PROTOCOL EP0100 AMENDMENT 4

AN OPEN-LABEL, SINGLE-ARM, MULTICENTER STUDY OF LEVETIRACETAM AS MONOTHERAPY OR ADJUNCTIVE TREATMENT OF PARTIAL SEIZURES IN PEDIATRIC EPILEPTIC SUBJECTS RANGING FROM 1 MONTH TO LESS THAN 4 YEARS OF AGE

PHASE 3

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Final Protocol	06 Feb 2017	Not applicable
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SERIOUS ADVERSE EVENT REPORTING

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ADF	average daily frequency
AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	blood pressure
CDMS	clinical data management system
CI	confidence interval
CNS	central nervous system
CPM	Clinical Project Manager
CPMP	Committee for Proprietary Medicinal Products
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
DRC	daily record card
ECG	electrocardiogram
eCRF	electronic Case Report form
EDC	electronic data capture
EDV	Early Discontinuation Visit
EEG	electroencephalogram
EMA/EMEA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPSP	Good Postmarketing Study Practice
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
ILAE	International League Against Epilepsy
IMP	investigational medicinal product
IND	Investigational New Drug

IRB	Institutional Review Board
IRT	interactive response technology
IVRS	interactive voice response system
IWRX	interactive web response system
LEV	levetiracetam
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NDA	New Drug Application
PDILI	potential drug-induced liver injury
PK	pharmacokinetic(s)
PK-PPS	Pharmacokinetic Per-Protocol Set
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	Per-Protocol Set
PS	Patient Safety
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SS	Safety Set
TEAE	treatment-emergent adverse event
TMF	trial master file
ULN	upper limit of normal
VNS	vagal nerve stimulation
WBC	white blood cell

1 SUMMARY

EP0100 is an open-label, single-arm, multicenter study with levetiracetam (LEV) as monotherapy or adjunctive treatment to evaluate the efficacy and safety of LEV in Japanese subjects aged 1 month to <4 years with partial seizures. The study will consist of 2 periods. The First Period is designed to confirm efficacy of LEV, and the Second Period is designed to evaluate the long-term efficacy and safety of LEV. Subjects with uncontrolled partial seizures will be enrolled into the Selection Period of the First Period.

Seizure counts during the 2 weeks prior to Visit 1 will be used as a Retrospective Baseline. All eligible subjects will enter a 6-week Evaluation Period. Subjects aged 1 month to <6 months will be started on LEV 14mg/kg/day at Visit 3 (Week 0). The dose may be increased by LEV 14mg/kg/day for subjects aged 1 month to <6 months at 2-week intervals to a maximum dose of 42mg/kg/day. Subjects aged 6 months to <4 years will be started on LEV 20mg/kg/day at Visit 3 (Week 0). The dose may be increased by LEV 20mg/kg/day at 2-week intervals to a maximum dose of 60mg/kg/day.

At Visit 6 (Week 6), subjects may enter the Second Period or enter the Down-Titration Period followed by a Safety Follow-Up Period. Subjects who do not enter the Second Period will be down-titrated. The dose will be decreased by LEV 14mg/kg/day for subjects aged 1 month to <6 months or by LEV 20mg/kg/day for subjects aged 6 months to <4 years at 2-week intervals to 0mg/kg/day. Subjects who withdraw from the study at the minimum age-related dose do not need to down-titrate. In order to provide LEV to subjects who completed the First Period, the Second Period will be conducted until approval or the program is discontinued.

All subjects who do not enter the Second Period will enter the Safety Follow-Up Period, regardless of whether they down-titrate LEV.

After approval in Japan for the indication of LEV as monotherapy or adjunctive treatment in patients aged 1 month to <4 years with partial seizures, this clinical study (Phase 3) will be continued as a postmarketing clinical study (Phase 4). All subjects who are still in the study as of the date of approval will be considered to have completed the study. After the date of approval, subjects should visit the investigational site as soon as possible to complete the study by switching to commercial LEV or discontinuing LEV after the assessments specified in Section 8.5 “Early Discontinuation Visit” in the protocol.

After the study is continued as a postmarketing clinical study (Phase 4), the LEV dry syrup 50% prescribed during the study period will continue to be used, and the labeling of the IMP will not be changed. There will also be no change in the handling and storage conditions of the IMP.

After the date of approval, EP0100 shall be continued as a postmarketing clinical study (Phase 4), and the description of EP0100 in this protocol shall read as follows. The term "clinical study" should be replaced with "postmarketing clinical study," the term "clinical trial" should be replaced with "postmarketing clinical study", the term "this (clinical) study" should be replaced with "this postmarketing clinical study", the term "protocol" should be replaced with "postmarketing clinical study protocol", the term "investigator" should be replaced with "investigator for postmarketing clinical study", the term "subinvestigator" should be replaced with "subinvestigator for postmarketing clinical study", the term "IMP" should be replaced with "IMP for postmarketing clinical study ", the term "Investigator’s Brochure" should be replaced with "package insert or precautions information", the term "Phase 3" should be replaced with

"Phase 4", the term "subject's ID card" should be replaced with "subject's ID card for postmarketing clinical study participation", and the term "Good Clinical Practice (GCP)" should be replaced with "GCP and Good Postmarketing Study Practice (GPSP)".

2 INTRODUCTION

Epilepsy is one of the most common and challenging neurological disorders. About 65 million people worldwide are estimated to have epilepsy (Thurman et al, 2011). In Japan, the number of patients with epilepsy is estimated to be approximately 216,000 (MHLW, 2011). In addition, epilepsy affects 0.5% to 1% of the Japanese population (Inoue, 2005). There is also a report that suggests the total number of patients with epilepsy in Japan is approximately 1 million (Ueda, 2007). The incidence varies greatly with age, with high rates occurring in childhood, falling to low levels in early adult life, but with a second peak in those aged over 65 years. In many people, particularly children, the condition may remit, although a significant proportion will have epilepsy lifelong. The disease duration is often determined by the underlying cause. As appropriate treatment in the initial stages of epilepsy is said to have a major impact on prognosis and mental development (Berg et al, 2014; Kwan and Brodie, 2001), it is important to provide appropriate pharmacotherapy at an early stage and prescribe treatment with a high level of safety in order to maintain patients' daily and social activities in their long lives ahead.

Levetiracetam has been developed as adjunctive therapy in the treatment of partial seizures in children aged 1 month to <4 years with epilepsy in N01009 and the open-label extension study N01148. The European Medicines Agency (EMA) and US Food and Drug Administration (FDA) approved the indication of adjunctive treatment in children down to 1 month of age with partial seizures in Sep 2009 and Dec 2011, respectively. UCB also conducted a noninterventional, post authorization safety study (N01357, Jan 2011 through Nov 2013), as agreed with the EMA. The objective of the study was to collect safety and efficacy data on Keppra® in clinical practice in subjects aged 1 month to <12 months with epilepsy. The study was conducted as a part of a risk management plan after obtaining approval for the indication in the EU (Sep 2009).

In Japan, an open-label, single-arm, multicenter study (N01223) demonstrated that long-term adjunctive treatment with LEV (20mg/kg/day or 1000mg/day to 60mg/kg/day or 3000mg/day) was effective in Japanese children aged 4 to <16 years with partial seizures. The Pharmaceuticals and Medical Devices Agency (PMDA) approved the indication of LEV as adjunctive therapy in Japanese children aged 4 to <16 years with uncontrolled partial seizures in May 2013.

For the purpose of this study, the seizure type classification will follow the 1981 International League Against Epilepsy (ILAE) classification of epileptic seizures, which speaks of partial seizures, classified as simple partial seizures (no alteration of consciousness), complex partial seizures (with alteration of consciousness), and secondarily generalized seizures, and defines generalized seizure types, referred to as absence seizures (typical and atypical), myoclonic seizures, clonic seizures, tonic seizures, tonic-clonic seizures, and atonic seizures. Apart from myoclonic seizures, consciousness is almost invariably impaired from the onset of the seizure (ILAE, 1981, Appendix 1 [Section 17.1]).

Likewise, the classification of epilepsy syndromes will be used according to the 1989 ILAE-publication (ILAE, 1989, Appendix 2 [Section 17.2]).

This study is designed to confirm the dosage and administration for Japanese subjects aged 1 month to <4 years. The First Period is designed to confirm efficacy of LEV, and the Second Period is designed to evaluate the long-term efficacy and safety of LEV.

EP0100 was initially started with a design to evaluate the efficacy of LEV using the percent reduction from Baseline in partial seizure frequency based on the number of seizures recorded by video-electroencephalography (EEG) as the primary efficacy endpoint, but subject recruitment was extremely difficult. One of the major factors for the difficulty in recruitment was that the 48h video-EEG measurement was to be performed 3 times at Baseline, Week 2, and Week 6, thus increasing the burden on the subject/guardian. As a result, consent to participate in the study was not obtained from the guardian, and many potential subjects could not be screened for entry into the study. After consultation with the PMDA, the method of recording seizures was changed to a conventional patient diary, and the primary endpoint was changed to percent reduction in partial seizure frequency based on the patient diary. The percent reduction in partial seizure frequency calculated from the 48h video-EEG is included as an "other" efficacy variable.

3 STUDY OBJECTIVES

3.1 Primary objective

The primary objective of this study is to confirm the efficacy of LEV in reducing seizure frequency in the First Period compared to historical control as adjunctive treatment in pediatric epilepsy subjects aged 1 month to <4 years with partial seizures.

3.2 Secondary objectives

The secondary objectives are the following:

- To evaluate the safety and tolerability of LEV in the First Period in pediatric epilepsy subjects aged 1 month to <4 years with partial seizures
- To evaluate the efficacy of LEV in reducing seizure frequency in the First Period compared to historical control as monotherapy in pediatric epilepsy subjects aged 1 month to <4 years with partial seizures
- To evaluate long-term safety and tolerability of LEV in the combined First and Second Periods in pediatric epilepsy subjects aged 1 month to <4 years with partial seizures receiving long-term treatment with LEV at individualized doses
- To evaluate the efficacy of LEV in the combined First and Second Periods as monotherapy or adjunctive treatment in pediatric epilepsy subjects aged 1 month to <4 years with partial seizures
- To characterize pharmacokinetics (PK) of LEV in the First and Second Periods in epileptic pediatric subjects aged 1 month to <4 years

4 STUDY VARIABLES

4.1 Efficacy variables

Efficacy variables are defined separately for the First Period and the combined First and Second Periods, and for the type of therapy, if applicable.

4.1.1 Efficacy variables for subjects on adjunctive therapy

4.1.1.1 Primary efficacy variable

4.1.1.1.1 First Period

The primary efficacy variable for subjects on adjunctive therapy is the percent reduction in partial seizure frequency per week from Baseline to Visit 6.

4.1.1.1.2 Combined First and Second Periods

There is no primary efficacy variable for the combined First and Second Periods for subjects on adjunctive therapy.

4.1.1.2 Secondary efficacy variables

4.1.1.2.1 First Period

The secondary efficacy variable for the First Period is the following:

- Percent reduction in partial seizure frequency per week from Baseline to Visit 4 and Visit 5

4.1.1.2.2 Combined First and Second Periods

The secondary efficacy variables for the combined First and Second Periods are the following:

- For each visit, percent reduction in partial seizure frequency per week from Baseline
- For each visit, percent reduction in partial seizure frequency per week from Baseline grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100%

4.1.1.3 Other efficacy variables

4.1.1.3.1 First Period

The other efficacy variables for the First Period for the number of seizures based on the 48h video-EEG recorded through Protocol Amendment 2 are the following:

- Percent reduction in average daily frequency (ADF) of partial seizure frequency monitored by the 48h video-EEG at Visit 4 and Visit 6 compared to Baseline
- Percent reduction in ADF of partial of seizure frequency monitored by the 48h video-EEG grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100% based on the Evaluation Period 48h video-EEG at Visit 4 and Visit 6 compared to Baseline

4.1.1.3.2 Combined First and Second Periods

The other efficacy variables for the combined First and Second Periods are the following:

- For each visit, percent reduction in all type of seizure frequency per week from Baseline
- For each visit, percent reduction in all type of seizure frequency per week from Baseline grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100%

4.1.2 Efficacy variables for subjects on monotherapy

4.1.2.1 Primary efficacy variable for subjects on monotherapy

There is no primary efficacy variable for subjects on monotherapy.

4.1.2.2 Secondary efficacy variables

4.1.2.2.1 First Period

There is no secondary efficacy variable for the First Period.

4.1.2.2.2 Combined First and Second Periods

The secondary efficacy variables for the combined First and Second Periods are the following:

- For each visit, percent reduction in partial seizure frequency per week from Baseline
- For each visit, percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100%

4.1.2.3 Other efficacy variables

4.1.2.3.1 First Period

The other efficacy variables for the First Period for the number of seizures based on the 48h video-EEG recorded through Protocol Amendment 2 are the following:

- Percent reduction in ADF of partial seizure frequency monitored by the 48h video-EEG to Visit 4 and Visit 6 compared to Baseline
- Percent reduction in ADF of partial of seizure frequency monitored by the 48h video-EEG grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100% based on the Evaluation Period 48h video-EEG at Visit 4 and Visit 6 compared to Baseline

4.1.2.3.2 Combined First and Second Periods

The other efficacy variables for the combined First and Second Periods are the following:

- For each visit, percent reduction in all types of seizure frequency per week from Baseline
- For each visit, percent reduction in all types of seizure frequency per week from Baseline grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100%
- Percentage of subjects who are continuously 6-month seizure-free monitored by the patient diary

4.2 Pharmacokinetic and pharmacodynamic variables

Levetiracetam (parent compound only) plasma levels is defined as the other PK variable.

4.3 Safety variables

4.3.1 Primary safety variable

There is no primary safety variable.

4.3.2 Secondary safety variables

4.3.2.1 First Period

The secondary safety variables for the First Period are the following:

- Incidence of treatment-emergent adverse events (TEAEs)
- Incidence of treatment-emergent serious adverse events (SAEs)
- Incidence of TEAEs leading to discontinuation from study medication

4.3.2.2 Combined First and Second Periods

The secondary safety variables for the combined First and Second Periods are the following:

- Incidence of TEAEs
- Incidence of treatment-emergent SAEs
- Incidence of TEAEs leading to discontinuation from study medication

4.3.3 Other safety variables

The other safety variables are the following:

- Adverse events (AEs) (variables other than secondary safety variables)
- Laboratory tests (blood chemistry and hematology)
- Vital signs
- Body weight and height
- Physical and neurological examination

5 STUDY DESIGN

5.1 Study description

5.1.1 Overall

EP0100 is an open-label, single-arm, multicenter study with LEV as monotherapy or adjunctive treatment to evaluate the efficacy and safety of LEV (14mg/kg/day to 42mg/kg/day for subjects aged at 1 month to <6 months, 20mg/kg/day to 60mg/kg/day for subjects aged at 6 months to <4 years) in the treatment of partial seizures over the First Period (6 weeks), followed by the long-term follow-up (Second Period) in pediatric subjects.

5.1.2 First Period

Eligible subjects will enter the First Period (6 weeks). Subjects aged 1 month to <6 months will be started on LEV 14mg/kg/day at Visit 3 (Week 0). The dose may be increased by LEV 14mg/kg/day for subjects aged 1 month to <6 months at 2-week intervals to a maximum dose of LEV 42mg/kg/day. Subjects aged 6 months to <4 years will be started on LEV 20mg/kg/day at Visit 3 (Week 0). The dose may be increased by LEV 20mg/kg/day at 2-week intervals to a maximum dose of 60mg/kg/day. The dose will be increased if seizure freedom has not been

attained according to the patient diary. However, if there is a safety concern for the subject in the opinion of the investigator, the dose can be kept.

For the subjects aged 1 month to <12 months who have cluster seizures several times a day and are being treated on an inpatient basis under a physician's supervision, the dose can be increased without waiting for the 2-week interval. If the subject is hospitalized and under supervision of a physician, the following rapid titration procedure (dose and interval) will be performed as the most rapid case: dose increments of LEV 14mg/kg/day for subjects aged 1 to <6 months and LEV 20mg/kg/day for subjects aged 6 months to <4 years at 1-day intervals.

If an intolerable AE occurs during the First Period, the dose can be decreased only once as a fallback option. The dose will be decreased by LEV 14 mg/kg/day for subjects aged 1 month to <6 months or LEV 20mg/kg/day for subjects aged 6 months to <4 years. After decreasing the dose, a re-increase will not be allowed during the First Period.

At Visit 6 (Week 6), subjects may enter either the Second Period or the Down-Titration Period, followed by the Safety Follow-Up Period. Subjects who do not enter the Second Period will be down-titrated. The dose will be decreased by LEV 14mg/kg/day for subjects aged 1 month to <6 months or by LEV 20mg/kg/day at 2-week intervals to 0mg/kg/day. Subjects who withdraw from the study at the minimum age-related dose do not need to down-titrate.

All subjects who do not enter the Second Period will enter the Down-Titration Period, followed by the Safety Follow-Up Period.

5.1.3 Second Period

Subjects who complete the First Period will have a visit every 4 weeks ±7 days relative to Visit 3 for the first 6 months of administration and then every 12 weeks ±14 days thereafter. Subjects will continue to receive LEV 14 to 42mg/kg/day in subjects aged 1 month to <6 months or LEV 20 to 60mg/kg/day for subjects aged ≥6 months <4 years at the discretion of the Investigator.

When subjects aged <6 months at the time of study enrollment reach 6 months of age, they can take a maximum of LEV 60mg/kg/day.

A final visit will be required 2 weeks ±7 days after the final dose of LEV, or sooner if the subject will continue LEV (prescribed by the primary care provider as commercial LEV) after study completion.

5.1.4 Study duration per subject

The study duration is as follows:

Retrospective Baseline Period

Seizure counts during the 2 weeks prior to Visit 1 will be used as a Retrospective Baseline Period.

First Period

- Selection Period (maximum of 9 days)
- Evaluation Period (6 weeks)
- Down-Titration Period (up to 4 weeks)

- Safety Follow-Up Period (2 weeks)

Second Period

- Maintenance Period (until approval or the program is discontinued)
- Down-Titration Period (up to 4 weeks)
- Safety Follow-Up Period (2 weeks)

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

5.1.5 Planned number of subjects and sites

The planned number of evaluable subjects in the First Period will be a total of 38 subjects for the primary efficacy analysis. Subjects will be enrolled into 4 age groups (1 month to <6 months, 6 months to <1 year, 1 year to <2 years, and 2 years to <4 years), with a minimum of 5 subjects in each age group.

The planned number of monotherapy subjects will be a total of 10 subjects.

It is planned to have those subjects recruited in approximately 20 sites.

5.1.6 Anticipated regions and countries

The study will be conducted in Japan.

5.2 Schedule of study assessments

For Visit 4 through Visit 6, planned clinic visits should be scheduled as indicated with a window of ±4 days relative to Visit 3. For Visit 8 through Visit 15, planned clinic visits should be scheduled as indicated with a window of ±7 days relative to Visit 3. From Visit 16 onward, planned clinic visits should be scheduled as indicated with a window of ±14 days relative to Visit 3.

Table 5–1: Schedule of assessments

	First Period						Second Period										
	Selection Period		Evaluation Period[a]				Maintenance Period[b]										
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16[c]…	V17[d]…
Visit **Study Week**	**D-9 to D-2**	**D-2 to D0**	**W0**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W18**	**W22**	**W26**	**W32**	**W38**	**W50…**	**W62…**
Written informed consent	X																
Inpatient				X		X											
Registration	X		X														
Eligibility assessment	X		X														
Medical/procedures history	X																
Demographics	X																
AED history	X																
Epilepsy history	X																
Physical examination	X																
Neurological examination	X																
Vital signs[e]	X		X	X	X	X		X		X	X	X	X		X	X	X
Seizure counts[f]	X		X	X	X	X		X		X	X	X	X		X	X	X
Laboratory safety assessment[h]	X			X	X	X				X			X		X	X	X
LEV plasma level				X	X	X		X		X	X	X	X				
Body weight	X		X	X	X	X		X		X	X	X	X		X	X	X
Height	X												X			X	
Concomitant AED(s)	X		X[g]	X	X	X		X		X	X	X	X		X	X	X
Concomitant non-AED(s)	X		X[g]	X	X	X		X		X	X	X	X		X	X	X

Table 5–1: Schedule of assessments

	First Period						Second Period										
	Selection Period		Evaluation Period[a]				Maintenance Period[b]										
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16[c]…	V17[d]…
Visit **Study Week**	**D-9 to D-2**	**D-2 to D0**	**W0**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W18**	**W22**	**W26**	**W32**	**W38**	**W50…**	**W62…**
Concomitant medical procedures	X		X[g]	X	X	X		X		X	X	X	X		X	X	X
Adverse events	X		X[g]	X	X	X		X		X	X	X	X		X	X	X
Dispense/return study drug			X[i]	X	X	X		X		X	X	X	X		X	X	X
Study drug compliance				X	X	X		X		X	X	X	X		X	X	X
ECG	X												X			X	
CT scan/MRI[j]	X																
EEG[k]	X																
IVRS/IWRS	X		X	X	X	X		X		X	X	X	X		X	X	X
Dispense/collect DRC	X[l]		X	X	X	X		X		X	X	X	X		X	X	X
Dispense subject's ID card	X																
Fallback option[m]				X	X												
C-SSRS[n]																X[n]	X[n]

AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; CT=computed tomography; D=day; DRC=daily record card; ECG=electrocardiogram; EDV=Early Discontinuation Visit; EEG=electroencephalogram; ID=identification; IVRS=interactive voice response system; IWRS=interactive web response system; LEV=levetiracetam; MRI=magnetic resonance imaging; SFU=Safety Follow-Up; V=visit; W=week

Note: See Table 5–3 for the schedule of assessments for the Down-Titration and SFU Periods.

[a] After beginning the study medication, subjects who withdraw prematurely must have W6 evaluations and the EDV evaluations.

[b] In the Maintenance Period, visits will occur every 4 weeks from V8 to V13, and every 12 weeks thereafter.

[c] Even numbered visits.

[d] Odd numbered visits.

[e] Including temperature, blood pressure, and heart rate.

[f] At V1, collect seizure count for seizures that occurred in the prior 2 weeks.

Table 5–1: Schedule of assessments

	First Period						Second Period										
	Selection Period		Evaluation Period[a]				Maintenance Period[b]										
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16[c]…	V17[d]…
Visit	D-9 to D-2	D-2 to D0	W0	W2	W4	W6	W8	W10	W12	W14	W18	W22	W26	W32	W38	W50…	W62…
Study Week																	

[g] Recorded from end of V1 through V3.
[h] If clinically significant laboratory abnormalities are present at V1, repeat samples must be obtained for blood chemistry and hematology. The results should be available prior to V3, and UCB or its designee should be contacted regarding clinically significant abnormalities.
[I] Dispense study drug at V3.
[j] Only for subjects who have not had a CT scan or MRI confirming the absence of a progressive lesion since being diagnosed with epilepsy, or have changes on physical examination which would suggest a lesion has occurred since the last imaging procedure.
[k] If the EEG exam was not performed prior to V1, the assessment needs to be completed, and results must be available prior to V3.
[l] Dispense DRC.
[m] Fallback option is permitted. See Section 5.1.2 for details.
[n] C-SSRS to be performed at each visit for subjects aged ≥6 years.

Table 5–2: Schedule of assessments for subjects who are 48h video-EEG failures

Not applicable.

Table 5–3: Schedule of assessments for Down-Titration and SFU Periods

Visit	EDV[a]			SFU[b]
Study Week	W0	W2	W4	
Vital signs[c]	X	X	X	X
Seizure counts	X	X	X	X
Laboratory safety assessments	X			X
Body weight	X	X	X	X
Height	X			X
Concomitant AED(s)	X	X	X	X
Concomitant non-AED(s)	X	X	X	X
Concomitant medical procedures	X	X	X	X
Adverse events	X	X	X	X
Dispense/return study drug	X	X	X	
Study drug compliance	X	X	X	
ECG	X			X[d]
IVRS/IWRS	X	X	X	X
Dispense/collect DRC	X	X	X	X[e]
C-SSRS[f]	X[f]	X[f]	X[f]	X[f]

AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; CT=computed tomography; D=day; DRC=daily record card; ECG=electrocardiogram; EDV=Early Discontinuation Visit; ID=identification; IVRS=interactive voice response system; IWRS=interactive web response system; LEV=levetiracetam; MRI=magnetic resonance imaging; SFU=Safety Follow-Up; V=visit; W=week

[a] The dose will be decreased by LEV 14mg/kg/day for subjects aged 1 month to <6 months or by LEV 20mg/kg/day for subjects aged 6 months to <4 years at 2-week intervals to 0mg/kg/day.

[b] Two weeks after final dose of study drug.

[c] Including temperature, blood pressure, and heart rate.

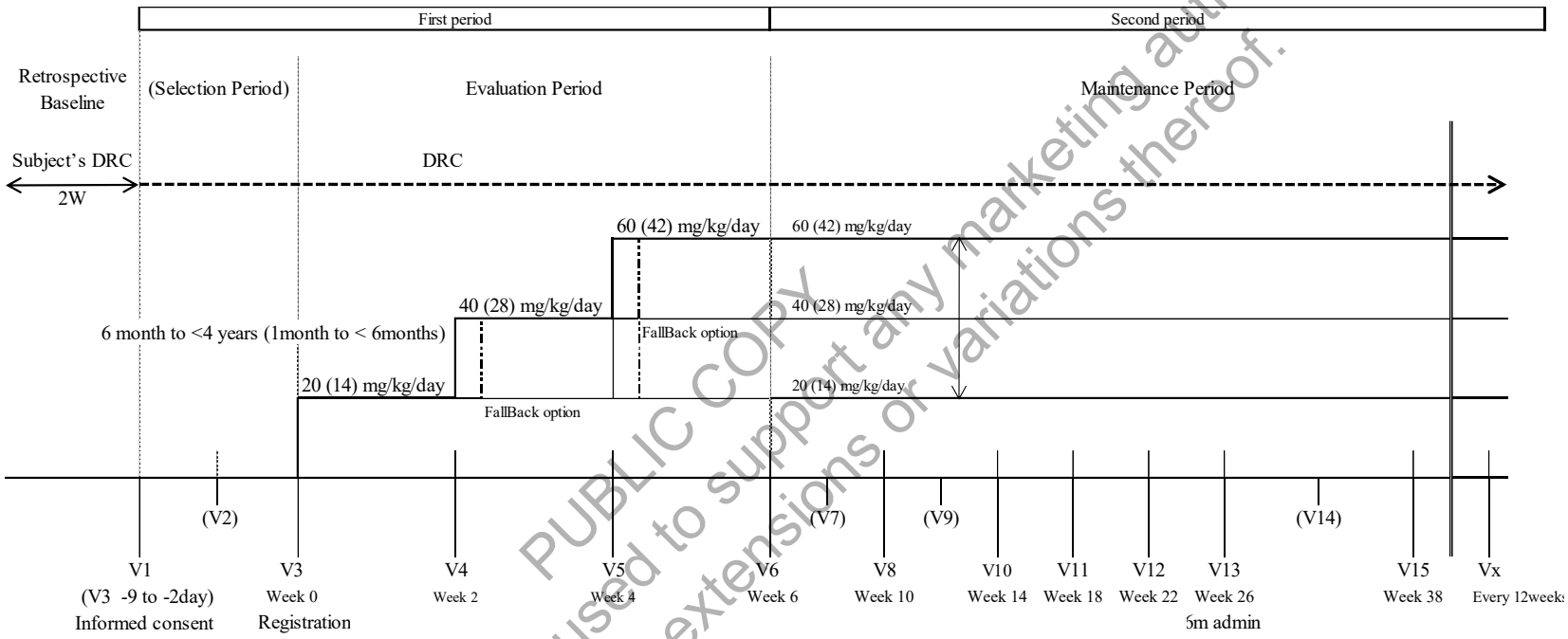
[d] Performed only if abnormal at EDV.

