of study medication. This analysis set will be used for summaries of all parameters.

11.2 General statistical considerations

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

11.3 Planned safety and other analyses

11.3.1 Safety analyses

Treatment-emergent AEs (TEAEs) will be defined as those events which started on or after the date of first dose of IMP in SP1042, or events in which severity worsened on or after the date of first dose of IMP in SP1042. Adverse events which occur within 30 days after final dose of IMP in SP1042 will be considered treatment emergent.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities® (MedDRA), and tabulated by body system and preferred term. The incidence of TEAEs will also be summarized by intensity. Serious AEs and AEs which lead to premature discontinuation will be tabulated and listed.

All TEAEs, AEs leading to withdrawal, and SAEs will be summarized descriptively.

Available data related to laboratory tests will be presented in subject data listings.

11.4 Handling of protocol deviations

Important protocol deviations are deviations from the protocol that could potentially have a meaningful impact on study conduct or on the key safety outcomes for an individual subject. The criteria for identifying important protocol deviations and the classification of important protocol deviations will be defined within the appropriate protocol-specific document (eg, the Protocol Deviation Specification). To the extent feasible, rules for identifying protocol deviations will be defined without review of the data and without consideration of the frequency of occurrence of such deviations.

Important protocol deviations will be reviewed as part of the ongoing data cleaning process prior to database lock.

11.5 Handling of dropouts or missing data

For evaluation of safety variables, subjects who prematurely discontinue the study will be evaluated based on the data collected at each visit attended.

11.6 Planned interim analysis and data monitoring

No interim analysis or data monitoring is planned in the study.

11.7 Determination of sample size

No formal sample size calculations have been performed for this study as there are no statistical hypotheses being tested. The sample size will be determined by the number of subjects in SP0994 who have been treated with LCM that are eligible to enter this open-label follow-up study. It is anticipated that approximately 150 subjects who receive LCM in SP0994 will participate in this follow-up study.

12 ETHICS AND REGULATORY REQUIREMENTS

12.1 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. A CRF 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.

12.2 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.

12.3 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 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.

12.4 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).

12.5 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.

13 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 REFERENCES

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15 APPENDICES

15.1 Protocol Amendment 1

Rationale for the amendment

The purpose of this amendment is to correct a typographical error noted in the visit schedule for the study. As per Table 5-1: Schedule of study assessments, a total of 6 visits: V2, V3, V4, V5, V6, and V7 have been mentioned in the Treatment Phase at Weeks 26, 52, 78, 104, 130, and 156. The last visit in the Treatment Phase, ie, Visit 7/Week 156, has been deleted since this coincides with the Termination Visit and was mentioned in error in the Treatment Phase.

The maximum total duration of the study will be 164 weeks, including up to a 156-week Treatment Phase duration (with visits scheduled every 26 weeks) and up to an 8-week End-of-Study Phase. Last study drug dispensing in the Treatment Phase will occur at V6/Week 130 and the subsequent visit scheduled after 26 weeks, ie, Visit 7/Week 156 will be the same as the Termination Visit. Hence, Visit 7/Week 156, was deleted since the Termination Visit is listed separately.

Modifications and changes

Global changes

The following changes were made throughout the protocol:

- Deletion of Visit 7/Week 156 throughout the protocol

Specific changes

Change #1

Table 5-1: Schedule of study assessments

Table heading rows were updated. Footnote “b” was updated and Footnote “j” was added.