[e] Collect DRC.

[f] C-SSRS to be performed at each visit for subjects aged ≥6 years.

5.3 Schematic diagram

Figure 5–1: Schematic for subjects in the First and Second Periods



6m admin=6 months of administration; DRC=daily record card; V=Visit; W=weeks
Note: The value in parentheses for dose is for subjects 1 month to <6 months of age.

5.4 Rationale for study design and selection of dose

Levetiracetam has been developed as adjunctive therapy in the treatment of partial seizures in children aged 1 month to <4 years with epilepsy. The EMA and FDA have approved the new indication as adjunctive treatment in children down to 1 month of age with partial seizures in Sep 2009 and Dec 2011, respectively. The approved dosage and administration for infants aged 1 month to < 6 months is 14 to 42 mg/kg/day, and for young children aged 6 months to <4 years, the approved dose is 20 to 60 mg/kg/day. These dose ranges were determined based on the results of N01288, a population PK analysis. The results show that the recommended dose ranges are 14 to 42mg/kg/day for infants aged <6 months, approximately 70% of the dose for 4-year-olds (20 to 60mg/kg/day, demonstrating equivalent exposure to 1000 to 3000mg/kg/day in adults) and 20 to 60mg/kg/day for children aged 6 months or older (the same dose range as for 4-year-olds). At the PMDA consultation, they suggested that the final dosage and administration (including up-titration method) should be established based on a confirmatory study. Based on this suggestion, EP0100 is planned to evaluate the efficacy of LEV at the same dosage approved by FDA and EMA, and the dose will be increased at 2-week intervals during the 6-week Evaluation Period.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

Subjects who complete the First Period can start the Second Period without re-confirmation of the inclusion/exclusion criteria.

6.1 Inclusion criteria

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

1a. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the parent(s) or legal representative. Subject/legal representative/caregiver is considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, or medication intake according to the judgment of the Investigator.

2a. Subject must have a diagnosis of epilepsy with partial onset seizures (ie, seizures of focal onset), whether or not secondarily generalized.

Subject has had an EEG and a brain computerized tomography (CT) scan or brain magnetic imaging (MRI) consistent with a diagnosis of localized epilepsy according to the International Classification of Epilepsies and Epileptic Syndromes (1989) (see Section 17.2) and consistent with partial onset seizures according to the Classification of Epileptic Seizures (1981) (see Section 17.1). If the EEG and brain CT scan and brain MRI were not performed prior to the Screening Visit (Visit 1), the assessment needs to be completed and results must be available prior to Visit 3.

3. Subject must be male or female from 1 month to <4 years of age. Pre-term infants aged <1 year are to be stratified into an appropriate age category using the best estimate of their corrected gestational age.

4. For subjects on adjunctive therapy, subject must be on a stable AED regimen (ie, a maximum of 2 AEDs) for the Selection and Evaluation Periods of the study. Minor adjustments to the

dose of current AEDs are allowed only prior to Visit 1. Monotherapy subjects must not receive AED treatment, receive temporary AED treatment, or switch an AED prior to Visit 1.

5. Subject weighs ≥3.0kg.
6. Subject may have Vagal Nerve Stimulation (VNS) which has been implanted for at least 6 months prior to Visit 1; the settings must be stable for at least 2 months prior to Visit 1. Activated VNS must be counted as 1 of the 2 AEDs.

7a. Subject must have experienced at least 2 observable partial seizures (ie, seizures of focal onset as determined by EEG), with or without secondary generalization during each 7-day period during the 2 weeks prior to Visit 1. This time period (the 2 weeks prior to Visit 1) will be referred to as the Retrospective Baseline Period. This seizure information (including type, frequency, and date) must have been recorded on a daily record card (DRC) in order to be acceptable.

8. Deleted.
9. Deleted.
10. If epilepsy surgery has been performed prior to study entry, subjects must have a documented failed epilepsy surgery outcome at least 4 weeks prior to Visit 1.
11. The use of intermittent benzodiazepines, phenobarbitals, and phenytoins is allowed as long as the frequency is not greater than 1 single administration per week for at least 2 weeks prior to Visit 1 and throughout study participation. If benzodiazepines are used more than once a week, they must be considered as 1 of the AEDs.

6.2 Exclusion criteria

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

1. Subject has been taking any medication (other than their concomitant AEDs) that influences the central nervous system (CNS) for which they had not been on a stable regimen for at least 1 month prior to Visit 1.
2. Subject is taking any medication that may interfere with the absorption, distribution, metabolism, or excretion of the concomitant AEDs or LEV during the course of the study.
3. Subject has received any investigational medication or device within 30 days prior to Visit 1.
4. Subject has taken LEV prior to the study.
5. Subjects using felbamate who have presented with clinically significant abnormalities for WBCs, RBCs, platelets, and/or hepatic function during felbamate treatment, and subjects who are taking felbamate <1year from the date of Visit 1.
6. Subject has a history of status epilepticus requiring hospitalization during the 30 days prior to Visit 1, except for status epilepticus occurring during the first 10 days of life.
7. Subject has a treatable seizure etiology (ie, febrile seizures).
8. Subject is on a ketogenic diet (concomitantly or within 30 days prior to Visit 1).
9. Subject has epilepsy secondary to progressing cerebral diseases.

10. Subject has a current diagnosis of Rasmussen's syndrome, Landau-Kleffner disease or Lennox-Gastaut syndrome.
11. Subject has clinically significant deviations from reference range values for renal function or any of the other laboratory parameters required for this study, as determined by the Investigator.
12. Subject has any clinically significant acute or chronic illness (as determined during the physical examination or from other information available to the Investigator).
13. Subject has an allergy to pyrrolidine derivatives or a history of multiple drug allergies.
14. Subject is known to have a terminal illness.
15. Subject has a disorder or condition that may interfere with the absorption, distribution, metabolism, or excretion of medications.
16. Subject has a history of or presence of pseudoseizures.
17. Subject has any medical condition that might interfere with the subject's study participation (ie, serious infection, scheduled elective surgery, severe scalp eczema, etc.).
18. Subject has ≥3x upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

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

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

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

6.3 Withdrawal criteria

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

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

1. Subject must be withdrawn if there is an occurrence of status epilepticus, seizure clustering, or generalized tonic-clonic seizure, if unknown for the subject. If seizure frequency is increased, subject can be withdrawn for safety reasons, at the discretion of the Investigator.
2. Subject develops an illness that would interfere with his/her continued participation.
3. Subject is noncompliant with the study procedures or medications in the opinion of the investigator.

4. Subject takes prohibited concomitant medications as defined in this protocol.
5. Parent or legal guardian withdraws his/her consent.
6. The sponsor or a regulatory agency requests withdrawal of the subject.
7. Subject ≥6 years of age has active suicidal ideation without specific plan as indicated by a positive response ("Yes") to question 4 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and may be withdrawn from the study based upon the investigator's judgment of benefit/risk of continuing the subject in the study/on study medication.
8. Subject ≥6 years of age has active suicidal ideation with a specific plan as indicated by a positive response ("Yes") to question 5 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.
9. Subject who has cluster seizures prior to Visit 1 intermittently takes benzodiazepines, phenobarbitals, or phenytoins more than 1 single administration per week during the study period.
10. Subject on monotherapy needs to add another AED during the First Period.

Investigators should attempt to obtain information on subjects in the case of withdrawal. 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 CRF must document the primary reason for withdrawal.

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

6.3.1 Potential drug-induced liver injury IMP discontinuation criteria

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

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

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

The PDILI criterion below requires immediate discontinuation of IMP:

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

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

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

Evaluation of PDILI must be initiated as described in Section 11.2.1. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

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

7 STUDY TREATMENT(S)

7.1 Description of investigational medicinal product

Levetiracetam dry syrup 50% (white to off-white granules) for oral administration will be used in this study. Levetiracetam injection (100mg/mL) will also be used.

7.2 Treatments to be administered

Each subject will be weighed in kg and will receive 2 equal oral doses of LEV dry syrup 50% dissolved in water; 1 in the morning and 1 in the evening. The weight obtained at every visit will be used to calculate the dose of study medication (mg per kg) for the entire study.

If the subject cannot take LEV dry syrup under a fasting state during the First Period, LEV 100mg/mL concentrate for solution for infusion (clear, colorless, sterile solution) can be used for a maximum of 4.5 consecutive days at each dose at the Investigator's discretion. Levetiracetam injection is infused intravenously over 15 minutes per dose.

The weight and amount of individual dose will be recorded in the CRF and in the drug accountability log for the site. Medication will be allocated by the IVRS.

First Period

Once the subject has fulfilled the eligibility criteria, the subject will enter the Evaluation Period.

Study medication should be given as 2 equally divided doses administered twice daily. The first intake of newly dispensed study medication should occur at Visit 3. Subjects should take IMP according to instructions provided by the Investigator.

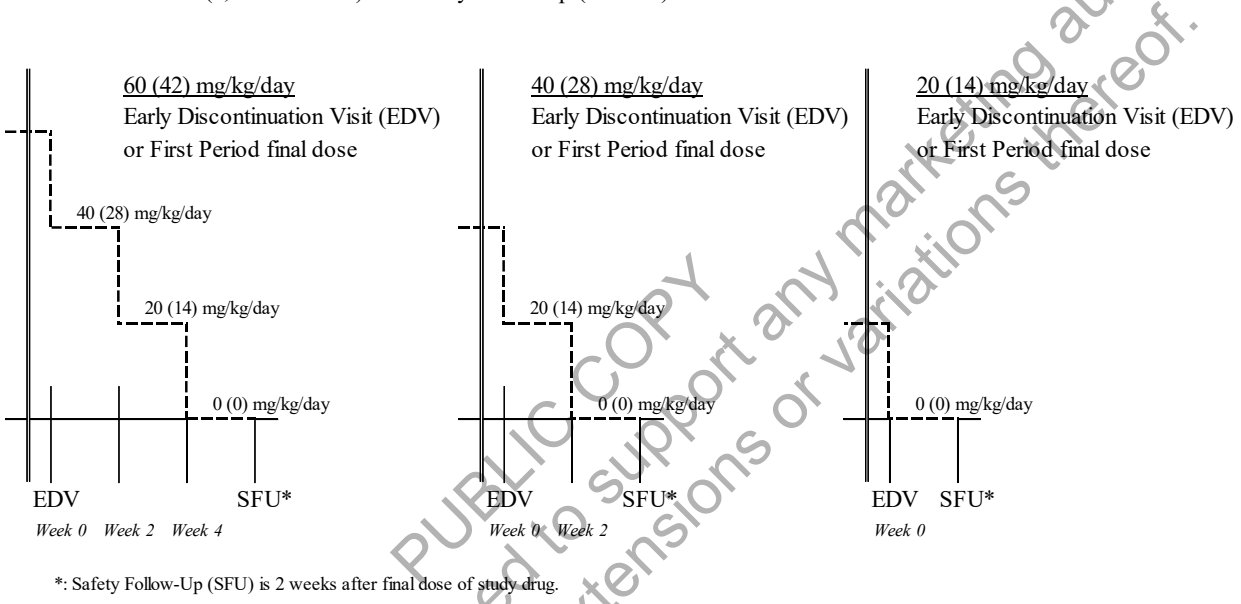
Subjects aged 1 month to <6 months will be started on LEV 14mg/kg/day at Visit 3 (Week 0). The dose may be increased by LEV 14mg/kg/day for subjects aged 1 month to <6 months at 2-week intervals to a maximum dose of LEV 42mg/kg/day. Subjects aged 6 months to <4 years will be started on LEV 20mg/kg/day at Visit 3 (Week 0). The dose may be increased by LEV 20mg/kg/day at 2-week intervals to a maximum dose of 60mg/kg/day.

At the end of the Evaluation Period, subjects will enter into the Second Period. Subjects who do not enter the Second Period will enter the Down-Titration Period, followed by the Safety Follow-Up Period.

The Down-Titration Period (up to 4 weeks) will consist of the following:

- The dose will be decreased by 14mg/kg/day for subjects aged 1 month to <6 months or by 20mg/kg/day for subjects aged 6 months to <4 years at 2-week intervals to 0mg/kg/day.

Figure 7–1: Schematic for Down-Titration and Safety Follow-Up Periods



EDV=Early Discontinuation Visit; SFU=Safety Follow-Up; V=Visit
Note: The value in parentheses for dose is for subjects 1 month to <6 months of age.

The down-titration procedure needs to be applied in case of early discontinuation.

Second Period

For continuing subjects, if a dose adjustment becomes necessary, the investigators will increase or decrease the dose by at least a 2-week interval. One increase or decrease in the dose should not exceed LEV 14mg/kg/day for subjects aged 1 month to <6 months or LEV 20mg/kg/day for subjects aged 6 months to <4 years for the 2-week interval. The dosage can be adjusted to LEV 14, 28 and 42mg/kg/day LEV for subjects aged 1 month to <6 months or LEV 20, 40 and 60mg/kg/day for subjects aged 6 months to <4 years at the Investigator's discretion for the benefit/risk for individual subjects.

Subjects who withdraw or complete the Second Period will enter the Down-Titration Period, followed by the Safety Follow-Up Period.

7.3 Packaging

A 100g-volume of LEV dry syrup 50% will be filled in a 250mL bottle. Each bottle will be packaged individually. The needed number of the bottles will be dispensed to each study site.

The research pharmacist at the study site(s) will fill out each sachet with the prescribed amount of LEV dry syrup 50%.

Levetiracetam injection (100mg/mL) will be packaged in 5mL glass vials (500mg/5mL). A dose of the drug (500mg to 1500 mg) must be diluted in 100mL of saline, lactate Ringer's solution, or 5% glucose solution. Consideration should be given to reducing the dilution volume for use in children by referring to the dilute concentration for adult use. The drug should be used immediately after dilution.

7.4 Labeling

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

7.5 Handling and storage requirements

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

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

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

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, damaged (due to breakage or wastage), not used, partially used, disposed of at the study site, or returned to the sponsor or designee must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

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

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

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

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 (<80% or >120% 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

An accurate record of treatments other than the IMP must be kept in the clinic chart (source documentation) and the Case Report form (CRF). This record should include the name of the medication, the dose, the date(s) of administration, and the indication for use.

7.8.1 Permitted concomitant treatments (medications and therapies)

First Period

Subjects on adjunctive therapy must be on a stable regimen of 1 or a maximum of 2 other AEDs for the Selection and Evaluation Periods (Appendix 3 [Section 17.3]). No new AEDs may be added or current AEDs discontinued for at least 2 weeks prior to Visit 1. Minor adjustments to the dose of current AEDs are allowed prior to Visit 1 only.

Subjects on adjunctive therapy who have VNS that have been implanted for at least 6 months prior to Visit 1 are allowed as long as the settings have been stable for at least 2 months prior to Visit 1. Activated VNS must be counted as 1 of the 2 AEDs.

The use of intermittent benzodiazepines, phenobarbitals, and phenytoins is allowed as long as the frequency is not greater than 1 single administration per week for at least 2 weeks prior to Visit 1 and during the First Period. If benzodiazepines are used more than once a week, they must be considered as 1 of the AEDs.

Second Period

The Investigator (or designee) will be allowed to change the type, dosage and administration, or discontinue/resume concomitant AEDs to optimize tolerability and seizure reduction for each subject after 3 months of the start of the Second Period. Changes in concomitant AED(s) will be allowed only if the dose of LEV has been stable for the previous 2 weeks; LEV dose must remain stable during changes to concomitant AED(s). Subjects may take no more than 3 concomitant AEDs except when temporary (≤12 weeks) use of an additional AED is required to switch to a new AED (ie, taper from old AED during titration of new AED). New AED(s) may be added only when the subject has not optimally or adequately responded to a maximum tolerated dose of LEV. The concomitant AED(s) can be carefully tapered or discontinued at the discretion of the investigator. Monotherapy with LEV is permitted. Increasing the dose of LEV and/or concomitant AED(s), as well as addition of a new AED should be done at a visit (scheduled or unscheduled). There are no restrictions for concomitant AED(s) during the Down-Titration Period, considering subject safety.

The use of intermittent benzodiazepines, phenobarbitals, and phenytoins is allowed as long as the frequency is not greater than 1 single administration per week during the Second Period. If benzodiazepines are used more than once a week, they must be considered as 1 of the AEDs.

7.8.2 Prohibited concomitant treatments (medications and therapies)

First Period

Medications that may influence the central nervous system, ie, neuroleptics, antidepressants, psychostimulants, anticholinergics, tranquilizers, hypnotics, and narcotic analgesics should be avoided. If the use of CNS-influencing medication cannot be avoided, the subject must be on a stable regimen of the medication for at least 1 month prior to Visit 1.

Second Period

No concomitant treatments are prohibited during the Second Period.

7.9 Blinding

This is an open-label study.

7.10 Randomization and numbering of subjects

To enroll a subject (Visit 1), the Investigator or designee will contact the interactive response technology (IRT) and provide brief details about the subject to be enrolled. Each subject will receive a 5-digit number assigned at screening that serves as the subject identifier throughout the study. The subject number will be required in all communication between the Investigator or designee and the IRT regarding a particular subject. Subject numbers and kit numbers will be tracked via the IRT.

8 STUDY PROCEDURES BY VISIT

The following will be obtained or assessed according to the Schedule of study assessments. Prior to any study activities, the subject's legal representative will be asked to read and sign an Informed Consent form that has been approved by an IRB/IEC and which complies with regulatory requirements. The subject's legal representative will be given adequate time to consider any information concerning the study, given to them by the Investigator or designee. As part of the informed consent procedure, the subject's legal representative will be given the opportunity to ask the Investigator any questions regarding potential risks and benefits of participation in the study.

8.1 First Period

See Section 5.2 for the schedule of assessments for the First Period. The visit window for Visit 4 through Visit 6 is ±4 days. Visit 1 assessments will be performed for all subjects.

8.1.1 Selection Period

8.1.1.1 Visit 1/Day -9 to Day -2 (Screening)

- Written informed consent
- Register subject
- Assess subject eligibility
- Perform EEG (for subjects who have not had an EEG confirming the consistent with a diagnosis of localized epilepsy and the consistent with partial onset seizures.)
- Collect demographic information

- Collect medical/procedures history, including AED and epilepsy history
- Physical examination
- Neurological examination
- Obtain vital sign measurements (blood pressure, pulse rate, and body temperature)
- Collect seizure count for seizures that occurred in the prior 2 weeks
- Collect blood samples for safety laboratory assessments
- Record body weight and height
- Record concomitant medications (AEDs and non-AEDs) and medical procedures
- Record AEs
- Perform ECG
- Perform CT scan or MRI (for subjects who have not had a CT scan or MRI confirming the absence of a progressive lesion since being diagnosed with epilepsy, or have changes on physical examination that would suggest a lesion has occurred since the last imaging procedure.
- Contact IVRS/IWRS
- Dispense DRC
- Dispense subject identification card

8.1.1.2 Visit 2/Day -2 to Day 0

Not applicable.

8.1.2 Evaluation Period

8.1.2.1 Visit 3 (Week 0)

- Register subject
- Confirm subject eligibility
- Obtain vital sign measurements (blood pressure, pulse rate, and body temperature)
- Collect seizure count (record seizure count from after Visit 1 to Visit 3 based on the DRC)
- Record body weight
- Record concomitant medications (AEDs and non-AEDs) and medical procedures from after Visit 1 to Visit 3
- Record AEs from after Visit 1 to Visit 3
- Dispense study drug
- Contact IVRS/IWRS
- Dispense/collect DRC

8.1.2.2 Visit 4 (Week 2)

- Obtain vital sign measurements (blood pressure, pulse rate, and body temperature)
- Collect blood samples for safety laboratory assessments
- Collect blood samples for LEV plasma level
- Record body weight
- Record concomitant medications (AEDs and non-AEDs) and medical procedures
- Record AEs
- Collect seizure count from DRC
- Dispense/collect DRC
- Study drug compliance
- Confirm if fallback option is necessary and reason(s) to decrease the dosage
- Contact IVRS/IWRS
- Dispense/collect study drug

8.1.2.3 Visit 5 (Week 4)

- Obtain vital sign measurements (blood pressure, pulse rate, and body temperature)
- Collect seizure count
- Collect blood samples for safety laboratory assessments
- Collect blood samples for LEV plasma level
- Record body weight
- Record concomitant medications (AEDs and non-AEDs) and medical procedures
- Record AEs
- Dispense/collect study drug
- Study drug compliance
- Confirm if fallback option is necessary and reason(s) to decrease the dosage
- Contact IVRS/IWRS
- Dispense/collect DRC

8.1.3 Visit 6 (Week 6)

- Obtain vital sign measurements (blood pressure, pulse rate, and body temperature)
- Collect blood samples for safety laboratory assessments
- Collect blood samples for LEV plasma level
- Record body weight

- Record concomitant medications (AEDs and non-AEDs) and medical procedures
- Record AEs
- Collect seizure count
- Dispense/collect DRC
- Study drug compliance
- Contact IVRS/IWRS
- Dispense/collect study drug

8.2 Second Period

8.2.1 Visit 7 (Week 8)

Not applicable.

8.2.2 Visit 8 (Week 10)

- Obtain vital sign measurements (blood pressure, pulse rate, and body temperature)
- Collect seizure count
- Collect blood sample for LEV plasma level
- Record body weight
- Record concomitant medications (AEDs and non-AEDs) and medical procedures
- Record AEs
- Dispense/collect study drug
- Study drug compliance
- Contact IVRS/IWRS
- Dispense/collect DRC

8.2.3 Visit 9 (Week 12)

Not applicable.

8.2.4 Visit 10 (Week 14)

- Obtain vital sign measurements (blood pressure, pulse rate, and body temperature)
- Collect seizure count
- Collect blood samples for safety laboratory assessments
- Collect blood sample for LEV plasma level
- Record body weight
- Record concomitant medications (AEDs and non-AEDs) and medical procedures
- Record AEs

- Dispense/collect study drug
- Study drug compliance
- Contact IVRS/IWRS
- Dispense/collect DRC

8.2.5 Visit 11 (Week 18)

- Obtain vital sign measurements (blood pressure, pulse rate, and body temperature)
- Collect seizure count
- Collect blood sample for LEV plasma level
- Record body weight
- Record concomitant medications (AEDs and non-AEDs) and medical procedures
- Record AEs
- Dispense/collect study drug
- Study drug compliance
- Contact IVRS/IWRS
- Dispense/collect DRC

8.2.6 Visit 12 (Week 22)

- Obtain vital sign measurements (blood pressure, pulse rate, and body temperature)
- Collect seizure count
- Collect blood sample for LEV plasma level
- Record body weight
- Record concomitant medications (AEDs and non-AEDs) and medical procedures
- Record AEs
- Dispense/collect study drug
- Study drug compliance
- Contact IVRS/IWRS
- Dispense/collect DRC

8.2.7 Visit 13 (Week 26)

- Obtain vital sign measurements (blood pressure, pulse rate, and body temperature)
- Collect seizure count
- Collect blood samples for safety laboratory assessments

- Collect blood sample for LEV plasma level
- Record body weight and height
- Record concomitant medications (AEDs and non-AEDs) and medical procedures
- Record AEs
- Dispense/collect study drug
- Study drug compliance
- Perform ECG
- Contact IVRS/IWRS
- Dispense/collect DRC

8.2.8 Visit 14 (Week 32)

Not applicable.

8.2.9 Visit 15 (Week 38)

- Obtain vital sign measurements (blood pressure, pulse rate, and body temperature)
- Collect seizure count
- Collect blood samples for safety laboratory assessments
- Record body weight
- Record concomitant medications (AEDs and non-AEDs) and medical procedures
- Record AEs
- Dispense/collect study drug
- Study drug compliance
- Contact IVRS/IWRS
- Dispense/collect DRC

8.2.10 Visit 16 (Week 50)

From Visit 16 onward, visits will occur every 12 weeks until approval or discontinuation of development.

- Obtain vital sign measurements (blood pressure, pulse rate, and body temperature)
- Collect seizure count
- Collect blood samples for safety laboratory assessments
- Record body weight
- Record height (assessment will occur every 24 weeks during visits with even numbers)
- Record concomitant medications (AEDs and non-AEDs) and medical procedures

- Record AEs
- Dispense/collect study drug
- Study drug compliance
- Perform ECG (assessment will occur every 24 weeks during visits with even numbers)
- Contact IVRS/IWRS
- Dispense/collect DRC
- C-SSRS (will be performed at each visit for subjects aged ≥6 years)

8.3 Direct Enrollment

Not applicable.

8.4 Safety Follow-Up Visit (if applicable)

The Safety Follow-Up Visit will occur 2 weeks after the final dose of study medication and will include the following assessments:

- Obtain vital sign measurements (blood pressure, pulse rate, and body temperature)
- Collect seizure count
- Collect blood samples for safety laboratory assessments
- Record body weight
- Record height
- Record concomitant medications (AEDs and non-AEDs) and medical procedures
- Record AEs
- Perform ECG (to be performed only if abnormal at EDV)
- Contact IVRS/IWRS
- Collect DRC
- C-SSRS (will be performed for subjects aged ≥6 years)

8.5 Early Discontinuation Visit

- Obtain vital sign measurements (blood pressure, pulse rate, and body temperature)
- Collect seizure count
- Collect blood samples for safety laboratory assessments (at Week 0 only)
- Record body weight
- Record height (at Week 0 only)
- Record concomitant medications (AEDs and non-AEDs) and medical procedures
- Record AEs

- Dispense/collect study drug
- Study drug compliance
- Perform ECG (at Week 0 only)
- Contact IVRS/IWRS
- Dispense/collect DRC
- C-SSRS (will be performed for subjects aged ≥6 years)

8.6 Unscheduled Visit (if applicable)

Unscheduled visits can be conducted at the discretion of the investigator (eg, due to an AE). All information, including reasons for the visit, any information on AEs, etc, should be collected in the source documents and recorded in the appropriate sections of the eCRF.

During the Unscheduled Visit, the following assessments will be performed:

- Concomitant medications
- Concomitant AEDs
- Vital signs (blood pressure, pulse rate, and body temperature)
- Body weight
- AE reporting
- Review withdrawal criteria

In addition to the required assessments listed above, additional assessments may be performed at the investigator's discretion.

9 ASSESSMENT OF EFFICACY

The primary and secondary efficacy variables are based on the partial seizure frequency per week as measured by patient diary.

10 ASSESSMENT OF PHARMACOKINETIC VARIABLE

Blood samples for the determination of LEV plasma concentrations will be collected according to the tabular schedules of study procedures (see Section 5.2). Dose amounts, dosing dates, and times for the 3 previous LEV doses before blood sampling must be recorded in the eCRF. The date and time of blood sampling must be recorded.

Actual sampling times will be recorded in the eCRF to the minute.

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

11 ASSESSMENT OF SAFETY

11.1 Adverse events

11.1.1 Definitions

11.1.1.1 Adverse event

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

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

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

11.1.1.2 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, but are not limited to, potential Hy's Law [see Section 11.1.1.3], allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)

- Initial inpatient hospitalization or prolongation of hospitalization

  (A patient admitted to a hospital, even if he/she is released on the same day, meets the criteria for the initial inpatient hospitalization. An emergency room visit that results in admission to the hospital would also qualify for the initial inpatient hospitalization criteria. However, emergency room visits that do not result in admission to the hospital would not qualify for this criteria and, instead, should be evaluated for 1 of the other criteria in the definition of serious [eg, life-threatening adverse experience, important medical event].

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

11.1.1.3 Adverse events of special interest

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

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

11.1.2 Procedures for reporting and recording adverse events

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

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

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

11.1.2.1 Description of adverse events

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

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

11.1.2.2 Rule for repetition of an adverse event

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

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

11.1.2.3 Additional procedures for reporting serious adverse events

If an SAE is reported, UCB must be informed within 24 hours of receipt of this information by the site (see contact information for SAE reporting listed in the Serious Adverse Event Reporting section at the front of the protocol). The investigator must forward to UCB (or its representative) a duly completed "Investigator SAE Report Form for Development Drug" (SAE report form) provided by UCB, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions. Information recorded on this form will be entered into the global safety database.

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

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

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

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

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

11.1.3 Follow up of adverse events

An AE should be followed until it has resolved, has a stable sequelae, the investigator determines that it is no longer clinically significant, or the subject is lost to follow up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest; further details regarding follow up of PDILI events is provided in Section 11.2.1.4.

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

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

11.1.4 Suspected transmission of an infectious agent via a medicinal product

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

11.1.5 Overdose of investigational medicinal product

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

11.1.6 Safety signal detection

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

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

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

11.2 Laboratory measurements

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

The following laboratory parameters will be measured:

Table 11–1: Laboratory measurements

Hematology	Chemistry
Red blood cell count	AST
Hemoglobin	ALT
Hematocrit	GGT
Platelet count	ALP
White blood cell count	Total bilirubin
Neutrophil count	BUN
Lymphocyte count	Creatinine
Monocyte count	Creatinine clearance
Eosinophil count	Sodium
Basophil count	Potassium
Reticulocyte count	Calcium
MCV	Total protein
MCH	Albumin
MCHC	

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT=gamma-glutamyltransferase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; WBC=white blood cell

11.2.1 Evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 6.3.1, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 11.1.1.3), and, if applicable, also reported as an SAE (see Section 11.1.1.2).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 11–2 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 11.2.1.1). The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 11.2.1.4).

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

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

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

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

When IMP is stopped due to PDILI (as described in Section 6.3.1), IMP must be permanently discontinued unless a subsequent alternative diagnosis fully explains the hepatic findings. If a subsequent alternative diagnosis fully explains the hepatic findings, and the requirements provided in Section 11.2.1.3 are met, rechallenge with IMP may be appropriate.

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

The table below summarizes the approach to investigate PDILI.

Table 11–2: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN[b]	NA	Hepatology consult.[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 11.2.1.3); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values.[d]
≥8xULN	NA	NA				
≥3xULN	NA	Yes		Immediate, temporary or permanent, IMP discontinuation.		
≥3xULN (and ≥2x baseline) and <5xULN	<2xULN	No	Discussion with Medical Monitor required if the criterion that allows for IMP continuation is met.	Further investigation – immediate IMP discontinuation not required (see Section 11.2.1.2).	Not required unless otherwise medically indicated (at discretion of investigator).	

Table 11–2: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥5xULN (and ≥2x baseline) and <8xULN	<2xULN	No	Hepatology consult if there is no evidence of resolution (see Follow up requirements).[c] Discussion with Medical Monitor required.	IMP discontinuation required if any of the following occur: Subject cannot comply with monitoring schedule. Liver chemistry values continue to increase during 2 week monitoring period. Liver chemistry values remain ≥5xULN (and ≥2x baseline) after 2 week monitoring period.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 11.2.1.3).	Monitoring of liver chemistry values at least twice per week for 2 weeks.[d] Immediate IMP discontinuation required if liver chemistry values continue to increase. After 2 weeks of monitoring liver chemistry values: Discontinue IMP if levels remain ≥5xULN (and ≥2x baseline); monitor until values normalize, stabilize, or return to within baseline values.[d] Continue IMP if levels are no longer ≥5xULN (and ≥2x baseline); continue to monitor at least twice per week until values normalize, stabilize, or return to within baseline values.[d]

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

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

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

[c] Details provided in Section 11.2.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

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

11.2.1.1 Consultation with Medical Monitor and local hepatologist

Potential drug-induced liver injury events require notification of the Medical Monitor within 24 hours (eg, by laboratory alert), and the subject must be discussed with the Medical Monitor as soon as possible. If required, the subject must also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section 11.2.1.3) and SAE report (if applicable).

11.2.1.2 Immediate action: determination of IMP discontinuation

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

The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and ranges from continuation of IMP (followed by immediate investigation) to immediate and permanent discontinuation (see Section 6.3.1 and Table 11–2 for details).

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

11.2.1.3 Testing: identification/exclusion of alternative etiology

The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are detailed in Table 11–3 (laboratory measurements) and Table 11–4 (additional information). Results of the laboratory measurements and information collected are to be submitted to the sponsor on the corresponding CRF. If the medical history of the subject indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable.

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

The following measurements are to be assessed:

Table 11–3: PDILI laboratory measurements

Virology-related	Hepatitis A IgM antibody
	HBsAg
	Hepatitis E IgA antibody
	HBcAb-IgM
	Hepatitis C RNA
	Cytomegalovirus IgM antibody
	Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophile antibody or monospot testing)
Immunology	Anti-nuclear antibody (qualitative and quantitative)
	Anti-smooth muscle antibody (qualitative and quantitative)
	Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative)
Hematology	Eosinophil count
Urinalysis	Toxicology screen
Chemistry	Amylase
	If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
Additional	Prothrombin time/INR[a]
	PK sample

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

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

The following additional information is to be collected:

Table 11–4: PDILI information to be collected

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

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

11.2.1.4 Follow-up evaluation

Potential drug-induced liver injury events require follow-up monitoring as described in Section Section 11.2.1. Monitoring should continue until liver chemistry values normalize, stabilize, or return to baseline. Determination of stabilization is at the discretion of the investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

11.3 Other safety measurements

11.3.1 Physical examination

A physical examination will be performed by medically qualified clinicians licensed to perform the examination at Visit 1. Height will be measured according to schedule of study assessments.

11.3.2 Neurological examination

A neurological examination will be performed at Visit 1. The neurological examination should be conducted by a medically qualified clinician with documented training in the conduct of

neurological examinations. The investigator or subinvestigator is responsible for confirming the diagnosis of partial seizures or other epilepsy syndrome.

11.3.3 Vital signs and body weight

Blood pressure (systolic and diastolic), pulse rate, and body temperature will be measured at all visits. Body weight will be determined according to the schedule of study assessments.

11.3.4 12-lead ECG

Standard 12-lead ECGs will be performed according to the schedule of study assessments.

11.3.5 Assessment of suicidality

Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2008). For subjects ≥6 years of age, this scale will be used to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be completed according to the tabular schedule of study procedures.

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

12 STUDY MANAGEMENT AND ADMINISTRATION

12.1 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.

12.2 Monitoring

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

12.2.1 Definition of source data

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

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. Photocopies and/or printouts of eCRFs are not considered acceptable source documents. Source documents should be kept in a secure, limited access area.

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

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

12.2.2 Source data verification

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

12.3 Data handling

12.3.1 Case Report form completion

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

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

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

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

Detailed instructions will be provided in the eCRF Completion Guidelines.

12.3.2 Database entry and reconciliation

Case Report forms/external electronic data will be entered/loaded into a validated electronic database using a clinical data management system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. Case Report form data are entered into the clinical database using independent, double-data entry, with the exception of comment fields, which are verified by a second person. The data are entered into the eCRFs once and are subsequently verified if the study is performed using electronic data capture.

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

12.3.3 Subject Screening and Enrollment log/Subject Identification Code list

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

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

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

12.4 Termination of the study

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

If the study is prematurely terminated or suspended, UCB (or its representative) will inform the investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The IRB/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.

12.5 Archiving and data retention

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

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

It is responsibility of UCB (or designee) to inform the record retainer as to when the documents should no longer to be retained. The record retainer (or designee) 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 record retainer (or designee) will also notify UCB should he/she relocate or move the study related files to a location other than that specified in the sponsor's trial master file.

12.6 Audit and inspection

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

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

12.7 Good Clinical Practice

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

13 STATISTICS

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

13.1 Definition of analysis sets

The following sets are defined for this study:

- Enrolled Set (ES)
- Safety Sets:
  - SS_A (Safety Set [Adjunctive therapy])
  - SS_M (Safety Set [Monotherapy])
- Full Analysis Sets:
  - FAS_A (Full Analysis Set [Adjunctive therapy])
  - FAS_M (Full Analysis Set [Monotherapy])
- Pharmacokinetic Per-Protocol Set (PK-PPS)

If not stated otherwise, presentation of:

- Disposition and important protocol deviations are based on the ES
- Demographics, other baseline characteristics, safety, and exposure data are based on the SS_A and SS_M
- Efficacy data are based on the FAS_A and FAS_M.

13.1.1 Enrolled Set

The ES will consist of all subjects enrolled (which include all subjects screened) into the Selection Period.

13.1.2 Safety Set

The SS_A will include all enrolled subjects on adjunctive therapy who receive at least 1 dose of study medication in the Evaluation Period.

The SS_M will include all enrolled subjects on monotherapy who receive at least 1 dose of study medication in the Evaluation Period.

13.1.3 Full Analysis Set

The FAS_A will consist of all subjects in the SS_A who have at least 1 post-Baseline efficacy assessment.

The FAS_M will consist of all subjects in the SS_M who have at least 1 post-Baseline efficacy assessment.

13.1.4 Per Protocol Set

Not applicable.

13.1.5 Other analysis sets

The PK-PPS will consist of all subjects in the SS_A and SS_M for whom at least 1 valid LEV plasma concentration-time record and dosing information are available.

13.2 Handling of data for subjects who were enrolled prior to protocol amendment 3

Subjects who were directly enrolled in the Second Period based on the protocol prior to Amendment 3 will also be included in the efficacy and safety analysis with remapping of visit numbers to correspond to the ones for subjects who enrolled in the First Period. Details will be found in the SAP.

13.3 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. Unless otherwise specified, Baseline will refer to the Visit 1 to Visit 3 assessments or the last non-missing data collected prior to the first dose of IMP.

13.4 Planned efficacy analyses

All efficacy analysis will be performed for the FAS_A or FAS_M depending on therapy.

13.4.1 Analysis of the primary efficacy variable for adjunctive treatment

The percent reduction in partial seizures per week from Baseline to Visit 6 will be calculated as:

$$\frac{\text{Number of partial seizures per week at Baseline} - \text{Number of seizures per week at Visit 6}}{\text{Number of partial seizures per week at Baseline}} \times 100$$

Descriptive statistics (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum) will be calculated for the percent reduction in partial seizure frequency per week from Visit 6 by age category (3 categories: 1 month to <1 year, 1 year to <2 years, and 2 years to <4 years), and for all subjects combined (overall). The corresponding 95% confidence interval for the median percent reduction at Visit 6 will also be provided by age category and overall. If the lower limit of the 95% confidence interval for overall is greater than the predefined threshold of 15.0%, the efficacy of LEV is significant. If this test shows a significant result, then it will be repeated for the corresponding Visit 4 and Visit 5 variable. In that case, the second test is also regarded as confirmatory as due to the hierarchical testing procedure no alpha adjustment is needed.

There is no primary efficacy variable for subjects on monotherapy.

13.4.2 Other efficacy analyses

Descriptive statistics (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum) will be calculated for the continuous secondary and other variables and absolute and relative frequencies will be calculated for the categorical secondary and other variables.

13.5 Planned safety and other analyses

Safety summaries will be performed for SS_A and SS_M depending on the therapy.

13.5.1 Safety analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). Adverse events will be summarized by MedDRA System Organ Class and Preferred Term. The incidence of SAEs, AEs leading to premature discontinuation, and related AEs, and the incidence of AEs by intensity will also be summarized for the First Period and the combined First and Second Periods.

For laboratory evaluations and vital signs descriptive statistic on the observed values and the change from baseline will be computed by analysis visits. The number of subjects reporting at least one treatment-emergent possibly clinically significant (PCS) value will be computed by analysis visits.

13.5.2 Other analyses

Descriptive statistics of plasma concentrations of LEV will be summarized by subgroups and total. Scatter plots of plasma LEV concentrations vs time after dosing will be produced by subgroups and total. In addition, these figures will be superimposed on scatter plots of plasma concentration vs time in N01223 and figures of LEV plasma concentration time profiles simulated based on the population PK model established in N01288. As needed, population PK analysis will be planned and described in a separate data analysis plan.

13.6 Handling of protocol deviations

Prior to taking a snapshot for the interim analysis for New Drug Application (NDA) submission, protocol deviations will be assessed if important or not important and if included into the relevant analysis set according to predefined specifications.

13.7 Handling of dropouts or missing data

Days with missing seizure data will not be used for the calculation of seizure frequency per week. If subjects drop out, their seizure counts over the available period will be used and transformed into seizure frequency per week, by dividing the number of seizures during the available period by the number of days of that period, multiplied by 7.

Safety variables will be analyzed insofar as they are available, without imputation or carrying values forward.

13.8 Planned interim analysis and data monitoring

No interim analyses are planned for this study. For regulatory purposes, a planned data cutoff will be made when the final subject who completes the First Period reaches Visit 13. All the efficacy and safety analysis planned in this protocol will be performed for NDA submission using the interim cutoff data followed by additional cutoff and/or final analysis for long-term follow-up evaluation.

13.9 Determination of sample size

Based on the previous placebo-controlled clinical studies for pediatric epilepsy patients that evaluated AEDs, the percent reduction in ADF of partial seizure frequency from Baseline for placebo is assumed to be no more than 10%. For the purposes of this study, a percent reduction in ADF of partial seizure frequency ≤10% is defined as non-effective. Therefore, when the lower limit of 95% confidence interval (CI) of median in the percent reduction in ADF of partial seizure frequency for LEV is greater than 10%, statistical significance is declared. Based on the N01009 data for the percent reduction in ADF of partial seizure frequency for LEV, a population of size N was randomly sampled with replacement repeatedly for 10,000 times for the sample size consideration. The probability was evaluated that the lower limit of 95% CI of median in the percent reduction in ADF of partial seizure frequency for LEV was greater than 10% by samples with size of N. A sample size of at least 34 subjects are required to obtain 90% power. Assuming 10% of subjects will be nonevaluable, 38 subjects will be enrolled.

Due to the change in the primary efficacy variable in Protocol Amendment 3, the sample size was reconsidered. When the placebo rate area is conservatively redefined as ≤15% and assuming there are no nonevaluable subjects, a sample size of 38 subjects will obtain ≥80% power. Therefore, no change in sample size is required.

14 ETHICS AND REGULATORY REQUIREMENTS

14.1 Informed consent

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

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

Prior to participation in the study, the 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.

14.2 Subject identification cards

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

14.3 Institutional Review Boards and Independent Ethics Committees

The study will be conducted under the auspices of an IRB/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.

14.4 Subject privacy

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

The investigator agrees that representatives of UCB, its designee, representatives of the relevant IRB/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).

14.5 Protocol amendments

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

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

15 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

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

16 REFERENCES

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17 APPENDICES

17.1 Appendix 1

International Classification of Epileptic Seizures (1981)

I. Partial seizures (focal, local)

A. Simple partial seizures (consciousness not impaired)

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

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

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

b) With automatisms

2. With impairment of consciousness at onset
   a) With impairment of consciousness only
   b) With automatisms

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

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

II. Generalized seizures (convulsive or non-convulsive)

A. 1. Absence seizures

a) Impairment of consciousness only
b) With mild clonic components
c) With atonic components
d) With tonic components
e) With automatisms
f) With autonomic components

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

2. Atypical absence

May have:

a) Changes in tone that are more pronounced than in A.1
b) Onset and/or cessation that is not abrupt

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

C. Clonic seizures

D. Tonic seizures

E. Tonic-clonic seizures

F. Atonic seizures - (Astatic)

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

III. Unclassified epileptic seizures

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

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

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

17.2 Appendix 2

International Classification of Epilepsies and Epileptic Syndromes (1989)

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

1.1 Idiopathic (with age-related onset)

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

1.2 Symptomatic

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

1.3 Cryptogenic

2. Generalized epilepsies and syndromes

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

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

2.2 Cryptogenic or symptomatic (in order of age)

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

2.3 Symptomatic

2.3.1 Non-specific etiology

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

2.3.2 Specific syndromes

3. Epilepsies and syndromes undetermined whether focal or generalized

3.1 With both generalized and focal seizures

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

3.2 Without unequivocal generalized or focal features

4. Special syndromes

4.1 Situation-related seizures (Gelegenheitsanfälle, Occasional seizures)

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

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

17.3 Appendix 3

The following is a list of antiepileptic drugs (generic name):

- Acetazolamide
- Acetylpheneturide
- Amino (diphenylhydantoin) valeric acid
- Barbexaclone
- Beclamide
- Brivaracetam
- Carbamazepine
- Carisbamate
- Clobazam
- Clonazepam
- Diclofenamide
- Eslicarbazepine
- Ethadione
- Ethosuximide
- Ethotoin
- Felbamate
- Fosphenytoin
- Gabapentin
- Ilepcimide
- Lacosamide
- Lamotrigine
- Levetiracetam
- Mesuximide
- Metharbital
- Methylphenobarbital
- Mephenytoin
- Nitrazepam
- Oxcarbazepine
- Paramethadione

- Perampanel
- Phenacemide
- Pheneturide
- Phenobarbital
- Phensuximide
- Phenytoin
- Pregabalin
- Primidone
- Progabide
- Retigabine
- Rufinamide
- Stiripentol
- Sultiame
- Tiagabine
- Topiramate
- Trimethadione
- Valproic acid
- Valpromide
- Vigabatrin
- Zonisamide

Note: An AED that contains more than one compound in this list is not counted as 1 AED.

The number of compounds contained in 1 AED is counted as the number of AED administered.

It is prohibited that subjects take levetiracetam other than IMP during the study. Antiepileptic drugs that have not been approved in Japan are prohibited.

17.4 Protocol Amendment 1

Rationale for the amendment

The purpose of this amendment is the following:

- Correct inconsistencies between Table 5-1, Table 5-2, and Section 8
- Clarify permitted concomitant treatments
- Clarify withdrawal criteria

In addition, minor administrative edits including typographical changes for formatting and/or spelling errors have been made.

The following shows the changes made in Amendment 1 compared to the original protocol, dated 06 Feb 2016.

Modifications and changes

Specific changes

Change #1:

Table 5–1: Schedule of assessments for subjects who are not 48h video-EEG failures

	First Period						Second Period										
	Selection Period		Evaluation Period[a]				Maintenance Period[b]										
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16[c]	V17[d]
Visit **Study Week**	**D-9 to D-2**	**D-2 to D0**	**W0**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W18**	**W22**	**W26**	**W32**	**W38**	**W5**	**W62**
Written informed consent	X																
Inpatient		X		X		X											
Registration	X		X														
Eligibility assessment	X	X	X														
Medical/procedures history	X																
Demographics	X																
AED history	X																
Epilepsy history	X																
Physical examination	X																
Neurological examination	X																
Vital signs[e]	X		X	X	X	X		X		X	X	X	X		X	X	X
Seizure counts[f]	X		X	X	X	X		X		X	X	X	X		X	X	X
Laboratory safety assessment	X	X[h]		X	X	X				X			X		X	X	X
LEV plasma level				X[i]	X	X[i]		X		X	X	X	X				
Body weight	X		X	X	X	X		X		X	X	X	X		X	X	X
Height	X												X			X[i]	
Concomitant AED(s)	X		X[g]	X	X	X		X		X	X	X	X		X	X	X
Concomitant non-AED(s)	X		X[g]	X	X	X		X		X	X	X	X		X	X	X
Concomitant medical procedures	X		X[g]	X	X	X		X		X	X	X	X		X	X	X

Table 5–1: Schedule of assessments for subjects who are not 48h video-EEG failures

	First Period						Second Period										
	Selection Period		Evaluation Period[a]				Maintenance Period[b]										
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16[c]	V17[d]
Visit **Study Week**	**D-9 to D-2**	**D-2 to D0**	**W0**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W18**	**W22**	**W26**	**W32**	**W38**	**W5**	**W62**
Adverse events	X		X[g]	X	X	X		X		X	X	X	X		X	X	X
Dispense/return study drug			X[k]	X	X	X		X		X	X	X	X		X	X	X
Study drug compliance				X	X	X		X		X	X	X	X		X	X	X
ECG	X												X			X	
CT scan/MRI[l]	X																
Video-EEG[m]		X		X		X											
IVRS/IWRS	X		X	X	X	X		X		X	X	X	X		X	X	X
Dispense/collect DRC	X[n]	X[n]	X	X	X	X		X		X	X	X	X		X	X	X
Dispense subject's ID card	X																
Fallback option[o]				X	X												
C-SSRS[p]																X	X

AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; CT=computed tomography; D=day; DRC=daily record card; ECG=electrocardiogram; EDV=Early Discontinuation Visit; EEG=electroencephalogram; ID=identification; IVRS=interactive voice response system; IWRS=interactive web response system; LEV=levetiracetam; MRI=magnetic resonance imaging; SFU=Safety Follow-Up; V=visit; W=week

Note: See Table 5–3 for the schedule of assessments for the Down-Titration and SFU Periods.

[a] After beginning the study medication, subjects who withdraw prematurely must have W6 evaluations and the EDV evaluations.

[b] In the Maintenance Period, visits will occur every 2 weeks from V7 to V10, every 4 weeks from V11 to V13, every 6 weeks between V14 and V15, and every 12 weeks thereafter.

[c] Even numbered visits.

[d] Odd numbered visits

[e] Including temperature, blood pressure, and heart rate.

[f] At V1, collect seizure count for seizures that occurred in the prior 2 weeks. At V2, V4, and V6, seizures will be counted by video-EEG and DRC. At all other visits, seizures will be counted by DRC only.

[g] Recorded from end of V1 through V3.

Table 5–1: Schedule of assessments for subjects who are not 48h video-EEG failures

	First Period						Second Period										
	Selection Period		Evaluation Period[a]				Maintenance Period[b]										
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16[c]	V17[d]
Visit Study Week	D-9 to D-2	D-2 to D0	W0	W2	W4	W6	W8	W10	W12	W14	W18	W22	W26	W32	W38	W5	W62

[h] If clinically significant laboratory abnormalities are present at V1, repeat samples must be obtained for blood chemistry and hematology. The results should be available prior to V2, and UCB or its designee should be contacted regarding clinically significant abnormalities.
[i] Blood samples will be obtained prior to receiving LEV and then at least 2h after dosing at V4 and V6.
[j] Height to be collected every 24 weeks at even numbered visits.
[k] Dispense study drug at V3.
[l] Only for subjects who have not had a CT scan or MRI confirming the absence of a progressive lesion since being diagnosed with epilepsy, or have changes on physical examination which would suggest a lesion has occurred since the last imaging procedure.
[m] All video-EEG data recording will be transmitted to a central reader for the purposes of data analysis.
[n] Dispense DRC at V1. Confirm DRC at V2.
[o] Fallback option is permitted. See Section 5.1.2 for details.
[p] C-SSRS to be performed at each visit for subjects aged ≥6 years.

Has been changed to

Table 5–1: Schedule of assessments for subjects who are not 48h video-EEG failures

	First Period						Second Period										
	Selection Period		Evaluation Period[a]				Maintenance Period[b]										
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16[c]…	V17[d]…
Visit **Study Week**	**D-9 to D-2**	**D-2 to D0**	**W0**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W18**	**W22**	**W26**	**W32**	**W38**	**W50…**	**W62…**
Written informed consent	X																
Inpatient		X		X		X											
Registration	X		X														
Eligibility assessment	X	X	X														
Medical/procedures history	X																
Demographics	X																
AED history	X																
Epilepsy history	X																
Physical examination	X																
Neurological examination	X																
Vital signs[e]	X		X	X	X	X		X		X	X	X	X		X	X	X
Seizure counts[f]	X	X	X	X	X	X		X		X	X	X	X		X	X	X
Laboratory safety assessment	X	X[h]		X	X	X				X			X		X	X	X
LEV plasma level				X[i]	X	X[i]		X		X	X	X	X				
Body weight	X		X	X	X	X		X		X	X	X	X		X	X	X
Height	X												X			X	
Concomitant AED(s)	X		X[g]	X	X	X		X		X	X	X	X		X	X	X
Concomitant non-AED(s)	X		X[g]	X	X	X		X		X	X	X	X		X	X	X

Table 5–1: Schedule of assessments for subjects who are not 48h video-EEG failures

	First Period						Second Period										
	Selection Period		Evaluation Period[a]				Maintenance Period[b]										
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16[c]…	V17[d]…
Visit **Study Week**	**D-9 to D-2**	**D-2 to D0**	**W0**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W18**	**W22**	**W26**	**W32**	**W38**	**W50…**	**W62…**
Concomitant medical procedures	X		X[g]	X	X	X		X		X	X	X	X		X	X	X
Adverse events	X		X[g]	X	X	X		X		X	X	X	X		X	X	X
Dispense/return study drug			X[j]	X	X	X		X		X	X	X	X		X	X	X
Study drug compliance				X	X	X		X		X	X	X	X		X	X	X
ECG	X												X			X	
CT scan/MRI[k]	X																
Video-EEG[l]		X		X		X											
IVRS/IWRS	X		X	X	X	X		X		X	X	X	X		X	X	X
Dispense/collect DRC	X[m]	X[m]	X	X	X	X		X		X	X	X	X		X	X	X
Dispense subject's ID card	X																
Fallback option[n]				X	X												
C-SSRS[o]																X[o]	X[o]

AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; CT=computed tomography; D=day; DRC=daily record card; ECG=electrocardiogram; EDV=Early Discontinuation Visit; EEG=electroencephalogram; ID=identification; IVRS=interactive voice response system; IWRS=interactive web response system; LEV=levetiracetam; MRI=magnetic resonance imaging; SFU=Safety Follow-Up; V=visit; W=week

Note: See Table 5–3 for the schedule of assessments for the Down-Titration and SFU Periods.