Table 5-1: Schedule of study assessments

Assessments	Treatment Phase[ab]			End-of-Study Phase[c]	Unscheduled Visit[d]
Visit	**V1[e]**	**V2, V3,V4, V5,V6, V7**	**Early Termination /Termination Visit**	**Final Visit**	
Week	**W0**	**W26, W52, W78, W104, W130, W156**	**NA**	**NA**	**NA**
Written informed consent	X				
Demographic data	X				
Verification of inclusion/exclusion criteria	X				
Concomitant AEDs[f]	X	X	X	X	X
Concomitant medications	X	X	X	X	X
Concomitant medical procedures	X	X	X	X	X
Laboratory tests:					
Chemistry	X[g]	X	X	X	
Hematology	X[g]	X	X	X	
Urinalysis	X[g]	X	X	X	
Pregnancy Test[h]	X[g]	X	X	X	
Call IXRS[i]	X	X	X	X	
Dispense IMP	X	X	X		
Review/return IMP		X	X	X	
Withdrawal criteria		X			X

Table 5-1: Schedule of study assessments

Assessments	Treatment Phase[ab]			End-of-Study Phase[c]	Unscheduled Visit[d]
Visit	**V1[e]**	**V2, V3,V4, V5,V6, V7**	**Early Termination /Termination Visit**	**Final Visit**	
Week	**W0**	**W26, W52, W78, W104, W130, W156**	**NA**	**NA**	**NA**
Recording of adverse events[j]	X	X	X	X	X

AED=antiepileptic drug; IMP=investigational medicinal product; IXRS=Interactive Voice Response System; NA=not applicable; V=Visit; W=week; ECG=electrocardiogram

[a] A visit window of ±7 days relative to the Visit 1 is applicable for all regularly scheduled visits. A clinic visit will occur approximately every 26 weeks relative to the SP1042 Visit 1.

[b] Early Termination Visit must be completed for all subjects who prematurely discontinue from the study, followed by a Final Visit (End-of-Study Phase). The Final Visit will occur 2 weeks after the final dose of LCM.

[c] The End-of-Study Phase starts after the Early Termination Visit or Termination Visit. In case of LCM withdrawal and taper, the investigator is allowed to add any other AED during the End-of-Study Phase, following the investigator's medical judgment. A Final Visit will be completed 2 weeks after the final dose of LCM.

[d] An Unscheduled Visit may be performed at the discretion of the investigator. Such visits may be necessary if the dosage of LCM is to be adjusted. If an Unscheduled Visit is needed, then the assessments noted will be performed. Additional assessments may be performed at the investigator's discretion.

[e] Visit 1 for SP1042 will be the same as the Termination Visit of SP0994. Prior to or at Visit 1 of SP1042, the subject's informed consent will be signed and eligibility assessed, concomitant medications including AEDs will be recorded, AEs will be assessed, and LCM dispensed (call to IXRS).

[f] If circumstances obligate the investigator to add an additional AED treatment as a function of safety (eg, seizure control), the subject must be withdrawn from the study but the additional AED may be added prior to the subject's termination from the study if this treatment approach is in the best safety interest of the subject. The use of benzodiazepines as rescue for epilepsy is allowed if taken at a maximum frequency of once per week. The use of benzodiazepines for indications other than epilepsy rescue therapy is permitted.

[g] The designated procedures will serve as the point of data for both the Termination Visit of SP0994 and Visit 1 of SP1042.

[h] Urine pregnancy tests may be performed for all designated study visits.

[i] The IXRS should be called for any cases of dose adjustment.

[j] If the subject reports an AE which could be due to a cardiac condition, an electrocardiogram (ECG) should be performed. Signs and symptoms of depression and/or suicidal ideation or suicidal behavior should be monitored as a part of the AE assessment.

Has been changed to:

Table 5-1: Schedule of study assessments

Assessments	Treatment Phase[a]		Early Termination /Termination Visit[b]	End-of-Study Phase[c]	Unscheduled Visit[d]
Visit	**V1[e]**	**V2, V3, V4, V5, V6**		**Final Visit**	
Week	**W0**	**W26, W52, W78, W104, W130**	**NA**	**NA**	**NA**
Written informed consent	X				
Demographic data	X				
Verification of inclusion/exclusion criteria	X				
Concomitant AEDs[f]	X	X	X	X	X
Concomitant medications	X	X	X	X	X
Concomitant medical procedures	X	X	X	X	X
Laboratory tests:					
Chemistry	X[g]	X	X	X	
Hematology	X[g]	X	X	X	
Urinalysis	X[g]	X	X	X	
Pregnancy Test[h]	X[g]	X	X	X	
Call IXRS[i]	X	X	X	X	
Dispense IMP	X	X	X[j]		
Review/return IMP		X	X	X	
Withdrawal criteria		X			X