[a] After beginning the study medication, subjects who withdraw prematurely must have W6 evaluations and the EDV evaluations.

[b] In the Maintenance Period, visits will occur every 2 weeks from V7 to V10, every 4 weeks from V11 to V13, every 6 weeks between V14 and V15, and every 12 weeks thereafter.

[c] Even numbered visits.

[d] Odd numbered visits.

[e] Including temperature, blood pressure, and heart rate.

[f] At V1, collect seizure count for seizures that occurred in the prior 2 weeks. At V2, V4, and V6, seizures will be counted by video-EEG and DRC. At all other visits, seizures will be counted by DRC only.

Table 5–1: Schedule of assessments for subjects who are not 48h video-EEG failures

	First Period						Second Period										
	Selection Period		Evaluation Period[a]				Maintenance Period[b]										
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16[c]…	V17[d]…
Visit Study Week	D-9 to D-2	D-2 to D0	W0	W2	W4	W6	W8	W10	W12	W14	W18	W22	W26	W32	W38	W50…	W62…

[g] Recorded from end of V1 through V3.
[h] If clinically significant laboratory abnormalities are present at V1, repeat samples must be obtained for blood chemistry and hematology. The results should be available prior to V2, and UCB or its designee should be contacted regarding clinically significant abnormalities.
[i] Blood samples will be obtained prior to receiving LEV and then at least 2h after dosing at V4 and V6.
[j] Dispense study drug at V3.
[k] Only for subjects who have not had a CT scan or MRI confirming the absence of a progressive lesion since being diagnosed with epilepsy, or have changes on physical examination which would suggest a lesion has occurred since the last imaging procedure.
[l] All video-EEG data recording will be transmitted to a central reader for the purposes of data analysis.
[m] Dispense DRC at V1. Confirm DRC at V2.
[n] Fallback option is permitted. See Section 5.1.2 for details.
[o] C-SSRS to be performed at each visit for subjects aged ≥6 years.

Change #2:

Table 5–2: Schedule of assessments for subjects who are 48h video-EEG failures

	First Period				Second Period										
	Selection Period		Evaluation Period[a]		Maintenance Period[a, b]										
	V1	V2	V3 to V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16[c]	V17[d]
Visit Study Week	D-9 to D-2	D-2 to D0		W0	W2	W4	W6	W8	W12	W16	W20	W26	W32	W44	W56
Written informed consent	X														
Inpatient		X													
Registration	X			X											
Eligibility assessment	X	X		X											
Medical/procedures history	X														
Demographics	X														
AED history	X														
Epilepsy history	X														
Physical examination	X														
Neurological examination	X														
Vital signse	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Seizure counts	X[f]	X[g]		X	X	X	X	X	X	X	X	X	X	X	X
Laboratory safety assessment	X	X[h]			X	X	X			X		X	X	X	X
LEV plasma level					X	X	X	X	X	X	X	X			
Body weight	X			X	X	X	X	X	X	X	X	X	X	X	X
Height	X										X			X	
Concomitant AED(s)	X			X[i]	X	X	X	X	X	X	X	X	X	X	X
Concomitant non-AED(s)	X			X[i]	X	X	X	X	X	X	X	X	X	X	X

Table 5–2: Schedule of assessments for subjects who are 48h video-EEG failures

	First Period				Second Period										
	Selection Period		Evaluation Period[a]		Maintenance Period[a, b]										
	V1	V2	V3 to V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16[c]	V17[d]
Visit Study Week	D-9 to D-2	D-2 to D0		W0	W2	W4	W6	W8	W12	W16	W20	W26	W32	W44	W56
Concomitant medical procedures	X			X[i]	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X			X[i]	X	X	X	X	X	X	X	X	X	X	X
Dispense/return study drug				Xj	X	X	X	X	X	X	X	X	X	X	X
Study drug compliance					X	X	X	X	X	X	X	X	X	X	X
ECG	X										X			X	
CT scan/MRI[k]	X														
Video-EEG		X													
IVRS/IWRS	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Dispense/collect DRC	X[l]	X[l]		X	X	X	X	X	X	X	X	X	X	X	X
Dispense subject's ID card	X														
C-SSRS[m]														X	X

AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; CT=computed tomography; D=day; DRC=daily record card; ECG=electrocardiogram; EDV=Early Discontinuation Visit; EEG=electroencephalogram; ID=identification; IVRS=interactive voice response system; IWRS=interactive web response system; LEV=levetiracetam; MRI=magnetic resonance imaging; SFU=Safety Follow-Up; V=visit; W=week

Note: See Table 5–3 for the schedule of assessments for the Down-Titration and SFU Periods.

[a] After beginning the study medication, subjects who withdraw prematurely must have the EDV evaluations.

[b] In the Maintenance Period, visits will occur every 2 weeks from V7 to V10, every 4 weeks from V11 to V13, every 6 weeks between V14 and V15, and every 12 weeks thereafter.

[c] Even numbered visits.

[d] Odd numbered visits.

[e] Including temperature, blood pressure, and heart rate.

[f] Collect seizure count for seizures that occurred in the prior 2 weeks.

Table 5–2: Schedule of assessments for subjects who are 48h video-EEG failures

	First Period				Second Period										
	Selection Period		Evaluation Period[a]		Maintenance Period[a, b]										
	V1	V2	V3 to V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16[c]	V17[d]
Visit Study Week	D-9 to D-2	D-2 to D0		W0	W2	W4	W6	W8	W12	W16	W20	W26	W32	W44	W56

[g] Seizures will be counted by video-EEG and DRC.
[h] If clinically significant laboratory abnormalities are present at V1, repeat samples must be obtained for blood chemistry and hematology. The results should be available prior to V6, and UCB or its designee should be contacted regarding clinically significant abnormalities.
[i] Recorded from end of V1 through V6.
[j] Dispense study drug at V6.
[k] Only for subjects who have not had a CT scan or MRI confirming the absence of a progressive lesion since being diagnosed with epilepsy, or have changes on physical examination which would suggest a lesion has occurred since the last imaging procedure.
[l] Dispense DRC at V1. Confirm DRC at V2.
[m] C-SSRS to be performed at each visit for subjects aged ≥6 years.

Has been changed to

Table 5–2: Schedule of assessments for subjects who are 48h video-EEG failures

	First Period				Second Period										
	Selection Period		Evaluation Period[a]		Maintenance Period[a, b]										
	V1	V2		V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16[c]	V17[d]
Visit **Study Week**	D-9 to D-2	D-2 to D0	V3 to V5	W0	W2	W4	W6	W8	W12	W16	W20	W26	W32	W44	W56
Written informed consent	X														
Inpatient		X													
Registration	X			X											
Eligibility assessment	X	X		X											
Medical/procedures history	X														
Demographics	X														
AED history	X														
Epilepsy history	X														
Physical examination	X														
Neurological examination	X														
Vital signs[e]	X			X	X	X	X	X	X	X	X	X	X	X	X
Seizure counts[f]	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Laboratory safety assessment	X	X[g]			X	X	X			X		X	X	X	X
LEV plasma level					X	X	X	X	X	X	X	X			
Body weight	X			X	X	X	X	X	X	X	X	X	X	X	X
Height	X										X			X	
Concomitant AED(s)	X			X[h]	X	X	X	X	X	X	X	X	X	X	X
Concomitant non-AED(s)	X			X[h]	X	X	X	X	X	X	X	X	X	X	X

Table 5–2: Schedule of assessments for subjects who are 48h video-EEG failures

	First Period				Second Period										
	Selection Period		Evaluation Period[a]		Maintenance Period[a, b]										
	V1	V2		V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16[c]	V17[d]
Visit Study Week	D-9 to D-2	D-2 to D0	V3 to V5	W0	W2	W4	W6	W8	W12	W16	W20	W26	W32	W44	W56
Concomitant medical procedures	X			X[h]	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X			X[h]	X	X	X	X	X	X	X	X	X	X	X
Dispense/return study drug				X[i]	X	X	X	X	X	X	X	X	X	X	X
Study drug compliance					X	X	X	X	X	X	X	X	X	X	X
ECG	X										X			X	
CT scan/MRI[j]	X														
Video-EEG		X													
IVRS/IWRS	X			X	X	X	X	X	X	X	X	X	X	X	X
Dispense/collect DRC	X[k]	X[k]		X	X	X	X	X	X	X	X	X	X	X	X
Dispense subject's ID card	X														
C-SSRS[l]														X[l]	X[l]

AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; CT=computed tomography; D=day; DRC=daily record card; ECG=electrocardiogram; EDV=Early Discontinuation Visit; EEG=electroencephalogram; ID=identification; IVRS=interactive voice response system; IWRS=interactive web response system; LEV=levetiracetam; MRI=magnetic resonance imaging; SFU=Safety Follow-Up; V=visit; W=week

Note: See Table 5–3 for the schedule of assessments for the Down-Titration and SFU Periods.

[a] After beginning the study medication, subjects who withdraw prematurely must have the EDV evaluations.

[b] In the Maintenance Period, visits will occur every 2 weeks from V7 to V10, every 4 weeks from V11 to V13, every 6 weeks between V14 and V15, and every 12 weeks thereafter.

[c] Even numbered visits.

[d] Odd numbered visits.

[e] Including temperature, blood pressure, and heart rate.

[f] At V1, collect seizure count for seizures that occurred in the prior 2 weeks. At V2, seizures will be counted by video-EEG and DRC. At all other visits, seizures will be counted by DRC only.

Table 5–2: Schedule of assessments for subjects who are 48h video-EEG failures

	First Period				Second Period										
	Selection Period		Evaluation Period[a]		Maintenance Period[a, b]										
	V1	V2		V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16[c]	V17[d]
Visit Study Week	D-9 to D-2	D-2 to D0	V3 to V5	W0	W2	W4	W6	W8	W12	W16	W20	W26	W32	W44	W56

[g] If clinically significant laboratory abnormalities are present at V1, repeat samples must be obtained for blood chemistry and hematology. The results should be available prior to V6, and UCB or its designee should be contacted regarding clinically significant abnormalities.
[h] Recorded from end of V1 through V6.
[I] Dispense study drug at V6.
[j] Only for subjects who have not had a CT scan or MRI confirming the absence of a progressive lesion since being diagnosed with epilepsy, or have changes on physical examination which would suggest a lesion has occurred since the last imaging procedure.
[k] Dispense DRC at V1. Confirm DRC at V2.
[l] C-SSRS to be performed at each visit for subjects aged ≥6 years.

Change #3:

Table 5–3: Schedule of assessments for Down-Titration and SFU Periods

Visit	EDV[a]			SFU[b]
Study Week	W0	W2	W4	
Vital signs[c]	X	X	X	X
Seizure counts	X	X	X	X
Laboratory safety assessments	X			X
Body weight	X	X	X	X
Height	X			X
Concomitant AED(s)	X	X	X	X
Concomitant non-AED(s)	X	X	X	X
Concomitant medical procedures	X	X	X	X
Adverse events	X	X	X	X
Dispense/return study drug	X	X	X	
Study drug compliance	X	X	X	
ECG	X			X[d]
IVRS/IWRS	X	X	X	X
Dispense/collect DRC	X	X	X	X[e]
C-SSRS[f]	X	X	X	X

AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; CT=computed tomography; D=day; DRC=daily record card; ECG=electrocardiogram; EDV=Early Discontinuation Visit; EEG=electroencephalogram; ID=identification; IVRS=interactive voice response system; IWRS=interactive web response system; LEV=levetiracetam; MRI=magnetic resonance imaging; SFU=Safety Follow-Up; V=visit; W=week

[a] The dose will be decreased by LEV 14mg/kg/day for subjects aged 1 month to <6 months or by LEV 20mg/kg/day for subjects aged 6 months to <4 years at 2-week intervals to 0mg/kg/day.

[b] Two weeks after final dose of study drug.

[c] Including temperature, blood pressure, and heart rate.

[d] Performed only if abnormal at EDV.

[e] Collect DRC.

[f] C-SSRS to be performed at each visit for subjects aged ≥6 years.

Has been changed to

Table 5–3: Schedule of assessments for Down-Titration and SFU Periods

Visit	EDV[a]			SFU[b]
Study Week	W0	W2	W4	
Vital signs[c]	X	X	X	X
Seizure counts	X	X	X	X
Laboratory safety assessments	X			X
Body weight	X	X	X	X
Height	X			X
Concomitant AED(s)	X	X	X	X
Concomitant non-AED(s)	X	X	X	X
Concomitant medical procedures	X	X	X	X
Adverse events	X	X	X	X
Dispense/return study drug	X	X	X	
Study drug compliance	X	X	X	
ECG	X			X[d]
IVRS/IWRS	X	X	X	X
Dispense/collect DRC	X	X	X	X[e]
C-SSRS[f]	X[f]	X[f]	X[f]	X[f]

AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; CT=computed tomography; D=day; DRC=daily record card; ECG=electrocardiogram; EDV=Early Discontinuation Visit; EEG=electroencephalogram; ID=identification; IVRS=interactive voice response system; IWRS=interactive web response system; LEV=levetiracetam; MRI=magnetic resonance imaging; SFU=Safety Follow-Up; V=visit; W=week

[a] The dose will be decreased by LEV 14mg/kg/day for subjects aged 1 month to <6 months or by LEV 20mg/kg/day for subjects aged 6 months to <4 years at 2-week intervals to 0mg/kg/day.

[b] Two weeks after final dose of study drug.

[c] Including temperature, blood pressure, and heart rate.

[d] Performed only if abnormal at EDV.

[e] Collect DRC.

[f] C-SSRS to be performed at each visit for subjects aged ≥6 years.

Change #4:

6.1: Inclusion criteria

6. Subject may have Vagal Nerve Stimulation (VNS) which has been implanted for at least 6 months prior to Day -1; the settings must be stable for at least 2 months prior to Visit 1. Activated VNS must be counted as 1 of the 2 AEDs.

Has been changed to

6. Subject may have Vagal Nerve Stimulation (VNS) which has been implanted for at least 6 months prior to Visit 1; the settings must be stable for at least 2 months prior to Visit 1. Activated VNS must be counted as 1 of the 2 AEDs.

Change #5:

6.3: Withdrawal criteria

10. Subject on monotherapy needs to add another AED.

Has been changed to

10. Subject on monotherapy needs to add another AED during the First Period.

Change #6:

7.2: Treatments to be administered

If the subject cannot take LEV dry syrup under a fasting state during the First Period, LEV 100mg/mL concentrate for solution for infusion (clear, colorless, sterile solution) can be used for a maximum of 4.5 consecutive days at each dose at the Investigator's discretion.

Has been changed to

If the subject cannot take LEV dry syrup under a fasting state during the First Period, LEV 100mg/mL concentrate for solution for infusion (clear, colorless, sterile solution) can be used for a maximum of 4.5 consecutive days at each dose at the Investigator's discretion. Levetiracetam injection is infused intravenously over 15 minutes per dose.

Change #7:

7.2: Treatments to be administered

The following administration details have been added.

First Period

. . .

Subjects aged 1 month to <6 months will be started on LEV 14mg/kg/day at Visit 3 (Week 0). The dose may be increased by LEV 14mg/kg/day for subjects aged 1 month to <6 months at 2-week intervals to a maximum dose of LEV 42mg/kg/day. Subjects aged 6 months to <4 years will be started on LEV 20mg/kg/day at Visit 3 (Week 0). The dose may be increased by LEV 20mg/kg/day at 2-week intervals to a maximum dose of 60mg/kg/day.

Change #8:

7.9.1: Permitted concomitant treatments (medications and therapies)

First Period

The use of intermittent benzodiazepines is allowed as long as the frequency is not greater than 1 single administration per week for at least 2 weeks prior to Visit 1 and during the First Period. If benzodiazepines are used more than once a week, they must be considered as 1 of the AEDs.

Has been changed to

The use of intermittent benzodiazepines, phenobarbitals, and phenytoins is allowed as long as the frequency is not greater than 1 single administration per week for at least 2 weeks prior to Visit 1 and during the First Period. If benzodiazepines are used more than once a week, they must be considered as 1 of the AEDs.

Change #9:

7.8.1: Permitted concomitant treatments (medications and therapies)

Second Period

The use of intermittent benzodiazepines is allowed as long as the frequency is not greater than 1 single administration per week during the Second Period. If benzodiazepines are used more than once a week, they must be considered as 1 of the AEDs.

Has been changed to

The use of intermittent benzodiazepines, phenobarbitals, and phenytoins is allowed as long as the frequency is not greater than 1 single administration per week during the Second Period. If benzodiazepines are used more than once a week, they must be considered as 1 of the AEDs.

Change #10:

8.2.10: Visit 16 (Week 50)

The following text was added:

- C-SSRS (will be performed at each visit for subjects aged ≥6 years)

Change #11:

8.3: Direct enrollment

See Section 5.2 for the schedule of assessments for subjects who are 48h video-EEG failures at Visit 2. The C-SSRS will be performed at each visit for subjects aged ≥6 years.

Has been changed to

See Section 5.2 for the schedule of assessments for subjects who are 48h video-EEG failures at Visit 2.

Change #12:

8.4: Safety Follow Up Visit (if applicable)

The following text was added:

- Record height

Change #13:

8.6: Unscheduled Visit (if applicable)

- Vital signs (BP and pulse rate, including orthostatic assessments where feasible according to investigator judgment)

Has been changed to

- Vital signs (blood pressure, pulse rate, and body temperature)

Change #14:

Table 11–3: PDILI laboratory measurements

Virology-related	Hepatitis A IgM antibody
	HBsAg
	Hepatitis E IgM antibody
	HBcAb-IgM
	Hepatitis C RNA
	Cytomegalovirus IgM antibody
	Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophile antibody or monospot testing)
Immunology	Anti-nuclear antibody (qualitative and quantitative)
	Anti-smooth muscle antibody (qualitative and quantitative)
	Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative)
Hematology	Eosinophil count
Urinalysis	Toxicology screen
Chemistry	Amylase
	If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
Additional	Prothrombin time/INR[a]
	Serum pregnancy test
	PK sample

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

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

Has been changed to

Table 11–3: PDILI laboratory measurements

Virology-related	Hepatitis A IgM antibody
	HBsAg
	Hepatitis E IgA antibody
	HBcAb-IgM
	Hepatitis C RNA
	Cytomegalovirus IgM antibody
	Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophile antibody or monospot testing)
Immunology	Anti-nuclear antibody (qualitative and quantitative)
	Anti-smooth muscle antibody (qualitative and quantitative)
	Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative)
Hematology	Eosinophil count
Urinalysis	Toxicology screen
Chemistry	Amylase
	If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
Additional	Prothrombin time/INR[a]
	PK sample

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

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

Change #15:

Section 13.1: Definition of analysis sets

The Safety Set (SS) will include all enrolled subjects in the First Period or the Second Period who will be administrated at least 1 dose of study medication.

First Period

The SS (for the First Period) will include all enrolled subjects in the First Period who receive at least 1 dose of study medication. The FAS (for the First Period and adjunctive therapy) will consist of all subjects in the SS who receive adjunctive therapy, have at least 24h of usable Selection Period video-EEG time, and have at least 1 post-baseline efficacy assessment from either the Evaluation Period video-EEG time or DRCs.

. . .

The Pharmacokinetic Per Protocol Set (PK-PPS) will consist of all subjects in the SS for whom at least 1 valid LEV plasma concentration-time record and dosing information are available.

Has been changed to

Section 13.1: Definition of analysis sets

The Safety Set (SS) will include all enrolled subjects in the First Period or the Second Period who will be administrated at least 1 dose of study medication.

The Pharmacokinetic Per Protocol Set (PK-PPS) will consist of all subjects in the SS for whom at least 1 valid LEV plasma concentration-time record and dosing information are available.

First Period

The SS (for the First Period) will include all enrolled subjects in the First Period who receive at least 1 dose of study medication. The FAS (for the First Period and adjunctive therapy) will consist of all subjects in the SS who receive adjunctive therapy, have at least 24h of usable Selection Period video-EEG time, and have at least 1 post-baseline efficacy assessment from either the Evaluation Period video-EEG time or DRCs.

17.5 Protocol Amendment 2

Rationale for the amendment

The purpose of this amendment is to update the long-term efficacy and safety assessments so that they are more appropriate, taking into account 48h video-EEG failures.

In addition, minor administrative edits including typographical changes for formatting have been made.

The following shows the changes made in Protocol Amendment 2 compared to Protocol Amendment 1, dated 16 Jun 2017.

Modifications and changes

Specific changes

Change #1:

Section 3.2: Secondary objectives

- To evaluate long-term safety and tolerability of LEV in the Second Period in pediatric epilepsy subjects aged 1 month to <4 years with partial seizures receiving long-term treatment with LEV at individualized doses
- To evaluate the efficacy of LEV in the Second Period based on the daily record card (DRC) as monotherapy or adjunctive treatment in pediatric epilepsy subjects aged 1 month to <4 years with partial seizures

Has been changed to

Section 3.2: Secondary objectives

- To evaluate long-term safety and tolerability of LEV in the combined First and Second Periods in pediatric epilepsy subjects aged 1 month to <4 years with partial seizures receiving long-term treatment with LEV at individualized doses
- To evaluate the efficacy of LEV in the combined First and Second Periods based on the daily record card (DRC) as monotherapy or adjunctive treatment in pediatric epilepsy subjects aged 1 month to <4 years with partial seizures

Change #2:

Section 4.1: Efficacy Variables

Section 4.1.1: Efficacy variables for subjects on adjunctive therapy

Efficacy variables are defined separately for the First Period and the Second Period.

Has been changed to

Section 4.1: Efficacy variables

Efficacy variables are defined separately for the First Period and the combined First and Second Periods, and for the type of therapy, if applicable.

Section 4.1.1: Efficacy variables for subjects on adjunctive therapy

Change #3:

Section 4.1.1.1.2: Second Period

There is no primary efficacy variable for the Second Period.

Has been changed to

Section 4.1.1.1.2: Combined First and Second Periods

There is no primary efficacy variable for the combined First and Second Periods for subjects on adjunctive therapy.

Change #4:

Section 4.1.1.2.1: First Period

- Percent reduction in ADF of partial seizure frequency grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, 50% to <75%, 75% to <100% and 100% on the Evaluation Period 48h video-EEG compared to the Selection Period 48h video-EEG at Visit 4 and Visit 6 for the First Period
- Percent reduction in ADF of electro-clinical partial seizure frequency at Visit 4 and Visit 6 for the First Period

Has been changed to

Section 4.1.1.2.1: First Period

- Percent reduction in ADF of partial seizure frequency grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100% based on the Evaluation Period 48h video-EEG compared to the Selection Period 48h video-EEG at Visit 4 and Visit 6
- Percent reduction in ADF of electro-clinical partial seizure frequency at Visit 4 and Visit 6
- Percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline at Visit 4, Visit 5, and Visit 6

Change #5:

Section 4.1.1.2.2: Second Period

- Percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline during the Maintenance Period for the Second Period
- Percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, 50% to <75%, 75% to <100%, and 100% during the Maintenance Period for the Second Period

Has been changed to

Section 4.1.1.2.2: Combined First and Second Periods

The secondary efficacy variables for the combined First and Second Periods are the following:

- For each analysis visit, percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline during the combined Evaluation and Maintenance Periods for subjects who are not 48h video-EEG failures, and the combined Dose adjustment and Maintenance Periods for subjects who are 48h video-EEG failures
- For each analysis visit, percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100% during the combined Evaluation and Maintenance Periods for subjects who are not 48h video-EEG failures, and the combined Dose adjustment and Maintenance Periods for subjects who are 48h video-EEG failures

Refer to Section 13.2 for the definition of each analysis visit.

Change #6:

Section 4.1.1.3.1: First Period

- Percent reduction in ADF of all types of seizure frequency monitored by the 48h video-EEG at Visit 4 and Visit 6 for the First Period
- Percent reduction in ADF of all type of seizure frequency monitored by the 48h video-EEG grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, 50% to <75%, 75% to <100%, and 100% on the Evaluation Period 48h video-EEG compared to the Selection Period 48h video-EEG at Visit 4 and Visit 6 for the First Period
- Percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline during the Evaluation Period for the First Period

Has been changed to

Section 4.1.1.3.1: First Period

The other efficacy variables for the First Period are the following:

- Percent reduction in ADF of all types of seizure frequency monitored by the 48h video-EEG at Visit 4 and Visit 6
- Percent reduction in ADF of all type of seizure frequency monitored by the 48h video-EEG grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100% based on the Evaluation Period 48h video-EEG compared to the Selection Period 48h video-EEG at Visit 4 and Visit 6
- Percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline during the Evaluation Period

Change #7:

Section 4.1.1.3.2: Second Period

- Percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline by visit during the Maintenance Period for the Second Period
- Percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, 50% to <75%, 75% to <100%, and 100% by visit during the Maintenance Period for the Second Period (A,M)

Has been changed to

Section 4.1.1.3.2: Combined First and Second Periods

There are no other efficacy variables for the combined First and Second Periods.

Change #8:

Added new section:

Section 4.1.2.1: Primary efficacy variable

There is no primary efficacy variable for subjects on monotherapy.

Change #9:

Section 4.1.2.1: Secondary efficacy variables

Section 4.1.2.1.1: First Period

- Percent reduction in ADF of partial seizure frequency monitored by the 48h video-EEG at Visit 4 and Visit 6 for the First Period
- Percent reduction in ADF of partial seizure frequency grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, 50% to <75%, 75% to <100% and 100% on the Evaluation Period 48h video-EEG compared to the Selection Period 48h video-EEG at Visit 4 and Visit 6 for the First Period
- Percent reduction in ADF of electro-clinical partial seizure frequency at Visit 4 and Visit 6 for the First Period

Has been changed to

Section 4.1.2.2: Secondary efficacy variables

Section 4.1.2.2.1: First Period

The secondary efficacy variables for the First Period are the following:

- Percent reduction in ADF of partial seizure frequency monitored by the 48h video-EEG at Visit 4 and Visit 6

- Percent reduction in ADF of partial seizure frequency grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100% based on the Evaluation Period 48h video-EEG compared to the Selection Period 48h video-EEG at Visit 4 and Visit 6
- Percent reduction in ADF of electro-clinical partial seizure frequency at Visit 4 and Visit 6

Change #10:

Section 4.1.2.1.2: Second Period

- Percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline during the Maintenance Period for the Second Period
- Percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, 50% to <75%, 75% to <100%, and 100% during the Maintenance Period for the Second Period
- Subjects who are continuously 6-month seizure-free monitored by the patient diary during the Maintenance Period for the Second Period

Has been changed to

Section 4.1.2.2.2: Combined First and Second Periods

The secondary efficacy variables for the combined First and Second Periods are the following:

- For each analysis visit, percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline during the combined Evaluation and Maintenance Periods for subjects who are not 48h video-EEG failures, and the combined Dose adjustment and Maintenance Periods for subjects who are 48h video-EEG failures
- For each analysis visit, percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100% during the combined Evaluation and Maintenance Periods for subjects who are not 48h video-EEG failures, and the combined Dose adjustment and Maintenance Periods for subjects who are 48h video-EEG failures

Refer to Section 13.2 for the definition of each analysis visit.

Change #11:

Section 4.1.2.1.3: Other efficacy variables

Section 4.1.2.1.3.1: First Period

- Percent reduction in ADF of all types of seizure frequency monitored by the 48h video-EEG at Visit 4 and Visit 6 for the First Period
- Percent reduction in ADF of all type of seizure frequency monitored by the 48h video-EEG grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, 50% to <75%, 75% to <100%, and 100% on the Evaluation Period 48h video-EEG compared to the Selection Period 48h video-EEG at Visit 4 and Visit 6 for the First Period

- Percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline during the Evaluation Period for the First Period

Has been changed to

Section 4.1.2.3: Other efficacy variables

Section 4.1.2.3.1: First Period

The other efficacy variables for the First Period are the following:

- Percent reduction in ADF of all types of seizure frequency monitored by the 48h video-EEG at Visit 4 and Visit 6
- Percent reduction in ADF of all type of seizure frequency monitored by the 48h video-EEG grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100% based on the Evaluation Period 48h video-EEG compared to the Selection Period 48h video-EEG at Visit 4 and Visit 6
- Percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline during the Evaluation Period

Change #12:

Section 4.1.2.1.3.2: Second Period

- Percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline by visit during the Maintenance Period for the Second Period
- Percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, 50% to <75%, 75% to <100%, and 100% by visit during the Maintenance Period for the Second Period
- Subjects who are continuously seizure-free monitored by the patient diary by analysis period during the Maintenance Period for the Second Period

Section 4.1.2.1.3.3: First and Second Period Combined

- Subjects who are continuously 6-month seizure-free monitored by the patient diary during the First Period and the Second Period

Has been changed to

Section 4.1.2.3.2: Combined First and Second Periods

The other efficacy variable for the combined First and Second Periods is the following:

- Subjects who are continuously 6-month seizure-free monitored by the patient diary during the combined Evaluation and Maintenance Periods for subjects who are not 48h video-EEG failures, and the combined Dose adjustment and Maintenance Periods for subjects who are 48h video-EEG failures

Change #13:

Added new section:

Section 4.3.1: Primary safety variable

There is no primary safety variable.

Change #14:

Section 4.3.1: Secondary safety variables

- Incidence of TEAEs during the First Period
- Incidence of SAEs during the First Period
- Incidence of TEAEs led to discontinuation during the First Period
- Incidence of TEAEs during the Second Period
- Incidence of SAEs during the Second Period
- Incidence of TEAEs leading to discontinuation during the Second Period

Has been changed to

Section 4.3.2: Secondary safety variables

Section 4.3.2.1: First Period

The secondary safety variables for the First Period are the following:

- Incidence of TEAEs
- Incidence of SAEs
- Incidence of TEAEs led to discontinuation

Section 4.3.2.2: Combined First and Second Periods

The secondary safety variables for the combined First and Second Periods are the following:

- Incidence of TEAEs
- Incidence of SAEs
- Incidence of TEAEs leading to discontinuation

Change #15:

Section 4.3.2: Other safety variables

Has been changed to

Section 4.3.3: Other safety variables

The other safety variables are the following:

Change #16:

Table 5-2: Schedule of assessments for subjects who are 48h video-EEG failures

	First Period				Second Period										
	Selection Period		Evaluation Period[a]		Maintenance Period[a, b]										
	V1	V2		V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16[c]…	V17[d]…
Visit Study Week	D-9 to D-2	D-2 to D0	V3 to V5	W0	W2	W4	W6	W8	W12	W16	W20	W26	W32	W44…	W56…
Written informed consent	X														
Inpatient		X													
Registration	X			X											
Eligibility assessment	X	X		X											
Medical/procedures history	X														
Demographics	X														
AED history	X														
Epilepsy history	X														
Physical examination	X														
Neurological examination	X														
Vital signse	X			X	X	X	X	X	X	X	X	X	X	X	X
Seizure countsf	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Laboratory safety assessment	X	X[g]			X	X	X			X		X	X	X	X
LEV plasma level					X	X	X	X	X	X	X	X			
Body weight	X			X	X	X	X	X	X	X	X	X	X	X	X
Height	X										X			X	
Concomitant AED(s)	X			X[h]	X	X	X	X	X	X	X	X	X	X	X
Concomitant non-AED(s)	X			X[h]	X	X	X	X	X	X	X	X	X	X	X

Concomitant medical procedures	X			Xh	X	X	X	X	X	X	X	X	X	X
Adverse events	X			Xh	X	X	X	X	X	X	X	X	X	X
Dispense/return study drug				Xi	X	X	X	X	X	X	X	X	X	X
Study drug compliance					X	X	X	X	X	X	X	X	X	X
ECG	X									X			X	
CT scan/MRIj	X													
Video-EEG		X												
IVRS/IWRS	X			X	X	X	X	X	X	X	X	X	X	X
Dispense/collect DRC	X[k]	X[k]		X	X	X	X	X	X	X	X	X	X	X
Dispense subject's ID card	X													
C-SSRS l													Xl	Xl

AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; CT=computed tomography; D=day; DRC=daily record card; ECG=electrocardiogram; EDV=Early Discontinuation Visit; EEG=electroencephalogram; ID=identification; IVRS=interactive voice response system; IWRS=interactive web response system; LEV=levetiracetam; MRI=magnetic resonance imaging; SFU=Safety Follow-Up; V=visit; W=week

Note: See Table 5-3 for the schedule of assessments for the Down-Titration and SFU Periods.

[a] After beginning the study medication, subjects who withdraw prematurely must have the EDV evaluations.

[b] In the Maintenance Period, visits will occur every 2 weeks from V7 to V10, every 4 weeks from V11 to V13, every 6 weeks between V14 and V15, and every 12 weeks thereafter.

[c] Even numbered visits.

[d] Odd numbered visits.

[e] Including temperature, blood pressure, and heart rate.

[f] At V1, collect seizure count for seizures that occurred in the prior 2 weeks. . At V2, seizures will be counted by video-EEG and DRC. At all other visits, seizures will be counted by DRC only.

[g] If clinically significant laboratory abnormalities are present at V1, repeat samples must be obtained for blood chemistry and hematology. The results should be available prior to V6, and UCB or its designee should be contacted regarding clinically significant abnormalities.

[h] Recorded from end of V1 through V6.

[I] Dispense study drug at V6.

[j] Only for subjects who have not had a CT scan or MRI confirming the absence of a progressive lesion since being diagnosed with epilepsy, or have changes on physical examination which would suggest a lesion has occurred since the last imaging procedure.

[k] Dispense DRC at V1. Confirm DRC at V2.

[l] C-SSRS to be performed at each visit for subjects aged ≥6 years.

Has been changed to

Table 5-2: Schedule of assessments for subjects who are 48h video-EEG failures

	First Period			Second Period											
	Selection Period			Dose Adjustment Period[a]				Maintenance Period[a, b]							
	V1	V2		V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16c…	V17d…
Visit **Study Week**	D-9 to D-2	D-2 to D0	V3 to V5	W0	W2	W4	W6	W8	W12	W16	W20	W26	W32	W44…	W56…
Written informed consent	X														
Inpatient		X													
Registration	X			X											
Eligibility assessment	X	X		X											
Medical/procedures history	X														
Demographics	X														
AED history	X														
Epilepsy history	X														
Physical examination	X														
Neurological examination	X														
Vital signs[e]	X			X	X	X	X	X	X	X	X	X	X	X	X
Seizure counts[f]	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Laboratory safety assessment	X	X[g]			X	X	X			X		X	X	X	X
LEV plasma level					X	X	X	X	X	X	X	X			
Body weight	X			X	X	X	X	X	X	X	X	X	X	X	X
Height	X										X			X	
Concomitant AED(s)	X			X[h]	X	X	X	X	X	X	X	X	X	X	X

Table 5-2: Schedule of assessments for subjects who are 48h video-EEG failures

	First Period			Second Period											
	Selection Period			Dose Adjustment Period[a]				Maintenance Period[a, b]							
	V1	V2		V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16c…	V17d…
Visit Study Week	D-9 to D-2	D-2 to D0	V3 to V5	W0	W2	W4	W6	W8	W12	W16	W20	W26	W32	W44…	W56…
Concomitant non-AED(s)	X			X[h]	X	X	X	X	X	X	X	X	X	X	X
Concomitant medical procedures	X			X[h]	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X			X[h]	X	X	X	X	X	X	X	X	X	X	X
Dispense/return study drug				X[i]	X	X	X	X	X	X	X	X	X	X	X
Study drug compliance					X	X	X	X	X	X	X	X	X	X	X
ECG	X										X			X	
CT scan/MRI[j]	X														
Video-EEG		X													
IVRS/IWRS	X			X	X	X	X	X	X	X	X	X	X	X	X
Dispense/collect DRC	X[k]	X[k]		X	X	X	X	X	X	X	X	X	X	X	X
Dispense subject's ID card	X														
C-SSRS [l]														X[l]	X[l]

AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; CT=computed tomography; D=day; DRC=daily record card; ECG=electrocardiogram; EDV=Early Discontinuation Visit; EEG=electroencephalogram; ID=identification; IVRS=interactive voice response system; IWRS=interactive web response system; LEV=levetiracetam; MRI=magnetic resonance imaging; SFU=Safety Follow-Up; V=visit; W=week

Note: See Table 5-3 for the schedule of assessments for the Down-Titration and SFU Periods.

[a] After beginning the study medication, subjects who withdraw prematurely must have the EDV evaluations.

[b] In the Maintenance Period, visits will occur every 2 weeks from V7 to V10, every 4 weeks from V11 to V13, every 6 weeks between V14 and V15, and every 12 weeks thereafter.

[c] Even numbered visits.

[d] Odd numbered visits.

[e] Including temperature, blood pressure, and heart rate.

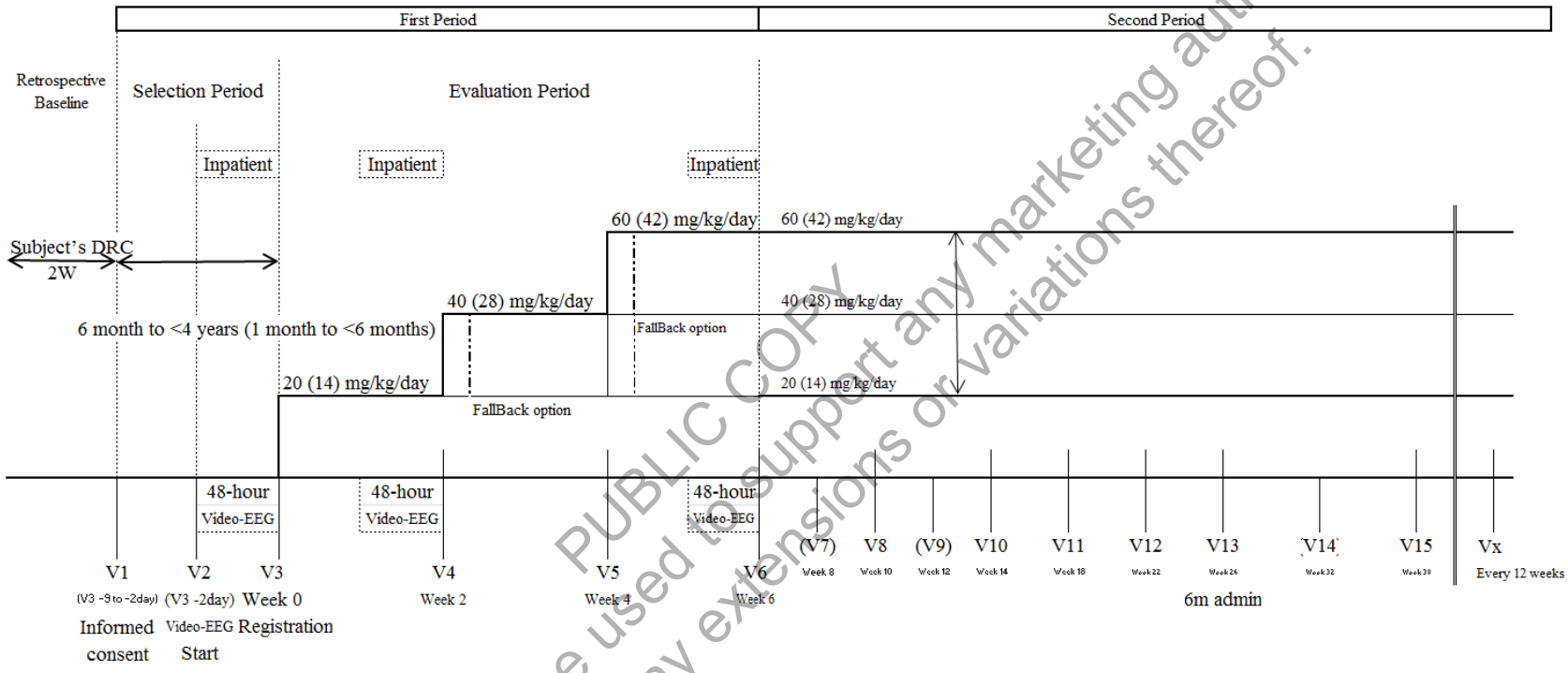
Table 5-2: Schedule of assessments for subjects who are 48h video-EEG failures

	First Period			Second Period											
	Selection Period			Dose Adjustment Period[a]				Maintenance Period[a, b]							
	V1	V2		V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16c…	V17d…
Visit Study Week	D-9 to D-2	D-2 to D0	V3 to V5	W0	W2	W4	W6	W8	W12	W16	W20	W26	W32	W44…	W56…

[f] At V1, collect seizure count for seizures that occurred in the prior 2 weeks. At V2, seizures will be counted by video-EEG and DRC. At all other visits, seizures will be counted by DRC only.
[g] If clinically significant laboratory abnormalities are present at V1, repeat samples must be obtained for blood chemistry and hematology. The results should be available prior to V6, and UCB or its designee should be contacted regarding clinically significant abnormalities.
[h] Recorded from end of V1 through V6.
[I] Dispense study drug at V6.
[j] Only for subjects who have not had a CT scan or MRI confirming the absence of a progressive lesion since being diagnosed with epilepsy, or have changes on physical examination which would suggest a lesion has occurred since the last imaging procedure.
[k] Dispense DRC at V1. Confirm DRC at V2.
[l] C-SSRS to be performed at each visit for subjects aged ≥6 years.

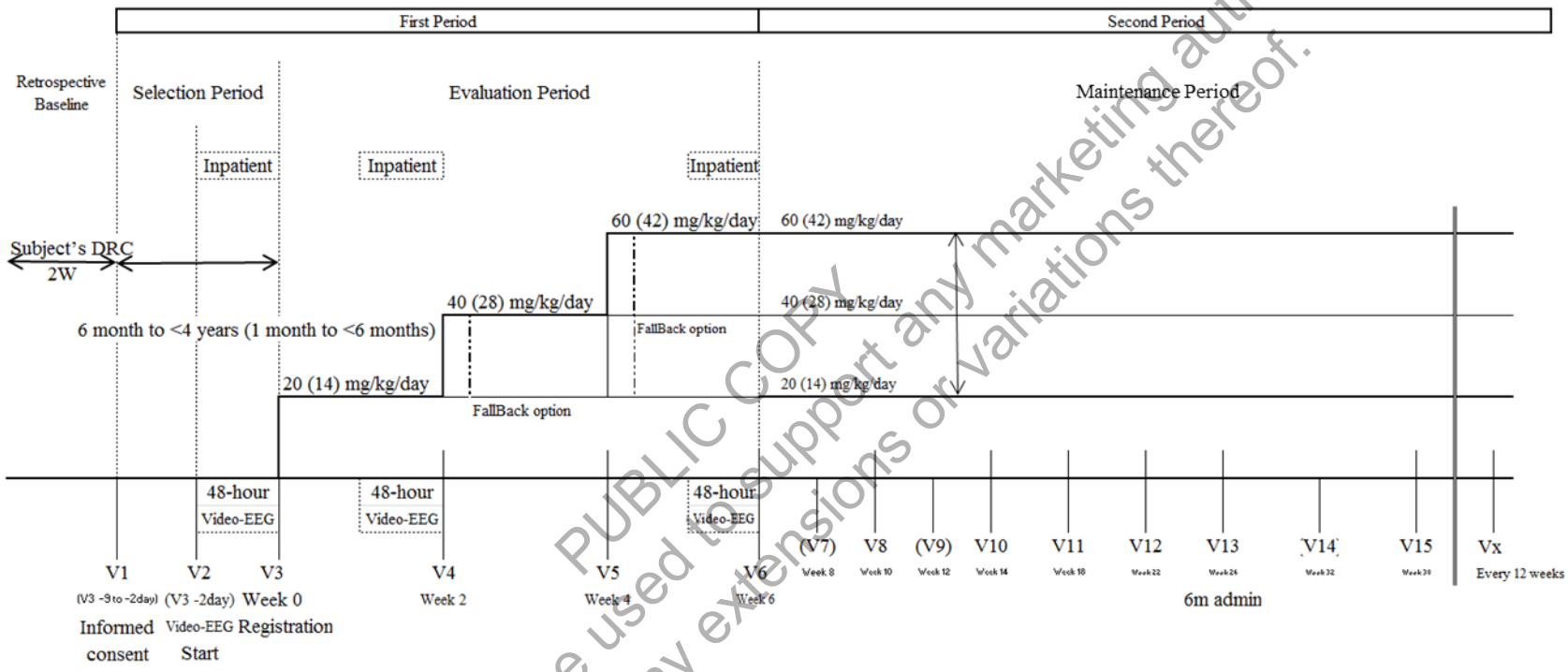
Change #17:

Figure 5-1: Schematic for subjects in the First and Second Periods



Has been changed to

Figure 5-1: Schematic for subjects in the First and Second Periods



Change #18:

Section 13.1: Definition of analysis sets

The Safety Set (SS) will include all enrolled subjects in the First Period or the Second Period who will be administrated at least 1 dose of study medication.

The Pharmacokinetic Per Protocol Set (PK-PPS) will consist of all subjects in the SS for whom at least 1 valid LEV plasma concentration-time record and dosing information are available.

First Period

The SS (for the First Period) will include all enrolled subjects in the First Period who receive at least 1 dose of study medication.

The FAS (for the First Period and adjunctive therapy) will consist of all subjects in the SS who receive adjunctive therapy, have at least 24h of usable Selection Period video-EEG time, and have at least 1 post-baseline efficacy assessment from either the Evaluation Period video-EEG time or DRCs.

The FAS (for the First Period and monotherapy) will consist of all subjects in the SS who receive monotherapy, have at least 24h of usable Selection Period video-EEG time, and have at least 1 post-baseline efficacy assessment from either the Evaluation Period video-EEG time or DRCs.

The Per-Protocol Set (PPS; for the First Period and adjunctive) will consist of all subjects in the FAS who have at least 24h of usable Evaluation Period video-EEG time and do not have important protocol deviations that affect the primary efficacy variable in the First Period.

Second Period

Safety Set 2 (SS2) (for the Second Period) will include all enrolled subjects in the Second Period who have receive at least 1 dose of study medication in the Second Period.

The Full Analysis Set 2 (FAS2) (for the Second Period and adjunctive therapy) will consist of all subjects in the SS2 who receive adjunctive therapy, have an assessable baseline, and have at least 1 post-baseline partial seizure from DRCs in the Second Period.

The FAS2 (for the Second Period and monotherapy) will consist of all subjects in the SS2 who receive monotherapy, have an assessable baseline, and at least 1 post-baseline partial seizure from DRCs in the Second Period.

The PPS is not defined for the Second Period.

Both Periods

The Full Analysis Set 3 (FAS3) (for both the First and Second Periods and monotherapy) will include all enrolled subjects in either the First Period or the Second Period who receive at least 1 dose of study medication in the either the First Period or the Second Period, have an assessable baseline, and at least 1 post-baseline partial seizure from DRCs in the First Period or Second Period.

Has been changed to

Section 13.1: Definition of analysis sets

The following sets are defined for this study:

- Enrolled Set (ES)
- Safety Sets:
  - SS A1 (Safety Set [Adjunctive therapy, First Period], ie, Safety Set for subjects on Adjunctive Therapy during the First Period)
  - SS M1 (Safety Set [Monotherapy, First Period])
  - SS A12 (Safety Set [Adjunctive therapy, combined First and Second Periods])
  - SS M12 (Safety Set [Monotherapy, combined First and Second Periods])
- Full Analysis Sets:
  - FAS A1 (Full Analysis Set [Adjunctive therapy, First Period], ie, Full Analysis Set for subjects on Adjunctive Therapy during the First Period)
  - FAS M1 (Full Analysis Set [Monotherapy, First Period])
  - FAS A12 (Full Analysis Set [Adjunctive therapy, combined First and Second Periods])
  - FAS M12 (Full Analysis Set [Monotherapy, combined First and Second Periods])
- Per-Protocol Set (PPS)
- Pharmacokinetic Per-Protocol Set (PK-PPS)

If not stated otherwise, presentation of:

- Disposition and important protocol deviations are based on the ES
- Demographics, other baseline characteristics, safety, and exposure data are based on the SS A12 and SS M12
- Efficacy data are based on the FAS A1, FAS M1, FAS A12, and FAS M12. Sensitivity analyses on the primary efficacy variable are repeated for the PPS.

Change #19:

Added new section:

Section 13.1.1: Enrolled Set

The ES will consist of all subjects enrolled (which include all subjects screened) into the Selection Period.

Change #20:

Added new section:

Section 13.1.2: Safety Set

First Period:

The SS A1 will include all enrolled subjects on adjunctive therapy in the First Period who receive at least 1 dose of study medication in the Evaluation Period.

The SS M1 will include all enrolled subjects on monotherapy in the First Period who receive at least 1 dose of study medication in the Evaluation Period.

Combined First and Second Periods:

The SS A12 will include all enrolled subjects on adjunctive therapy in the Evaluation, Dose adjustment, and Maintenance Periods who receive at least 1 dose of study medication in the Evaluation, Dose adjustment, or Maintenance Periods.

The SS M12 will include all enrolled subjects on monotherapy in the Evaluation, Dose adjustment, and Maintenance Periods who receive at least 1 dose of study medication in the Evaluation, Dose adjustment, or Maintenance Periods.

Change #21:

Added new section:

Section 13.1.3: Full Analysis Set

First Period:

The FAS A1 will consist of all subjects in the SS A1 who entered the First Period, who receive adjunctive therapy, have at least 24h of usable video-EEG time in the Selection Period, with at least 2 partial seizures, and have at least 1 post-baseline efficacy assessment from the First Period video-EEG time or DRCs in the Evaluation Period.

The FAS M1 will consist of all subjects in the SS M1 who entered the First Period, who receive monotherapy, have at least 24h of usable video-EEG time in the Selection Period, with at least 2 partial seizures, and have at least 1 post-baseline efficacy assessment from the First Period video-EEG time or DRCs in the Evaluation Period.

Combined First and Second Periods:

The FAS A12 will consist of all subjects in the SS A12, who receive adjunctive therapy, have at least 24h of usable video-EEG time in the Selection Period, and have at least 1 post-baseline efficacy assessment from the First Period video-EEG time, or DRCs in the Evaluation, Dose-adjustment, or Maintenance Period.

The FAS M12 will consist of all subjects in the SS M12, who receive monotherapy, have at least 24h of usable video-EEG time in the Selection Period, and have at least 1 post-baseline efficacy assessment from the First Period video-EEG time, or DRCs in the Evaluation, Dose-adjustment, or Maintenance Period.

Change #22:

Added new section:

Section 13.1.4: Per Protocol Set

The PPS (Adjunctive therapy and First Period) will consist of all subjects in the FAS A1 who have at least 24h of usable video-EEG time in the First Period, and do not have important protocol deviations that affect the primary efficacy variable in the Evaluation Period.

The PPS is not defined for the combined First and Second Periods.

Change #23:

Added new section:

Section 13.1.5: Other analysis sets

The PK-PPS will consist of all subjects in the SS A12 and SS M12 for whom at least 1 valid LEV plasma concentration-time record and dosing information are available.

Change #24:

Added new section:

Section 13.2: Definition of analysis visits

Table 13–1 presents the mapping of study visits to analysis visits for subjects who are not 48h video-EEG failures and for subjects who are 48h video-EEG failures. Analysis visits will be used for analysis of long-term safety and efficacy data.