Table 5-1: Schedule of study assessments

Assessments	Treatment Phase[a]		Early Termination /Termination Visit[b]	End-of-Study Phase[c]	Unscheduled Visit[d]
Visit	**V1[e]**	**V2, V3, V4, V5, V6**		**Final Visit**	
Week	**W0**	**W26, W52, W78, W104, W130**	**NA**	**NA**	**NA**
Recording of adverse events[k]	X	X	X	X	X

AED=antiepileptic drug; ECG=electrocardiogram; IMP=investigational medicinal product; IXRS=Interactive Voice Response System; LCM=lacosamide; NA=not applicable; V=Visit; W=week;

[a] A visit window of ±7 days relative to the Visit 1 is applicable for all regularly scheduled visits. A clinic visit will occur approximately every 26 weeks relative to the SP1042 Visit 1.

[b] The Termination Visit will be performed at Week 156 or earlier, ie, in countries where marketing application is approved and LCM is commercially available for monotherapy prior to Week 156, or UCB has determined that the clinical development program for the monotherapy indication will be formally discontinued prior to Week 156. An Early Termination Visit must be completed for all subjects who prematurely discontinue from the study, followed by a Final Visit (End-of-Study Phase). The Final Visit will occur 2 weeks after the final dose of LCM.

[c] The End-of-Study Phase starts after the Early Termination Visit or Termination Visit. In case of LCM withdrawal and taper, the investigator is allowed to add any other AED during the End-of-Study Phase, following the investigator's medical judgment. A Final Visit will be completed 2 weeks after the final dose of LCM.

[d] An Unscheduled Visit may be performed at the discretion of the investigator. Such visits may be necessary if the dosage of LCM is to be adjusted. If an Unscheduled Visit is needed, then the assessments noted will be performed. Additional assessments may be performed at the investigator's discretion.

[e] Visit 1 for SP1042 will be the same as the Termination Visit of SP0994. Prior to or at Visit 1 of SP1042, the subject's informed consent will be signed and eligibility assessed, concomitant medications including AEDs will be recorded, AEs will be assessed, and LCM dispensed (call to IXRS).

[f] If circumstances obligate the investigator to add an additional AED treatment as a function of safety (eg, seizure control), the subject must be withdrawn from the study but the additional AED may be added prior to the subject's termination from the study if this treatment approach is in the best safety interest of the subject. The use of benzodiazepines as rescue for epilepsy is allowed if taken at a maximum frequency of once per week. The use of benzodiazepines for indications other than epilepsy rescue therapy is permitted.

[g] The designated procedures will serve as the point of data for both the Termination Visit of SP0994 and Visit 1 of SP1042.

[h] Urine pregnancy tests may be performed for all designated study visits.

[i] The IXRS should be called for any cases of dose adjustment.

[j] Dispensing of LCM will be done at the Termination Visit/Early Termination Visit only if tapering of LCM is required.

[k] If the subject reports an AE which could be due to a cardiac condition, an electrocardiogram (ECG) should be performed. Signs and symptoms of depression and/or suicidal ideation or suicidal behavior should be monitored as a part of the AE assessment.

Change #2

Section 8.2: Heading

Visit 2, 3, 4, 5, 6, 7 (Week 26, 52, 78, 104, 130, 156)-Treatment Visits

Has been changed to:

Visit 2, 3, 4, 5, 6 (Week 26, 52, 78, 104, 130)-Treatment Visits

16 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

17 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.