Table 13-1: Analysis visit mapping table

Analysis Visit	Week number	Relative day since first study drug administration	Analysis window	Subjects who are not 48h video-EEG failures Study Visit (Relative day)	Subjects who are 48h video-EEG failures Study Visit (Relative day)
0	0	1	-	Visit 3	Visit 6
1	2	15	2 – 22	Visit 4	Visit 7
2	4	29	23 – 36	Visit 5	Visit 8
3	6	43	37 – 50	Visit 6	Visit 9
4	8	57	51 – 64	-	Visit 10
5	10	71	65 – 78	Visit 8 (Day 71[#])	-
6	12	85	79 – 95	-	Visit 11 (Day 85)
7	15	106	96 - 116	Visit 10 (Day 99)	Visit 12 (Day 113)
8	18	127	117 – 137	Visit 11 (Day 127)	-
9	21	148	138 – 158	Visit 12 (Day 155)	Visit 13 (Day 141)
10	24	169	159 – 179	-	-
11	27	190	180 – 200	Visit 13 (Day 183)	Visit 14 (Day 183)
12	30	211	201 – 231	-	Visit 15 (Day 225)
13	36	253	232 – 295	Visit 15 (Day 267)	-
14	48	337	296 – 379	Visit 16 (Day 351)	Visit 16 (Day 309)
15	60	421	380 – 463	Visit 17 (Day 435)	Visit 17 (Day 393)
16	72	505	464 – 547	Visit 18 (Day 519)	Visit 18 (Day 477)
17	84	589	548 – 631	Visit 19 (Day 603)	Visit 19 (Day 561)
Every 12 weeks					

[#] Day relative to first study drug intake

In the event that more than 1 assessment occurs within a given analysis visit window, the assessment closest to the target date will be used in summaries for the given visit. If 2 assessments are equally close to the target day, the latest assessment will be used.

Change #25:

Section 13.3: Planned efficacy analyses

All efficacy analysis will be performed for the FAS and also for the PPS as a supportive purpose for the First Period. The FAS2 will be utilized for efficacy analysis for the Second Period.

Has been changed to

Section 13.4: Planned efficacy analyses

All efficacy analysis will be performed for the FAS A1 or FAS M1 depending on therapy and also for the PPS as a supportive purpose for the First Period. The FAS A12 or FAS M12 will be utilized for efficacy analysis in the combined First and Second Periods.

Change #26:

Section 13.3.1: Analysis of the primary efficacy variable for adjunctive treatment

First Period

Descriptive statistics (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum) will be calculated for the percent reduction in ADF of partial seizures from the 48h Selection Period to the 48h Evaluation Period at Visit 6 by the age categories of 1 month to <6 months, 6 months to <1 year, 1 year to <2 years, and 2 years to <4 years; the dose categories of LEV 14, 28, and 42mg/kg/day for subjects aged 1 month to <6 months, and LEV 20, 40, and 60mg/kg/day for subjects aged 6 months to <4 years; and overall for the FAS. The corresponding 95% confidence interval for the median percent reduction at Visit 6 will also be provided by the age categories, dose categories, and overall. If the lower limit of the 95% confidence interval for overall is greater than the predefined threshold of 10.0%, the efficacy of LEV is significant. If this test shows a significant result, then it will be repeated for the corresponding Visit 4 variable. In that case, the second test is also regarded as confirmatory as due to the hierarchical testing procedure no alpha adjustment is needed. The analysis will be repeated for PPS supportively.

Has been changed to

Section 13.4.1: Analysis of the primary efficacy variable for adjunctive treatment

First Period

Descriptive statistics (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum) will be calculated for the percent reduction in ADF of partial seizures from the 48h Selection Period to the 48h Evaluation Period at Visit 6 by age category (3 categories: 1 month to <1 year, 1 year to <2 years, and 2 years to <4 years), and for all subjects combined (overall). The corresponding 95% confidence interval for the median percent reduction at Visit 6 will also be provided by age category and overall. If the lower limit of the 95% confidence interval for overall is greater than the predefined threshold of 10.0%, the efficacy of LEV is significant. If this test shows a significant result, then it will be repeated for the corresponding Visit 4 variable. In that case, the second test is also regarded as confirmatory as due to the hierarchical testing procedure no alpha adjustment is needed. The analysis will be repeated for PPS supportively.

Change #27:

Section 13.4: Planned safety and other analyses

Safety summaries will be performed for SS, SS2, and SS3.

Has been changed to

Section 13.5: Planned safety and other analyses

Safety summaries will be performed for SS A1, SS M1, SS A12, and SS M12 depending on the therapy and period.

Change #28:

Section 13.4.1: Safety analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). Adverse events will be summarized by MedDRA System Organ Class and Preferred Term. The incidence of SAEs, AEs leading to premature discontinuation, and related AEs, and the incidence of AEs by intensity will also be summarized by period.

For laboratory evaluations and vital signs descriptive statistic on the observed values and the change from baseline will be computed by visits. The number of subjects reporting at least one treatment-emergent possibly clinically significant (PCS) value will be computed by periods and visits.

Has been changed to

Section 13.5.1: Safety analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). Adverse events will be summarized by MedDRA System Organ Class and Preferred Term. The incidence of SAEs, AEs leading to premature discontinuation, and related AEs, and the incidence of AEs by intensity will also be summarized for the First Period and the combined First and Second Periods.

For laboratory evaluations and vital signs descriptive statistic on the observed values and the change from baseline will be computed by analysis visits. The number of subjects reporting at least one treatment-emergent possibly clinically significant (PCS) value will be computed by analysis visits.

Change #29:

Section 13.5: Handling of protocol deviations

Prior to unblinding, protocol deviations will be assessed if important or not important and if included into the relevant analysis set according to predefined specifications.

Has been changed to

Section 13.6: Handling of protocol deviations

Prior to taking a snapshot for the interim analysis for New Drug Application (NDA) submission, protocol deviations will be assessed if important or not important and if included into the relevant analysis set according to predefined specifications.

Change #30:

The following text has been added to the end of the section

Section 13.8: Planned interim analysis and data monitoring

All the efficacy and safety analysis planned in this protocol will be performed for NDA submission using the interim cutoff data followed by additional cutoff and/or final analysis for long-term follow-up evaluation.

17.6 Protocol Amendment 3

Rationale for the amendment

The purpose of this amendment is to change the primary efficacy variable from daily partial seizure frequency monitored by 48h video-EEG to partial seizure frequency per week from Baseline to Visit 6 as agreed with PMDA. Text was revised throughout to reflect the change from 48h video-EEG to patient diary.

In addition, minor administrative edits have been made.

The following shows the changes made in Protocol Amendment 3 compared to Protocol Amendment 2, dated 28 Jun 2018.

Modifications and changes

Specific changes

Change #1:

Section 1: Summary

EP0100 is an open-label, single-arm, multicenter study with levetiracetam (LEV) as monotherapy or adjunctive treatment to evaluate the efficacy and safety of LEV in Japanese subjects aged 1 month to <4 years with partial seizures. The study will consist of 2 periods. The First Period is designed to confirm efficacy of LEV, and the Second Period is designed to evaluate the long-term efficacy and safety of LEV. Subjects with uncontrolled partial seizures will be enrolled into the Selection Period of the First Period. Eligible subjects will be hospitalized, and a 48h video-electroencephalogram (EEG) will be performed. Subjects with at least 2 partial seizures during the 48h video-EEG will enter the Evaluation Period. Subjects with <2 partial seizures during the 48h video-EEG will directly enter the Second Period.

Seizure counts during the 2 weeks prior to Visit 1 will be used as a Retrospective Baseline. All eligible subjects will enter a 6-week Evaluation Period. Subjects aged 1 month to <6 months will be started on LEV 14mg/kg/day at Visit 3 (Week 0). The dose may be increased by LEV 14mg/kg/day for subjects aged 1 month to <6 months at 2-week intervals to a maximum dose of 42mg/kg/day. Subjects aged 6 months to <4 years will be started on LEV 20mg/kg/day at Visit 3 (Week 0). The dose may be increased by LEV 20mg/kg/day at 2-week intervals to a maximum dose of 60mg/kg/day. A 48h video-EEG will be performed 2 days prior to Visit 4 (Week 2) and Visit 6 (Week 6).

At Visit 6 (Week 6), subjects may enter the Second Period or enter the Down-Titration Period followed by a Safety Follow-Up Period. Subjects who do not enter the Second Period will be down-titrated. The dose will be decreased by LEV 14mg/kg/day for subjects aged 1 month to <6 months or by LEV 20mg/kg/day for subjects aged 6 months to <4 years at 2-week intervals to 0mg/kg/day. Subjects who withdraw from the study at the minimum age-related dose do not need to down-titrate. In order to provide LEV to subjects, the Second Period will be conducted until approval or the program is discontinued.

All subjects who do not enter the Second Period will enter the Safety Follow-Up Period, regardless of whether they down-titrate LEV.

Subjects can be enrolled in the Second Period if 1 of the following is met:

- Subject completes the First Period.
- Subject fails Screening, defined as <2 partial seizures during 48h video EEG, or did not have at least 24h of readable video-EEG data, or not able to measure a video-EEG for 24h due to their disease severity.

Subjects who fail Screening aged 1 month to <6 months will be started on LEV 14mg/kg/day at Visit 6 (Week 0). The dose may be increased by LEV 14mg/kg/day for subjects aged 1 month to <6 months at 2-week intervals to a maximum dose of LEV 42mg/kg/day. Subjects aged 6 months to <4 years will be started on LEV 20mg/kg/day at Visit 6 (Week 0). The dose may be increased by LEV 20mg/kg/day at 2-week intervals to a maximum dose of LEV 60mg/kg/day.

The primary objective of the study is to confirm the efficacy of LEV in the First Period based on 48h video-EEG compared to an historical control as adjunctive treatment in pediatric Japanese epilepsy subjects aged 1 month to <4 years with partial seizures.

Has been changed to

EP0100 is an open-label, single-arm, multicenter study with levetiracetam (LEV) as monotherapy or adjunctive treatment to evaluate the efficacy and safety of LEV in Japanese subjects aged 1 month to <4 years with partial seizures. The study will consist of 2 periods. The First Period is designed to confirm efficacy of LEV, and the Second Period is designed to evaluate the long-term efficacy and safety of LEV. Subjects with uncontrolled partial seizures will be enrolled into the Selection Period of the First Period.

Seizure counts during the 2 weeks prior to Visit 1 will be used as a Retrospective Baseline. All eligible subjects will enter a 6-week Evaluation Period. Subjects aged 1 month to <6 months will be started on LEV 14mg/kg/day at Visit 3 (Week 0). The dose may be increased by LEV 14mg/kg/day for subjects aged 1 month to <6 months at 2-week intervals to a maximum dose of 42mg/kg/day. Subjects aged 6 months to <4 years will be started on LEV 20mg/kg/day at Visit 3 (Week 0). The dose may be increased by LEV 20mg/kg/day at 2-week intervals to a maximum dose of 60mg/kg/day.

At Visit 6 (Week 6), subjects may enter the Second Period or enter the Down-Titration Period followed by a Safety Follow-Up Period. Subjects who do not enter the Second Period will be down-titrated. The dose will be decreased by LEV 14mg/kg/day for subjects aged 1 month to <6 months or by LEV 20mg/kg/day for subjects aged 6 months to <4 years at 2-week intervals to 0mg/kg/day. Subjects who withdraw from the study at the minimum age-related dose do not need to down-titrate. In order to provide LEV to subjects who completed the First Period, the Second Period will be conducted until approval or the program is discontinued.

All subjects who do not enter the Second Period will enter the Safety Follow-Up Period, regardless of whether they down-titrate LEV.

Change #2:

Section 2: Introduction

The following paragraph was added:

EP0100 was initially started with a design to evaluate the efficacy of LEV using the percent reduction from Baseline in partial seizure frequency based on the number of seizures recorded by video-electroencephalography (EEG) as the primary efficacy endpoint, but subject recruitment was extremely difficult. One of the major factors for the difficulty in recruitment was that the 48h video-EEG measurement was to be performed 3 times at Baseline, Week 2, and Week 6, thus increasing the burden on the subject/guardian. As a result, consent to participate in the study was not obtained from the guardian, and many potential subjects could not be screened for entry into the study. After consultation with the PMDA, the method of recording seizures was changed to a conventional patient diary, and the primary endpoint was changed to percent reduction in partial seizure frequency based on the patient diary. The percent reduction in partial seizure frequency calculated from the 48h video-EEG is included as an "other" efficacy variable.

Change #3:

Section 3.1: Primary objectives

The primary objective of this study is to confirm the efficacy of LEV in the First Period based on the 48h video-EEG compared to historical control as adjunctive treatment in pediatric epilepsy subjects aged 1 month to <4 years with partial seizures.

Has been changed to

The primary objective of this study is to confirm the efficacy of LEV in reducing seizure frequency in the First Period compared to historical control as adjunctive treatment in pediatric epilepsy subjects aged 1 month to <4 years with partial seizures.

Change #4:

Section 3.2: Secondary objectives

The second and fourth bullets

- To evaluate the efficacy of LEV in the First Period based on the 48h video-EEG compared to historical control as monotherapy in pediatric epilepsy subjects aged 1 month to <4 years with partial seizures
- To evaluate the efficacy of LEV in the combined First and Second Periods based on the daily record card (DRC) as monotherapy or adjunctive treatment in pediatric epilepsy subjects aged 1 month to <4 years with partial seizures

Has been changed to

- To evaluate the efficacy of LEV in reducing seizure frequency in the First Period compared to historical control as monotherapy in pediatric epilepsy subjects aged 1 month to <4 years with partial seizures
- To evaluate the efficacy of LEV in the combined First and Second Periods as monotherapy or adjunctive treatment in pediatric epilepsy subjects aged 1 month to <4 years with partial seizures

Change #5:

Section 4.1: Efficacy variables

4.1 Efficacy variables

Efficacy variables are defined separately for the First Period and the combined First and Second Periods, and for the type of therapy, if applicable.

4.1.1 Efficacy variables for subjects on adjunctive therapy

4.1.1.1 Primary efficacy variable

4.1.1.1.1 First Period

The primary efficacy variable for the First Period for subjects on adjunctive therapy is the percent reduction in average daily frequency (ADF) of partial seizure frequency (ie, change from the Selection Period to the Evaluation Period in daily partial seizure frequency monitored by the 48h video-EEG in their ADF) at Visit 6.

4.1.1.1.2 Combined First and Second Periods

There is no primary efficacy variable for the combined First and Second Periods for subjects on adjunctive therapy.

4.1.1.2 Secondary efficacy variables

4.1.1.2.1 First Period

The secondary efficacy variables for the First Period are the following:

- Percent reduction in ADF of partial seizure frequency monitored by the 48h video-EEG at Visit 4
- Percent reduction in ADF of partial seizure frequency grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100% based on the Evaluation Period 48h video-EEG compared to the Selection Period 48h video-EEG at Visit 4 and Visit 6
- Percent reduction in ADF of electro-clinical partial seizure frequency at Visit 4 and Visit 6
- Percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline at Visit 4, Visit 5, and Visit 6

4.1.1.2.2 Combined First and Second Periods

The secondary efficacy variables for the combined First and Second Periods are the following:

- For each analysis visit, percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline during the combined Evaluation and Maintenance Periods for subjects who are not 48h video-EEG failures, and the combined Dose adjustment and Maintenance Periods for subjects who are 48h video-EEG failures
- For each analysis visit, percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100% during the combined Evaluation and Maintenance Periods for subjects who are not 48h video-EEG failures, and the combined Dose adjustment and Maintenance Periods for subjects who are 48h video-EEG failures

Refer to Section 13.2 for the definition of each analysis visit.

4.1.1.3 Other efficacy variables

4.1.1.3.1 First Period

The other efficacy variables for the First Period are the following:

- Percent reduction in ADF of all types of seizure frequency monitored by the 48h video-EEG at Visit 4 and Visit 6
- Percent reduction in ADF of all type of seizure frequency monitored by the 48h video-EEG grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100% based on the Evaluation Period 48h video-EEG compared to the Selection Period 48h video-EEG at Visit 4 and Visit 6
- Percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline during the Evaluation Period

4.1.1.3.2 Combined First and Second Periods

There are no other efficacy variables for the combined First and Second Periods

4.1.2 Efficacy variables for subjects on monotherapy

4.1.2.1 Primary efficacy variable

There is no primary efficacy variable for subjects on monotherapy.

4.1.2.2 Secondary efficacy variables

4.1.2.2.1 First Period

The secondary efficacy variables for the First Period are the following:

- Percent reduction in ADF of partial seizure frequency monitored by the 48h video-EEG at Visit 4 and Visit 6
- Percent reduction in ADF of partial seizure frequency grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100% based on the Evaluation Period 48h video-EEG compared to the Selection Period 48h video-EEG at Visit 4 and Visit 6
- Percent reduction in ADF of electro-clinical partial seizure frequency at Visit 4 and Visit 6

4.1.2.2.2 Combined First and Second Periods

The secondary efficacy variables for the combined First and Second Periods are the following:

- For each analysis visit, percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline during the combined Evaluation and Maintenance Periods for subjects who are not 48h video-EEG failures, and the combined Dose adjustment and Maintenance Periods for subjects who are 48h video-EEG failures
- For each analysis visit, percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100% during the combined Evaluation and Maintenance Periods for

subjects who are not 48h video-EEG failures, and the combined Dose adjustment and Maintenance Periods for subjects who are 48h video-EEG failures

Refer to Section 13.2 for the definition of each analysis visit.

4.1.2.3 Other efficacy variables

4.1.2.3.1 First Period

The other efficacy variables for the First Period are the following:

- Percent reduction in ADF of all types of seizure frequency monitored by the 48h video-EEG at Visit 4 and Visit 6
- Percent reduction in ADF of all type of seizure frequency monitored by the 48h video-EEG grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100% based on the Evaluation Period 48h video-EEG compared to the Selection Period 48h video-EEG at Visit 4 and Visit 6
- Percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline during the Evaluation Period

4.1.2.3.2 Combined First and Second Periods

The other efficacy variable for the combined First and Second Periods is the following:

- Subjects who are continuously 6-month seizure-free monitored by the patient diary during the combined Evaluation and Maintenance Periods for subjects who are not 48h video-EEG failures, and the combined Dose adjustment and Maintenance Periods for subjects who are 48h video-EEG failures

Has been changed to

4.1 Efficacy variables

Efficacy variables are defined separately for the First Period and the combined First and Second Periods, and for the type of therapy, if applicable.

4.1.1 Efficacy variables for subjects on adjunctive therapy

4.1.1.1 Primary efficacy variable

4.1.1.1.1 First Period

The primary efficacy variable for subjects on adjunctive therapy is the percent reduction in partial seizure frequency per week from Baseline to Visit 6.

4.1.1.1.2 Combined First and Second Periods

There is no primary efficacy variable for the combined First and Second Periods for subjects on adjunctive therapy.

4.1.1.2 Secondary efficacy variables

4.1.1.2.1 First Period

The secondary efficacy variable for the First Period is the following:

- Percent reduction in partial seizure frequency per week from Baseline to Visit 4 and Visit 5

4.1.1.2.2 Combined First and Second Periods

The secondary efficacy variables for the combined First and Second Periods are the following:

- For each visit, percent reduction in partial seizure frequency per week from Baseline
- For each visit, percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100%

4.1.1.3 Other efficacy variables

4.1.1.3.1 First Period

The other efficacy variables for the First Period for the number of seizures based on the 48h video-EEG recorded through Protocol Amendment 2 are the following:

- Percent reduction in average daily frequency (ADF) of partial seizure frequency monitored by the 48h video-EEG at Visit 4 and Visit 6 compared to Baseline
- Percent reduction in ADF of partial of seizure frequency monitored by the 48h video-EEG grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100% based on the Evaluation Period 48h video-EEG at Visit 4 and Visit 6 compared to Baseline

4.1.1.3.2 Combined First and Second Periods

The other efficacy variables for the combined First and Second Periods are the following:

- For each visit, percent reduction in all type of seizure frequency per week from Baseline
- For each visit, percent reduction in all type of seizure frequency per week from Baseline grouped into 6 categories: ≤0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100%

4.1.2 Efficacy variables for subjects on monotherapy

4.1.2.1 Primary efficacy variable

There is no primary efficacy variable for subjects on monotherapy.

4.1.2.2 Secondary efficacy variables

4.1.2.2.1 First Period

There is no secondary efficacy variable for the First Period.

4.1.2.2.2 Combined First and Second Periods

The secondary efficacy variables for the combined First and Second Periods are the following:

- For each visit, percent reduction in partial seizure frequency per week from Baseline
- For each visit, percent reduction in partial seizure frequency per week monitored by the patient diary from Baseline grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100%

4.1.2.3 Other efficacy variables

4.1.2.3.1 First Period

- Percent reduction in ADF of partial seizure frequency monitored by the 48h video-EEG at Visit 4 and Visit 6 compared to Baseline
- Percent reduction in ADF of partial of seizure frequency monitored by the 48h video-EEG grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100% based on the Evaluation Period 48h video-EEG at Visit 4 and Visit 6 compared to Baseline

4.1.2.3.2 Combined First and Second Periods

The other efficacy variables for the combined First and Second Periods are the following:

- For each visit, percent reduction in all types of seizure frequency per week from Baseline
- For each visit, percent reduction in all type of seizure frequency per week from Baseline grouped into 6 categories: <0%, 0% to <25%, 25% to <50%, ≥50%, ≥75%, and 100%
- Percentage of subjects who are continuously 6-month seizure-free monitored by the patient diary 4.3

Change #6:

Section 4.3: Safety variables

4.3 Safety variables

4.3.1 Primary safety variable

There is no primary safety variable.

4.3.2 Secondary safety variables

4.3.2.1 First Period

The secondary safety variables for the First Period are the following:

- Incidence of TEAEs
- Incidence of SAEs
- Incidence of TEAEs led to discontinuation

4.3.2.2 Combined First and Second Periods

The secondary safety variables for the combined First and Second Periods are the following:

- Incidence of TEAEs
- Incidence of SAEs
- Incidence of TEAEs leading to discontinuation

4.3.3 Other safety variables

The other safety variables are the following:

- Adverse events (variables other than secondary safety variables)
- Laboratory tests (blood chemistry and hematology)
- Vital signs
- Body weight and height
- Physical and neurological examination

Has been changed to

4.3 Safety variables

4.3.1 Primary safety variable

There is no primary safety variable.

4.3.2 Secondary safety variables

4.3.2.1 First Period

The secondary safety variables for the First Period are the following:

- Incidence of treatment-emergent adverse events (TEAEs)
- Incidence of serious adverse events (SAEs)
- Incidence of TEAEs leading to discontinuation from study medication

4.3.2.2 Combined First and Second Periods

The secondary safety variables for the combined First and Second Periods are the following:

- Incidence of TEAEs
- Incidence of SAEs
- Incidence of TEAEs leading to discontinuation from study medication

4.3.3 Other safety variables

The other safety variables are the following:

- Adverse events (AEs) (variables other than secondary safety variables)
- Laboratory tests (blood chemistry and hematology)
- Vital signs
- Body weight and height
- Physical and neurological examination

Change #7:

Section 5.1.1: Study description, Overall

EP0100 is an open-label, single-arm, multicenter study with LEV as monotherapy or adjunctive treatment to evaluate the efficacy and safety of LEV (14mg/kg/day to 42mg/kg/day for subjects aged at 1 month to <6 months, 20mg/kg/day to 60mg/kg/day for subjects aged at 6 months to <4 years) in the treatment of partial seizures over the 6-week Evaluation Period (First Period), followed by the long-term follow-up (Second Period) in pediatric subjects.

Subjects with uncontrolled partial seizures will be enrolled into the Selection Period. If all inclusion criteria, with the exception of the seizure criterion for 48h video-EEG, and none of the exclusion criteria are met, eligible subjects will be hospitalized and a 48h video-EEG performed. Subjects with at least 2 partial seizures during the Selection Period 48h video-EEG will enter the Evaluation Period. Subjects with <2 partial seizures during the Selection Period 48h video-EEG will enter the Second Period.

If a subject does not have at least 24h of data due to an electrode separation during a 48h video-EEG, the electrode will be refitted, and the video-EEG recording will resume. In order to resume recording, the subject must be willing to continue, and it is safe to resume recording in the opinion of the investigator. In such cases, the subjects can enter the First Period only if at least a total of 24h of data from the additional video-EEG data are available at Visit 4.

Has been changed to

EP0100 is an open-label, single-arm, multicenter study with LEV as monotherapy or adjunctive treatment to evaluate the efficacy and safety of LEV (14mg/kg/day to 42mg/kg/day for subjects aged at 1 month to <6 months, 20mg/kg/day to 60mg/kg/day for subjects aged at 6 months to <4 years) in the treatment of partial seizures over the First Period (6 weeks), followed by the long-term follow-up (Second Period) in pediatric subjects.

Change #8:

Section 5.1.2: First Period

First and third paragraphs

Eligible subjects will enter a 6-week Evaluation Period. Subjects aged 1 month to <6 months will be started on LEV 14mg/kg/day at Visit 3 (Week 0). The dose may be increased by LEV 14mg/kg/day for subjects aged 1 month to <6 months at 2-week intervals to a maximum dose of LEV 42mg/kg/day. Subjects aged 6 months to <4 years will be started on LEV 20mg/kg/day at Visit 3 (Week 0). The dose may be increased by LEV 20mg/kg/day at 2-week intervals to a maximum dose of 60mg/kg/day. The dose will be increased if seizure freedom has not been attained according to the patient diary. However, if there is a safety concern for the subject in the opinion of the investigator, the dose can be kept.

…

If an intolerable AE occurs during the First Period, the dose can be decreased only once as a fallback option. The dose will be decreased by LEV 14 mg/kg/day for subjects aged 1 month to <6 months or LEV 20mg/kg/day for subjects aged 6 months to <4 years. After decreasing the

dose, a re-increase will not be allowed during the First Period. The fallback option can be performed during the First Period; however, it cannot be performed within 2 days prior to the start of 48h video-EEG in order to maintain the steady-state LEV plasma concentration.

Has been changed to

Eligible subjects will enter the First Period (6 weeks). Subjects aged 1 month to <6 months will be started on LEV 14mg/kg/day at Visit 3 (Week 0). The dose may be increased by LEV 14mg/kg/day for subjects aged 1 month to <6 months at 2-week intervals to a maximum dose of LEV 42mg/kg/day. Subjects aged 6 months to <4 years will be started on LEV 20mg/kg/day at Visit 3 (Week 0). The dose may be increased by LEV 20mg/kg/day at 2-week intervals to a maximum dose of 60mg/kg/day. The dose will be increased if seizure freedom has not been attained according to the patient diary. However, if there is a safety concern for the subject in the opinion of the investigator, the dose can be kept.

…

If an intolerable AE occurs during the First Period, the dose can be decreased only once as a fallback option. The dose will be decreased by LEV 14 mg/kg/day for subjects aged 1 month to <6 months or LEV 20mg/kg/day for subjects aged 6 months to <4 years. After decreasing the dose, a re-increase will not be allowed during the First Period.

Change #9:

Section 5.1.3: Second Period

Subjects can be enrolled in the Second Period if 1 of the following is met:

- Subject completes the First Period
- Subject fails Screening, defined as <2 partial seizures during 48h video EEG, or did not have at least 24h of readable video-EEG data, or not able to measure a video-EEG for 24h due to their disease severity. These subjects may directly enter the Second Period.

Subjects aged 1 month to <6 months who complete the First Period will take LEV 14mg/kg/day to 42mg/kg/day during the Second Period. Subjects aged 6 months to <4 years who complete the First Period will take LEV 20mg/kg/day to 60mg/kg/day during Second Period. Subjects who directly enroll into the Second Period will enter the Dose Adjustment Period in order to adjust LEV dose in the same manner as in the First Period. These subjects will then enter the Maintenance Period.

Subjects who complete the First Period will have a visit every 4 weeks ±7 days relative to the Visit 3 for the first 6 months of administration and then every 12 weeks ±14 days thereafter. Subjects will continue to receive LEV 14 to 42mg/kg/day in subjects aged 1 month to <6 months or LEV 20 to 60mg/kg/day for subjects aged ≥6 months <4 years at the discretion of the Investigator.

When subjects aged <6 months at the time of study enrollment reach 6 months of age, they can take a maximum of LEV 60mg/kg/day.

Subjects aged 1 month to <6 months who fail Screening will be started on LEV 14mg/kg/day at Visit 6 (Week 0). The dose may be increased by LEV 14mg/kg/day for subjects aged 1 month to

<6 months at 2-week intervals to a maximum dose of LEV 42mg/kg/day. Subjects aged 6 months to <4 years who fail Screening will be started on LEV 20mg/kg/day at Visit 6 (Week 0). The dose may be increased by 20mg/kg/day at 2-week intervals to a maximum dose of LEV 60mg/kg/day.

A final visit will be required approximately 2 weeks ±7 days after the final dose of LEV, or sooner if the subject will continue LEV (prescribed by the primary care provider as commercial LEV) after study completion.

Has been changed to

Subjects who complete the First Period will have a visit every 4 weeks ±7 days relative to Visit 3 for the first 6 months of administration and then every 12 weeks ±14 days thereafter. Subjects will continue to receive LEV 14 to 42mg/kg/day in subjects aged 1 month to <6 months or LEV 20 to 60mg/kg/day for subjects aged ≥6 months <4 years at the discretion of the Investigator.

When subjects aged <6 months at the time of study enrollment reach 6 months of age, they can take a maximum of LEV 60mg/kg/day.

A final visit will be required 2 weeks ±7 days after the final dose of LEV, or sooner if the subject will continue LEV (prescribed by the primary care provider as commercial LEV) after study completion.

Change #10:

Section 5.1.4: Study duration per subject

The study duration is as follows:

Retrospective Baseline Period

In order to evaluate LEV efficacy in the Second Period, seizure counts during the 2 weeks prior to Visit 1 will be used as a Retrospective Baseline Period.

First Period

- Selection Period (maximum of 9 days)
- Evaluation Period (6 weeks)
- Down-Titration Period (up to 4 weeks)
- Safety Follow-Up Period (2 weeks)

Second Period

- Dose Adjustment Period (6 weeks) (for directly enrolled subjects [ie, 48h video-EEG failures])
- Maintenance Period (until approval or the program is discontinued)
- Down-Titration Period (up to 4 weeks)
- Safety Follow-Up Period (2 weeks)

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

Has been changed to

The study duration is as follows:

Retrospective Baseline Period

Seizure counts during the 2 weeks prior to Visit 1 will be used as a Retrospective Baseline Period.

First Period

- Selection Period (maximum of 9 days)
- Evaluation Period (6 weeks)
- Down-Titration Period (up to 4 weeks)
- Safety Follow-Up Period (2 weeks)

Second Period

- Maintenance Period (until approval or the program is discontinued)
- Down-Titration Period (up to 4 weeks)
- Safety Follow-Up Period (2 weeks)

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

Change #11:

Section 5.2: Schedule of study assessments

For Visit 4 through Visit 6, planned clinic visits should be scheduled as indicated with a window of ±4 days relative to Visit 3. For Visit 8 through Visit 15, planned clinic visits should be scheduled as indicated with a window of ±7 days relative to Visit 3. From Visit 16 onward, planned clinic visits should be scheduled as indicated with a window of ±14 days relative to Visit 3. Subjects who fail the 48h video-EEG at Visit 2 will be directly enrolled. Directly enrolled subjects will skip Visit 3 to Visit 5 and will begin the Second Period at Visit 6. For Visit 7 through Visit 10, planned clinic visits should be scheduled as indicated with a window of ±4 days relative to Visit 6. For Visit 11 through Visit 15, planned clinic visits should be scheduled as indicated with a window of ±7 days relative to Visit 6. From Visit 16 onward, planned clinic visits should be scheduled as indicated with a window of ±14 days relative to Visit 6.

Has been changed to

For Visit 4 through Visit 6, planned clinic visits should be scheduled as indicated with a window of ±4 days relative to Visit 3. For Visit 8 through Visit 15, planned clinic visits should be scheduled as indicated with a window of ±7 days relative to Visit 3. From Visit 16 onward, planned clinic visits should be scheduled as indicated with a window of ±14 days relative to Visit 3.

Change #12:

Section 5.2: Schedule of study assessments

Table 5–2: Schedule of assessments for subjects who are not 48h video-EEG failures

	First Period						Second Period										
	Selection Period		Evaluation Period[a]				Maintenance Period[b]										
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16[c]…	V17[d]…
Visit **Study Week**	**D-9 to D-2**	**D-2 to D0**	**W0**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W18**	**W22**	**W26**	**W32**	**W38**	**W50…**	**W62…**
Written informed consent	X																
Inpatient		X		X		X											
Registration	X		X														
Eligibility assessment	X	X	X														
Medical/procedures history	X																
Demographics	X																
AED history	X																
Epilepsy history	X																
Physical examination	X																
Neurological examination	X																
Vital signs[e]	X		X	X	X	X		X		X	X	X	X		X	X	X
Seizure counts[f]	X	X	X	X	X	X		X		X	X	X	X		X	X	X
Laboratory safety assessment	X	X[h]		X	X	X				X			X		X	X	X
LEV plasma level				X[i]	X	X[i]		X		X	X	X	X				
Body weight	X		X	X	X	X		X		X	X	X	X		X	X	X
Height	X												X			X	
Concomitant AED(s)	X		X[g]	X	X	X		X		X	X	X	X		X	X	X
Concomitant non-AED(s)	X		X[g]	X	X	X		X		X	X	X	X		X	X	X
Concomitant medical procedures	X		X[g]	X	X	X		X		X	X	X	X		X	X	X

Table 5–2: Schedule of assessments for subjects who are not 48h video-EEG failures

	First Period						Second Period										
	Selection Period		Evaluation Period[a]				Maintenance Period[b]										
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16[c]…	V17[d]…
Visit **Study Week**	**D-9 to D-2**	**D-2 to D0**	**W0**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W18**	**W22**	**W26**	**W32**	**W38**	**W50…**	**W62…**
Adverse events	X		X[g]	X	X	X		X		X	X	X	X		X	X	X
Dispense/return study drug			X[j]	X	X	X		X		X	X	X	X		X	X	X
Study drug compliance				X	X	X		X		X	X	X	X		X	X	X
ECG	X												X			X	
CT scan/MRI[k]	X																
Video-EEG[l]		X		X		X											
IVRS/IWRS	X		X	X	X	X		X		X	X	X	X		X	X	X
Dispense/collect DRC	X[m]	X[m]	X	X	X	X		X		X	X	X	X		X	X	X
Dispense subject's ID card	X																
Fallback option[n]				X	X												
C-SSRS[o]																X[o]	X[o]

AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; CT=computed tomography; D=day; DRC=daily record card; ECG=electrocardiogram; EDV=Early Discontinuation Visit; EEG=electroencephalogram; ID=identification; IVRS=interactive voice response system; IWRS=interactive web response system; LEV=levetiracetam; MRI=magnetic resonance imaging; SFU=Safety Follow-Up; V=visit; W=week

Note: See Table 5–3 for the schedule of assessments for the Down-Titration and SFU Periods.

[a] After beginning the study medication, subjects who withdraw prematurely must have W6 evaluations and the EDV evaluations.

[b] In the Maintenance Period, visits will occur every 2 weeks from V7 to V10, every 4 weeks from V11 to V13, every 6 weeks between V14 and V15, and every 12 weeks thereafter.

[c] Even numbered visits.

[d] Odd numbered visits.

[e] Including temperature, blood pressure, and heart rate.

[f] At V1, collect seizure count for seizures that occurred in the prior 2 weeks. At V2, V4, and V6, seizures will be counted by video-EEG and DRC. At all other visits, seizures will be counted by DRC only.

[g] Recorded from end of V1 through V3.

Table 5–2: Schedule of assessments for subjects who are not 48h video-EEG failures

	First Period						Second Period										
	Selection Period		Evaluation Period[a]				Maintenance Period[b]										
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16[c]…	V17[d]…
Visit Study Week	D-9 to D-2	D-2 to D0	W0	W2	W4	W6	W8	W10	W12	W14	W18	W22	W26	W32	W38	W50…	W62…

[h] If clinically significant laboratory abnormalities are present at V1, repeat samples must be obtained for blood chemistry and hematology. The results should be available prior to V2, and UCB or its designee should be contacted regarding clinically significant abnormalities.
[i] Blood samples will be obtained prior to receiving LEV and then at least 2h after dosing at V4 and V6.
[j] Dispense study drug at V3.
[k] Only for subjects who have not had a CT scan or MRI confirming the absence of a progressive lesion since being diagnosed with epilepsy, or have changes on physical examination which would suggest a lesion has occurred since the last imaging procedure.
[l] All video-EEG data recording will be transmitted to a central reader for the purposes of data analysis.
[m] Dispense DRC at V1. Confirm DRC at V2.
[n] Fallback option is permitted. See Section 5.1.2 for details.
[o] C-SSRS to be performed at each visit for subjects aged ≥6 years.

Has been changed to

Table 5–2: Schedule of assessments

	First Period						Second Period										
	Selection Period		Evaluation Period[a]				Maintenance Period[b]										
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16[c]…	V17[d]…
Visit **Study Week**	**D-9 to D-2**	**D-2 to D0**	**W0**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W18**	**W22**	**W26**	**W32**	**W38**	**W50…**	**W62…**
Written informed consent	X																
Inpatient				X		X											
Registration	X		X														
Eligibility assessment	X		X														
Medical/procedures history	X																
Demographics	X																
AED history	X																
Epilepsy history	X																
Physical examination	X																
Neurological examination	X																
Vital signs[e]	X		X	X	X	X		X		X	X	X	X		X	X	X
Seizure counts[f]	X		X	X	X	X		X		X	X	X	X		X	X	X
Laboratory safety assessment	X			X	X	X				X			X		X	X	X
LEV plasma level				X	X	X		X		X	X	X	X				
Body weight	X		X	X	X	X		X		X	X	X	X		X	X	X
Height	X												X			X	
Concomitant AED(s)	X		X[g]	X	X	X		X		X	X	X	X		X	X	X
Concomitant non-AED(s)	X		X[g]	X	X	X		X		X	X	X	X		X	X	X

Table 5–2: Schedule of assessments

	First Period						Second Period										
	Selection Period		Evaluation Period[a]				Maintenance Period[b]										
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16[c]…	V17[d]…
Visit **Study Week**	**D-9 to D-2**	**D-2 to D0**	**W0**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W18**	**W22**	**W26**	**W32**	**W38**	**W50…**	**W62…**
Concomitant medical procedures	X		X[g]	X	X	X		X		X	X	X	X		X	X	X
Adverse events	X		X[g]	X	X	X		X		X	X	X	X		X	X	X
Dispense/return study drug			X[i]	X	X	X		X		X	X	X	X		X	X	X
Study drug compliance				X	X	X		X		X	X	X	X		X	X	X
ECG	X												X			X	
CT scan/MRI[j]	X																
EEG[k]	X																
IVRS/IWRS	X		X	X	X	X		X		X	X	X	X		X	X	X
Dispense/collect DRC	X[n]		X	X	X	X		X		X	X	X	X		X	X	X
Dispense subject's ID card	X																
Fallback option[m]				X	X												
C-SSRS[n]																X[o]	X[o]

AED=antiepileptic drug; C-SSRS=Columbia-Suicide Severity Rating Scale; CT=computed tomography; D=day; DRC=daily record card; ECG=electrocardiogram; EDV=Early Discontinuation Visit; EEG=electroencephalogram; ID=identification; IVRS=interactive voice response system; IWRS=interactive web response system; LEV=levetiracetam; MRI=magnetic resonance imaging; SFU=Safety Follow-Up; V=visit; W=week

Note: See Table 5–3 for the schedule of assessments for the Down-Titration and SFU Periods.

[a] After beginning the study medication, subjects who withdraw prematurely must have W6 evaluations and the EDV evaluations.

[b] In the Maintenance Period, visits will occur every 4 weeks from V8 to V13 and every 12 weeks thereafter.

[c] Even numbered visits.

[d] Odd numbered visits.

[e] Including temperature, blood pressure, and heart rate.

[f] At V1, collect seizure count for seizures that occurred in the prior 2 weeks.

[g] Recorded from end of V1 through V3.

Table 5–2: Schedule of assessments

	First Period						Second Period										
	Selection Period		Evaluation Period[a]				Maintenance Period[b]										
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16[c]…	V17[d]…
Visit **Study Week**	**D-9 to D-2**	**D-2 to D0**	**W0**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W18**	**W22**	**W26**	**W32**	**W38**	**W50…**	**W62…**

[h] If clinically significant laboratory abnormalities are present at V1, repeat samples must be obtained for blood chemistry and hematology. The results should be available prior to V2, and UCB or its designee should be contacted regarding clinically significant abnormalities.
[i] Dispense study drug at V3.
[j] Only for subjects who have not had a CT scan or MRI confirming the absence of a progressive lesion since being diagnosed with epilepsy, or have changes on physical examination which would suggest a lesion has occurred since the last imaging procedure.
[k] If the EEG exam was not performed prior to V1, the assessment needs to be completed, and results must be available prior to V3.
[l] Dispense DRC.
[m] Fallback option is permitted. See Section 5.1.2 for details.
[n] C-SSRS to be performed at each visit for subjects aged ≥6 years.

Change #13:

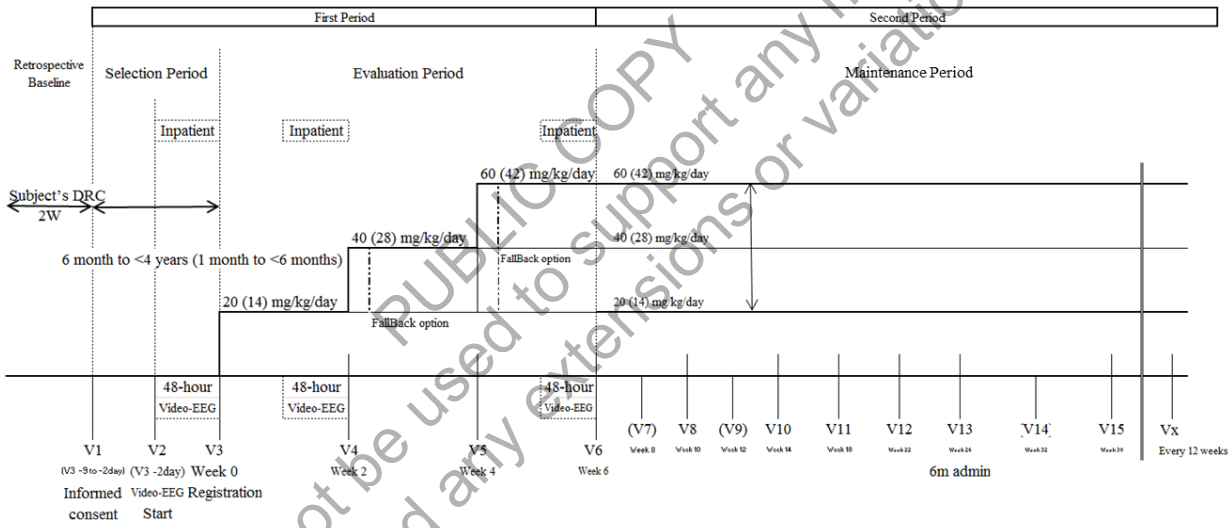
Section 5.2: Schedule of study assessments

Table 5-2 has been deleted.

Change #14:

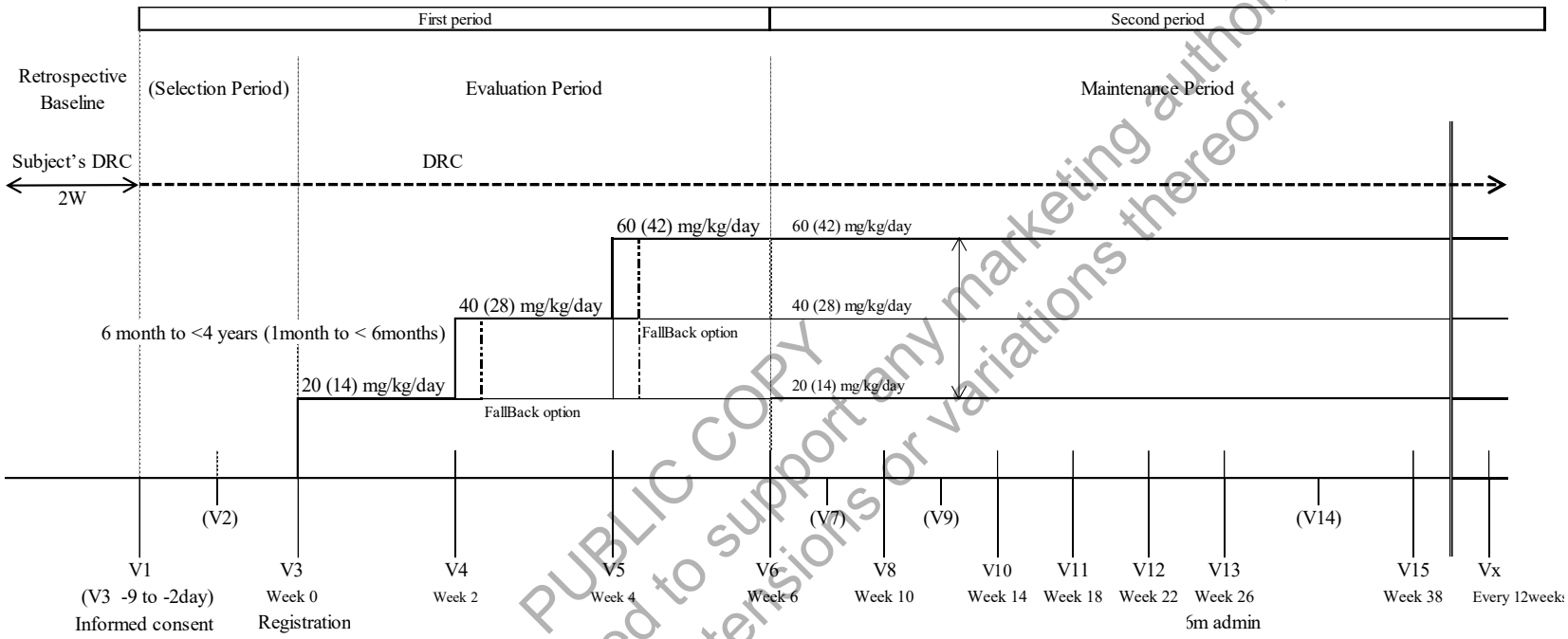
Section 5.3: Schematic diagram

Figure 5-1: Schematic for subjects in the First and Second Periods



Has been changed to

Figure 5-1: Schematic for subjects in the First and Second Periods



6m admin=6 months of administration; D=day; DRC=daily record card; EEG=electroencephalogram; RBL=retrospective baseline; V=Visit; W=weeks
Note: The value in parentheses for dose is for subjects 1 month to <6 months of age.

Change #15

Section 6.1: Inclusion criteria

Inclusion criterion #1

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the parent(s) or legal representative.

Has been changed to

1a. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the parent(s) or legal representative. Subject/legal representative/caregiver is considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, or medication intake according to the judgment of the Investigator.

Change #16

Section 6.1: Inclusion criteria

Inclusion criterion #2

2. Subject must have a diagnosis of epilepsy with partial onset seizures (ie, seizures of focal onset), whether or not secondarily generalized.

Has been changed to

2a. Subject must have a diagnosis of epilepsy with partial onset seizures (ie, seizures of focal onset), whether or not secondarily generalized.

Subject has had an EEG and a brain computerized tomography (CT) scan or brain magnetic imaging (MRI) consistent with a diagnosis of localized epilepsy according to the International Classification of Epilepsies and Epileptic Syndromes (1989) (see Section 17.2) and consistent with partial onset seizures according to the Classification of Epileptic Seizures (1981) (see Section 17.1). If the EEG and brain CT scan and brain MRI were not performed prior to the Screening Visit (Visit 1), the assessment needs to be completed and results must be available prior to Visit 3.

Change #17

Section 6.1: Inclusion criteria

Inclusion criterion #7

7. Subject must have experienced at least 2 partial seizures (ie, seizures of focal onset as determined by EEG), with or without secondary generalization during each 7-day period during the 2 weeks prior to Visit 1. This time period (the 2 weeks prior to Visit 1) will be referred to as the Retrospective Baseline Period. This seizure information (including type, frequency, and date) must have been recorded on a DRC in order to be acceptable.

Has been changed to

7a. Subject must have experienced at least 2 observable partial seizures (ie, seizures of focal onset as determined by EEG), with or without secondary generalization during each 7-day period during the 2 weeks prior to Visit 1. This time period (the 2 weeks prior to Visit 1) will be referred to as the Retrospective Baseline Period. This seizure information (including type, frequency, and date) must have been recorded on a daily record card (DRC) in order to be acceptable.

Change #18

Section 6.1: Inclusion criteria

Inclusion criteria #8 and #9 have been deleted.

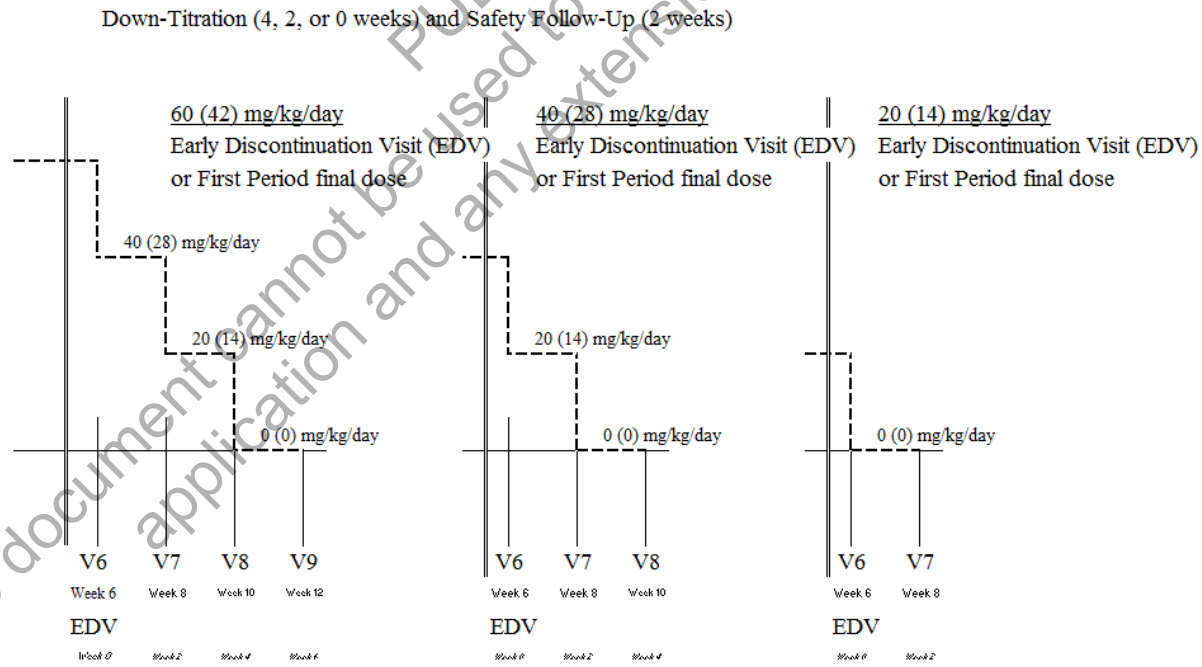
Change #19

Section 7.2: Treatments to be administered

First Period

Once the subject has fulfilled the eligibility criteria, he/she will be admitted to the clinic as an inpatient and the 48h video-EEG performed. After the Selection Period, the subject will enter the Evaluation Period.

Figure 7-1: Schematic for Down-Titration and Safety Follow-Up Periods



EDV=Early Discontinuation Visit; V=Visit

The down-titration procedure needs to be applied in case of early discontinuation.

Second Period

For continuing subjects, if a dose adjustment becomes necessary, the investigators will increase or decrease the dose by at least a 2-week interval. One increase or decrease in the dose should not exceed LEV 14mg/kg/day for subjects aged 1 month to <6 months or LEV 20mg/kg/day for subjects aged 6 months to <4 years for the 2-week interval. The dosage can be adjusted to LEV 14, 28 and 42mg/kg/day LEV for subjects aged 1 month to <6 months or LEV 20, 40 and 60mg/kg/day for subjects aged 6 months to <4 years at the Investigator's discretion for the benefit/risk for individual subjects.

For directly enrolled subjects (ie, 48h video-EEG failures), LEV dose can be up-titrated to 42mg/kg/day for subjects aged 1 month to <6 months or LEV 60mg/kg/day for subjects aged 6 months to less than 4 years. The initial dose is LEV 14mg/kg/day for the first 2 weeks, followed by 28mg/kg/day and 42mg/kg/day or LEV 20mg/kg/day for the first 2 weeks, followed by 40mg/kg/day and 60mg/kg/day for 2 weeks, respectively. After up-titration, if a dose adjustment becomes necessary, the investigator will increase or decrease the dose by at least a 2-week interval. Each increase or decrease in dose should not exceed LEV 14mg/kg/day for subjects aged 1 month to <6 months and LEV 20mg/kg/day for subjects aged 6 months to <4 years for the 2-week interval. The dosage can be adjusted to LEV 14, 28, and 42mg/kg/day for subjects aged 1 month to <6 months and LEV 20, 40, and 60mg/kg/day for subjects aged 6 months to <4 years at the Investigator's discretion based on the benefit/risk for the individual subject.

Subjects who withdraw or complete the Second Period will enter the Down-Titration Period, followed by the Safety Follow-Up Period.

Has been changed to

First Period

Once the subject has fulfilled the eligibility criteria, the subject will enter the Evaluation Period.

Study medication should be given as 2 equally divided doses administered twice daily. The first intake of newly dispensed study medication should occur at Visit 3 after the confirmation of seizure counts by 48h video-EEG. Subjects should take IMP according to instructions provided by Investigator.

Subjects aged 1 month to <6 months will be started on LEV 14mg/kg/day at Visit 3 (Week 0). The dose may be increased by LEV 14mg/kg/day for subjects aged 1 month to <6 months at 2-week intervals to a maximum dose of LEV 42mg/kg/day. Subjects aged 6 months to <4 years will be started on LEV 20mg/kg/day at Visit 3 (Week 0). The dose may be increased by LEV 20mg/kg/day at 2-week intervals to a maximum dose of 60mg/kg/day.

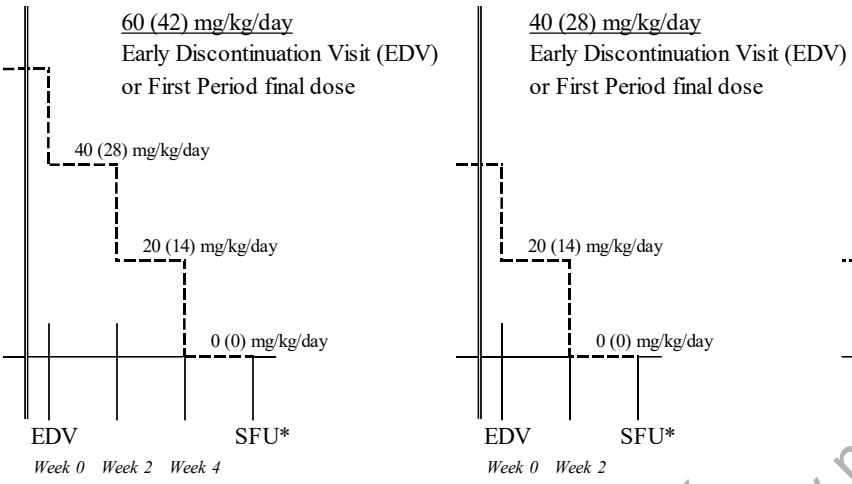
At the end of the Evaluation Period, subjects will enter into the Second Period. Subjects who do not enter the Second Period will enter the Down-Titration Period, followed by the Safety Follow-Up Period.

The Down-Titration Period (up to 4 weeks) will consist of the following:

- The dose will be decreased by 14mg/kg/day for subjects aged 1 month to <6 months or by 20mg/kg/day for subjects aged 6 months to <4 years at 2-week intervals to 0mg/kg/day.

Figure 7–1: Schematic for Down-Titration and Safety Follow-Up Periods

Down-Titration (4, 2 or 0 weeks) and Safety Follow-up (2 weeks)



*: Safety Follow-Up (SFU) is 2 weeks after final dose of study drug.

EDV=Early Discontinuation Visit; V=Visit
Note: The value in parentheses for dose is for subjects 1 month to <6 months of age.

The down-titration procedure needs to be applied in case of early discontinuation.

Second Period

For continuing subjects, if a dose adjustment becomes necessary, the investigators will increase or decrease the dose by at least a 2-week interval. One increase or decrease in the dose should not exceed LEV 14mg/kg/day for subjects aged 1 month to <6 months or LEV 20mg/kg/day for subjects aged 6 months to <4 years for the 2-week interval. The dosage can be adjusted to LEV 14, 28 and 42mg/kg/day LEV for subjects aged 1 month to <6 months or LEV 20, 40 and 60mg/kg/day for subjects aged 6 months to <4 years at the Investigator's discretion for the benefit/risk for individual subjects.

Subjects who withdraw or complete the Second Period will enter the Down-Titration Period, followed by the Safety Follow-Up Period.

Change #20

Section 8.1: First Period

See Section 5.2 for the schedule of assessments for the First Period. The visit window for Visit 4 through Visit 6 is ±4 days. Visit 1 assessments will be performed for all subjects. Subjects who are 48h video-EEG failures will skip the Evaluation Period and will proceed to the Second Period. Subjects who are directly enrolled will skip Visit 2 through Visit 6 and start the study at Visit 7 (see Section 8.3).

Has been changed to

See Section 5.2 for the schedule of assessments for the First Period. The visit window for Visit 4 through Visit 6 is ±4 days. Visit 1 assessments will be performed for all subjects.

Change #21

Section 8.1.1.1, Visit 1/Day -9 to Day -2 (Screening)

The following bullet was added:

- Perform EEG (for subjects who have not had an EEG confirming the consistent with a diagnosis of localized epilepsy and the consistent with partial onset seizures.)

Change #22

Section 8.1.1.2: Visit 2/Day -2 to Day 0

This section has changed to "Not applicable."

Change #23

Section 8.1.2.1: Visit 3 (Week 0)

The following paragraph was deleted:

Subjects who have at least 2 partial seizures during the 48h video-EEG will enter the Evaluation Period. Subjects who have 0 or 1 partial seizure during the 48h video-EEG will enter the Second Period (see Section 8.3).

Change #24

Section 8.1.2.2: Visit 4 (Week 2)

For the 2 days prior to Visit 4, subjects will be inpatients at the clinic in order to have the 48h video-EEG performed. During this time, they will remain under close medical surveillance. Blood sampling for safety is allowed during measurement of the 48h video-EEG. Blood sampling for PK should be conducted during measurement of the 48h video-EEG.

- Check the subject into the clinic
- Obtain vital sign measurements (blood pressure, pulse rate, and body temperature)
- Collect blood samples for safety laboratory assessments
- Collect blood samples for LEV plasma level prior to receiving LEV dose and then at least 2h after dosing
- Record body weight
- Record concomitant medications (AEDs and non-AEDs) and medical procedures

- Record AEs
- Collect seizure count from DRC
- Dispense/collect DRC
- Study drug compliance
- Perform 48h video-EEG. If a subject does not have at least 24h of data due to an electrode separation during the 48h video-EEG, the video-EEG may be continued without removing the electrodes if the subject is willing to continue the video-EEG and the video-EEG can be safely continued in the opinion of the investigator.
- Confirm if fallback option is necessary and reason(s) to decrease the dosage
- Contact IVRS/IWRS
- Dispense/collect study drug

Has been changed to

- Obtain vital sign measurements (blood pressure, pulse rate, and body temperature)
- Collect blood samples for safety laboratory assessments
- Collect blood samples for LEV plasma level
- Record body weight
- Record concomitant medications (AEDs and non-AEDs) and medical procedures
- Record AEs
- Collect seizure count from DRC
- Dispense/collect DRC
- Study drug compliance
- Confirm if fallback option is necessary and reason(s) to decrease the dosage
- Contact IVRS/IWRS
- Dispense/collect study drug

Change #25

Section 8.1.3: Visit 6 (Week 6)

For the 2 days prior to Visit 6, subjects will be inpatients at the clinic in order to have the 48h video-EEG performed. During this time, they will remain under close medical surveillance. Blood sampling for safety is allowed during measurement of the 48h video-EEG. Blood sampling for PK should be conducted during measurement of the 48h video-EEG.

- Check the subject into the clinic
- Obtain vital sign measurements (blood pressure, pulse rate, and body temperature)

- Collect blood samples for safety laboratory assessments
- Collect blood samples for LEV plasma level prior to receiving LEV dose and then at least 2h after dosing
- Record body weight
- Record concomitant medications (AEDs and non-AEDs) and medical procedures
- Record AEs
- Collect seizure count
- Dispense/collect DRC
- Study drug compliance
- Perform 48h video-EEG. If a subject does not have at least 24h of data due to an electrode separation during 48h video-EEG, the video-EEG may be continued without removing the electrodes if the subject is willing to continue the video-EEG and the video-EEG can be safely continued in the opinion of the investigator.
- Contact IVRS/IWRS
- Dispense/collect study drug

Has been changed to

- Obtain vital sign measurements (blood pressure, pulse rate, and body temperature)
- Collect blood samples for safety laboratory assessments
- Collect blood samples for LEV plasma level
- Record body weight
- Record concomitant medications (AEDs and non-AEDs) and medical procedures
- Record AEs
- Collect seizure count
- Dispense/collect DRC
- Study drug compliance
- Contact IVRS/IWRS
- Dispense/collect study drug

Change #26

Section 8.2.1: Visit 7 (Week 8)

This section has changed to "Not applicable."

Change #27

Section 8.2.3: Visit 9 (Week 12)

This section has changed to "Not applicable."

Change #28

Section 8.2.8: Visit 14 (Week 26)

This section has changed to "Not applicable."

Change #29

Section 8.3: Direct enrollment

This section has changed to "Not applicable."

Change #30

Section 8.5, Early discontinuation visit

- Obtain vital sign measurements (blood pressure, pulse rate, and body temperature)
- Collect seizure count
- Collect blood samples for safety laboratory assessments
- Record body weight and height
- Record concomitant medications (AEDs and non-AEDs) and medical procedures
- Record AEs
- Dispense/collect study drug
- Study drug compliance
- Perform ECG
- Contact IVRS/IXRS
- Dispense/collect DRC
- C-SSRS (will be performed for subjects aged ≥6 years)

Has been changed to

- Obtain vital sign measurements (blood pressure, pulse rate, and body temperature)
- Collect seizure count
- Collect blood samples for safety laboratory assessments <u>(at Week 0 only)</u>
- Record body weight

- Record height (at Week 0 only)
- Record concomitant medications (AEDs and non-AEDs) and medical procedures
- Record AEs
- Dispense/collect study drug
- Study drug compliance
- Perform ECG (at Week 0 only)
- Contact IVRS/IWRS
- Dispense/collect DRC
- C-SSRS (will be performed for subjects aged ≥6 years)

Change #31

Section 9: Assessment of efficacy

The primary and secondary efficacy variables are based on the ADF of partial seizures as measured by 48h video-EEG. Partial seizure count will be based on electrographic seizures with or without clinical correlate depending upon age as specified below.

Partial seizure frequency for subjects aged ≥1 month to ≤6 months will be based on electrographic seizures. Partial seizure frequency for subjects aged >6 months to <4 years will be based on electrographic seizures with an accompanying clinical correlate.

Electrographic seizures are defined as recognizable ictal patterns on an EEG involving ≥2 contiguous electrodes. The seizures are initiated as a unilateral or strongly asymmetric abnormal epileptiform discharge lasting a total of >10 seconds.

The video-EEG recordings will be evaluated by a central reader.

The ADF is calculated by:

$$\text{ADF} = \frac{\text{\# of partial seizures recorded on the \# hour video-EEG}}{\text{\# of hours}} \times 24$$

In the above formula, 48h is used for Selection ADF. If the subjects complete the Evaluation Period, 48h is used for Evaluation ADF. For subjects who drop out during the Evaluation Period, the number of hours will be the time from the start of the Evaluation Period video-EEG to withdrawal (in hours).

The video-EEG recordings from both the Selection and Evaluation Periods will be sent to a central reader for interpretation and recording of seizure frequency and type. In the event of a difference of opinion between the on-site epileptologist and the central reader, the central reader's opinion will determine subject eligibility.

Has been changed to

The primary and secondary efficacy variables are based on the partial seizure frequency per week as measured by patient diary.

Change #32

Section 11.3.5, Assessment of suicidality

First paragraph

Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2008). For subjects ≥6 years of age, this scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be completed according to the tabular schedule of study procedures.

Has changed to

Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2008). For subjects ≥6 years of age, this scale will be used to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be completed according to the tabular schedule of study procedures.

Change #33

Section 13.1, Definition of analysis sets

The following sets are defined for this study:

- Enrolled Set (ES)
- Safety Sets:
  - SS A1 (Safety Set [Adjunctive therapy, First Period], ie, Safety Set for subjects on Adjunctive Therapy during the First Period)
  - SS M1 (Safety Set [Monotherapy, First Period])
  - SS A12 (Safety Set [Adjunctive therapy, combined First and Second Periods])
  - SS M12 (Safety Set [Monotherapy, combined First and Second Periods])
- Full Analysis Sets:
  - FAS A1 (Full Analysis Set [Adjunctive therapy, First Period], ie, Full Analysis Set for subjects on Adjunctive Therapy during the First Period)
  - FAS M1 (Full Analysis Set [Monotherapy, First Period])
  - FAS A12 (Full Analysis Set [Adjunctive therapy, combined First and Second Periods])
  - FAS M12 (Full Analysis Set [Monotherapy, combined First and Second Periods])
- Per-Protocol Set (PPS)

- Pharmacokinetic Per-Protocol Set (PK-PPS)

If not stated otherwise, presentation of:

- Disposition and important protocol deviations are based on the ES
- Demographics, other baseline characteristics, safety, and exposure data are based on the SS A12 and SS M12
- Efficacy data are based on the FAS A1, FAS M1, FAS A12, and FAS M12. Sensitivity analyses on the primary efficacy variable are repeated for the PPS.

Has been changed to

The following sets are defined for this study:

- Enrolled Set (ES)
- Safety Sets:
  - SS_A (Safety Set [Adjunctive therapy])
  - SS_M (Safety Set [Monotherapy)
- Full Analysis Sets:
  - FAS_A (Full Analysis Set [Adjunctive therapy])
  - FAS_M (Full Analysis Set [Monotherapy])
- Pharmacokinetic Per-Protocol Set (PK-PPS)

If not stated otherwise, presentation of:

- Disposition and important protocol deviations are based on the ES
- Demographics, other baseline characteristics, safety, and exposure data are based on the SS A and SS M
- Efficacy data are based on the FAS_A and FAS_M.

Change #34

Section 13.1.2, Safety Set

First Period:

The SS A1 will include all enrolled subjects on adjunctive therapy in the First Period who receive at least 1 dose of study medication in the Evaluation Period.

The SS M1 will include all enrolled subjects on monotherapy in the First Period who receive at least 1 dose of study medication in the Evaluation Period.

Combined First and Second Periods:

The SS A12 will include all enrolled subjects on adjunctive therapy in the Evaluation, Dose adjustment, and Maintenance Periods who receive at least 1 dose of study medication in the Evaluation, Dose adjustment, or Maintenance Periods.

The SS M12 will include all enrolled subjects on monotherapy in the Evaluation, Dose adjustment, and Maintenance Periods who receive at least 1 dose of study medication in the Evaluation, Dose adjustment, or Maintenance Periods.

Has been changed to

First Period:

The SS_A will include all enrolled subjects on adjunctive therapy in the First Period who receive at least 1 dose of study medication in the Evaluation Period.

The SS_M will include all enrolled subjects on monotherapy in the First Period who receive at least 1 dose of study medication in the Evaluation Period.

Change #35

Section 13.1.3, Full Analysis Set

First Period:

The FAS A1 will consist of all subjects in the SS A1 who entered the First Period, who receive adjunctive therapy, have at least 24h of usable video-EEG time in the Selection Period, with at least 2 partial seizures, and have at least 1 post-baseline efficacy assessment from the First Period video-EEG time or DRCs in the Evaluation Period.

The FAS M1 will consist of all subjects in the SS M1 who entered the First Period, who receive monotherapy, have at least 24h of usable video-EEG time in the Selection Period, with at least 2 partial seizures, and have at least 1 post-baseline efficacy assessment from the First Period video-EEG time or DRCs in the Evaluation Period.

Combined First and Second Periods:

The FAS A12 will consist of all subjects in the SS A12, who receive adjunctive therapy, have at least 24h of usable video-EEG time in the Selection Period, and have at least 1 post-baseline efficacy assessment from the First Period video-EEG time, or DRCs in the Evaluation, Dose adjustment, or Maintenance Period.

The FAS M12 will consist of all subjects in the SS M12, who receive monotherapy, have at least 24h of usable video-EEG time in the Selection Period, and have at least 1 post-baseline efficacy assessment from the First Period video-EEG time, or DRCs in the Evaluation, Dose adjustment, or Maintenance Period.

Has been changed to

First Period:

The FAS_A will consist of all subjects in the SS_A who have at least 1 post-Baseline efficacy assessment.

The FAS_M will consist of all subjects in the SS_M who have at least 1 post-Baseline efficacy assessment.

Change #36

Section 13.1.4, Per Protocol Set

This section has changed to "Not applicable."

Change #37

Section 13.1.5, Other analysis sets

The PK-PPS will consist of all subjects in the SS A12 and SS M12 for whom at least 1 valid LEV plasma concentration-time record and dosing information are available.

Has been changed to

The PK-PPS will consist of all subjects in the SS_A and SS_M for whom at least 1 valid LEV plasma concentration-time record and dosing information are available.

Change #38

Section 13.2, Definitions of analysis visits

Table 13-1 presents the mapping of study visits to analysis visits for subjects who are not 48h video-EEG failures and for subjects who are 48h video-EEG failures. Analysis visits will be used for analysis of long-term safety and efficacy data.

Table 13–1: Analysis visit mapping table

Analysis Visit	Week number	Relative day since first study drug administration	Analysis window	Subjects who are not 48h video-EEG failures Study Visit (Relative day)	Subjects who are 48h video-EEG failures Study Visit (Relative day)
0	0	1	-	Visit 3	Visit 6
1	2	15	2 – 22	Visit 4	Visit 7
2	4	29	23 – 36	Visit 5	Visit 8
3	6	43	37 – 50	Visit 6	Visit 9
4	8	57	51 – 64	-	Visit 10
5	10	71	65 – 78	Visit 8 (Day 71[#])	-
6	12	85	79 – 95	-	Visit 11 (Day 85)
7	15	106	96 - 116	Visit 10 (Day 99)	Visit 12 (Day 113)
8	18	127	117 – 137	Visit 11 (Day 127)	-
9	21	148	138 – 158	Visit 12 (Day 155)	Visit 13 (Day 141)
10	24	169	159 – 179	-	-
11	27	190	180 – 200	Visit 13 (Day 183)	Visit 14 (Day 183)
12	30	211	201 – 231	-	Visit 15 (Day 225)
13	36	253	232 – 295	Visit 15 (Day 267)	-
14	48	337	296 – 379	Visit 16 (Day 351)	Visit 16 (Day 309)
15	60	421	380 – 463	Visit 17 (Day 435)	Visit 17 (Day 393)
16	72	505	464 – 547	Visit 18 (Day 519)	Visit 18 (Day 477)
17	84	589	548 – 631	Visit 19 (Day 603)	Visit 19 (Day 561)
Every 12 weeks					

[#] Day relative to first study drug intake

In the event that more than 1 assessment occurs within a given analysis visit window, the assessment closest to the target date will be used in summaries for the given visit. If 2 assessments are equally close to the target day, the latest assessment will be used.

Has been changed to

13.2 Handling of data for subjects who were enrolled prior to protocol amendment 3

Subjects who were directly enrolled in the Second Period based on the protocol prior to amendment 3 will also be included in the efficacy and safety analysis with remapping of visit numbers to correspond to the ones for subjects who enrolled in the First Period. Details will be found in the SAP.

Change #39

Section 13.4: Planned efficacy analyses

All efficacy analysis will be performed for the FAS A1 or FAS M1 depending on therapy and also for the PPS as a supportive purpose for the First Period. The FAS A12 or FAS M12 will be utilized for efficacy analysis in the combined First and Second Periods.

Has been changed to

All efficacy analysis will be performed for the FAS_A or FAS_M depending on therapy.

Change #40

Section 13.4.1: Analysis of the primary efficacy variable for adjunctive therapy

First Period

Descriptive statistics (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum) will be calculated for the percent reduction in ADF of partial seizures from the 48h Selection Period to the 48h Evaluation Period at Visit 6 by age category (3 categories: 1 month to <1 year, 1 year to <2 years, and 2 years to <4 years), and for all subjects combined (overall). The corresponding 95% confidence interval for the median percent reduction at Visit 6 will also be provided by age category and overall. If the lower limit of the 95% confidence interval for overall is greater than the predefined threshold of 10.0%, the efficacy of LEV is significant. If this test shows a significant result, then it will be repeated for the corresponding Visit 4 variable. In that case, the second test is also regarded as confirmatory as due to the hierarchical testing procedure no alpha adjustment is needed. The analysis will be repeated for PPS supportively.

Second Period

Not applicable

Has been changed to

The percent reduction in partial seizures per week from Baseline to Visit 6 will be calculated as:

$$\frac{\text{Number of partial seizures per week at Baseline} - \text{Number of seizures per week at Visit 6}}{\text{Number of partial seizures per week at Baseline}} \times 100$$

Descriptive statistics (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum) will be calculated for the percent reduction in partial seizure frequency per week from Visit 6 by age category (3 categories: 1 month to <1 year, 1 year to <2 years, and 2 years to <4 years), and for all subjects combined (overall). The corresponding 95% confidence interval for the median percent reduction at Visit 6 will also be provided by age category and overall. If the lower limit of the 95% confidence interval for overall is greater than the predefined threshold of 15.0%, the efficacy of LEV is significant. If this test shows a significant result, then it will be repeated for the corresponding Visit 4 variable. In that case, the second test is also regarded as confirmatory as due to the hierarchical testing procedure no alpha adjustment is needed.

There is no primary efficacy variable for subjects on monotherapy.

Change #41

Section 13.5: Planned safety analyses

Safety summaries will be performed for SS A1, SS M1, SS A12, and SS M12 depending on the therapy and period.

Has been changed to

Safety summaries will be performed for SS_A and SS_M depending on the therapy.

Change #42

Section 13.7: Handling of dropouts or missing data

For subjects with <24h of usable Evaluation Period video-EEG time including the subjects who discontinued without any Evaluation Period video-EEG time, partial seizure frequency in the Evaluation 48h video-EEG will be imputed by evaluable partial seizure frequency in Selection 48h video-EEG (ie, Baseline Observation Carry Forward [BOCF]). From the results of N01009 that the percent reduction from Selection in ADF was positive in most of subjects (>75%), BOCF imputation is considered as applicable. Other details about handling missing data will be defined in the SAP.

Has been changed to

Days with missing seizure data will not be used for the calculation of seizure frequency per week. If subjects drop out, their seizure counts over the available period will be used and transformed into seizure frequency per week, by dividing the number of seizures during the available period by the number of days of that period, multiplied by 7.

Safety variables will be analyzed insofar as they are available, without imputation or carrying values forward

Change #43

Section 13.9: Determination of sample size

The following paragraph was added:

Due to the change in the primary efficacy variable in protocol amendment 3, the sample size was reconsidered. When the placebo rate area is conservatively redefined as ≤15% and assuming there are no nonevaluable subjects, a sample size of 38 subjects will obtain ≥80% power. Therefore, no change in sample size is required.

17.7 Protocol Amendment 4

Rationale for the amendment

The purpose of this amendment is to comply with regulations in Japan for the conduct of postmarketing clinical studies.

EP0100 will be conducted as a clinical study (Phase 3) until approval is obtained for the indication of LEV as monotherapy or adjunctive treatment in patients aged 1 month to <4 years with partial seizures, and will continue as a postmarketing clinical study (Phase 4) after the date of approval until the study participant is switched to commercial LEV as soon as possible, or until LEV is discontinued after a period of dose reduction. In Japan, the meaning and expressions related to "clinical study" shall automatically be read as "postmarketing clinical study" after the date of approval in Japan.

In addition, minor administrative edits have been made.

The following shows the changes made in Protocol Amendment 4 compared to Protocol Amendment 3, dated 29 Jan 2020.

Modifications and changes

Specific changes

Change #1:

Sponsor Study Physician

Name:	[redacted]
Phone:	[redacted]

Has been changed to

Name:	[redacted]
Phone:	[redacted]

Change #2:

LIST OF ABBREVIATIONS

The following abbreviation was added:

GPSP	Good Postmarketing Study Practice

Change #3:

Section 1: Summary

The following paragraphs were added:

After approval in Japan for the indication of LEV as monotherapy or adjunctive treatment in patients aged 1 month to <4 years with partial seizures, this clinical study (Phase 3) will be

continued as a postmarketing clinical study (Phase 4). All subjects who are still in the study as of the date of approval will be considered to have completed the study. After the date of approval, subjects should visit the investigational site as soon as possible to complete the study by switching to commercial LEV or discontinuing LEV after the assessment specified in Section 8.5 “Early Discontinuation Visit” in the protocol.

After the study is continued as a postmarketing clinical study (Phase 4), the LEV dry syrup 50% prescribed during the study period will continue to be used, and the labeling of the IMP will not be changed. There will also be no change in the handling and storage conditions of the IMP.

After the date of approval, this clinical study shall be continued as a postmarketing clinical study (Phase 4), and the description of EP0100 in this protocol shall read as follows. The term "clinical study" should be replaced with "postmarketing clinical study," the term "clinical trial" should be replaced with "postmarketing clinical study", the term "this (clinical) study" should be replaced with "this postmarketing clinical study", the term "protocol" should be replaced with "postmarketing clinical study protocol", the term "investigator" should be replaced with "investigator for postmarketing clinical study", the term "subinvestigator" should be replaced with "subinvestigator for postmarketing clinical study", the term "IMP" should be replaced with "IMP for postmarketing clinical study ", the term "Investigator’s Brochure" should be replaced with "package insert or precautions information", the term "Phase 3" should be replaced with "Phase 4", the term "subject’s ID card" should be replaced with "subject’s ID card for postmarketing clinical study participation", and the term "Good Clinical Practice (GCP)" should be replaced with "GCP and Good Postmarketing Study Practice (GPSP)".

Change #4:

Section 4.3.2: Secondary safety variables

Section 4.3.2.1: First Period

- Incidence of serious adverse events (SAEs)

Section 4.3.2.2: Combined First and Second Periods

- Incidence of SAEs

Has been changed to

Section 4.3.2.1: First Period

- Incidence of treatment-emergent serious adverse events (SAEs)

Section 4.3.2.2: Combined First and Second Periods

- Incidence of treatment-emergent SAEs

Change #5:

Section 11.1.1.1 Adverse event

The following paragraph was added:

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

18 DECLARATION AND SIGNATURE OF INVESTIGATOR

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

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

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

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

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

Investigator:

Printed name	Date/Signature

19 SPONSOR DECLARATION

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

Approval Signatures

Name: ep0100-protocol-amendment-4

Version: 2.0

Document Number: CLIN-000214631

Title: ep0100-protocol-amendment-4

Approved Date: 28 Feb 2023

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 27-Feb-2023 00:01:37 GMT+0000
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Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 28-Feb-2023 03:11:32 GMT+0000