STATISTICAL ANALYSIS PLAN

Study: EP0069

Product: UCB0942

A double-blind, randomized, placebo-controlled study of the efficacy, safety/tolerability, and pharmacokinetic profile of UCB0942 in adult patients with highly drug-resistant focal epilepsy.

SAP/Amendment Number	Date
Final SAP	03 Jul 2015
Amendment 1	07 Oct 2016

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LIST OF ABBREVIATIONS

50%RR	50% responder rate
75%RR	75% responder rate
ADaM	analysis dataset model
AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUCτ	area under the plasma concentration-time curve over a dosing interval
BMI	body mass index
BPRS	Brief Psychiatric Rating Scale
BRV	brivaracetam
BUN	blood urea nitrogen
CF	correction factor
CI	confidence interval
CIWA-B	Clinical Institute Withdrawal Assessment-Benzodiazepines
C_{max}	maximum observed plasma drug concentration
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
CSR	clinical study report
C_{trough}	measured concentration at the end of a dosing interval at study state
CV	coefficient of variation
DAP	data analysis plan
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
ECG	electrocardiogram
ES	enrolled set
EudraCT	European Union Drug Regulating Authorities Clinical Trials

FAS	Full Analysis Set
FDA	Food and Drug Administration
HBsAg	hepatitis B surface antigen
HCV-Ab	hepatitis C antibody
HIV-1/2Ab	human immunodeficiency virus-1/2 antibody
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ILAE	International League Against Epilepsy
IMP	investigational medicinal product
LDH	lactate dehydrogenase
LEV	levetiracetam
MedDRA	Medical Dictionary for Regulatory Activities
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MINI	Mini International Neuropsychiatric Interview
MMSE	mini-mental state examination
mRNA	messenger RNA
n	number of observations
NCA	non-compartmental analysis
OLE	Open Label Extension study
PCST	potentially clinical significant treatment-emergent
PK	pharmacokinetic(s)
PK-PPS	Pharmacokinetic Per Protocol Set
PPS	Per Protocol Set
PR	pulse rate
PT	preferred term
QOLIE-31-P	Quality of Life Inventory in Epilepsy-31-P
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cells
RS	Randomized Set

SAE	serious adverse event
SAP	Statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SFU	Safety Follow-up
SI	Standard International
SOC	system organ class
SRG	Safety Review Group
SS	Safety Set
SSQ	seizure severity questionnaire
$t_{1/2}$	apparent terminal elimination half-life, reported in hours
TFL	table listing figure
t_{max}	time of occurrence of maximum observed plasma drug concentration
ULN	upper limit of normal
VNS	vagal nerve stimulation
WBC	white blood cell
WHODD	World Health Organization Drug Dictionary

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide all information that is necessary to perform the required statistical analysis of data collected in EP0069. It also defines the summary tables, listings, and figures (TFLs) to be included in the final Clinical Study Report (CSR) according to the protocol.

This SAP is based upon, and assumes familiarity, with the following study documents:

Protocol Amendment 4: 05 October 2016

Unless specified below, the study will be analyzed as described in the most recent version of the protocol (EudraCT-Number: 2014-003330-12).

If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, this SAP will be amended accordingly. If, after database lock, additional analyses are required to supplement the planned analyses described in this SAP, those unplanned analyses will not be described in the amended SAP but they will be described in a separate analysis plan. However, if analysis definitions have to be modified or updated, a SAP amendment will be required. The content of this SAP is compatible with the International Conference on Harmonization (ICH)/ Food and Drug Administration (FDA) E9 Guidance documents (ICH E9, 1998).

UCB is the Sponsor and PRA is the Contract Research Organization (CRO) for this study.

2 PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objective

The primary objective is to evaluate the efficacy of UCB0942 administered concomitantly with each subject's current, stable antiepileptic drug (AED) regimen in subjects who have 4 or more focal seizures with or without secondary generalization per week and who have failed to achieve seizure control with ≥4 AED regimens of adequate dose and duration.

2.1.2 Secondary objectives

The secondary objectives are to:

- Evaluate the safety and tolerability of UCB0942.
- Evaluate the pharmacokinetics (PK) of UCB0942 and its metabolites.

2.1.3 Exploratory objectives

The exploratory objectives are to:

- Identify genetic polymorphisms, gene expression patterns, plasma proteins, plasma lipids or other plasma substances that predict or are associated with disease etiology, drug response, or tolerability.
- Use video recordings to explore the effect of UCB0942 on seizure type, seizure severity, seizure duration and duration of the postictal period.
- Evaluate the efficacy of UCB0942 using exploratory efficacy variables.

2.2 Study variables

2.2.1 Efficacy variables

The periods for which the efficacy variables are calculated are described in Section 3.2.1.2.

2.2.1.1 Primary efficacy variable

Seizure frequency will be determined using subject diary cards. The subject will be instructed as to how to complete the diary and the procedure for completing the diary will be identical during the Inpatient and Outpatient Maintenance Periods.

The primary outcome measure is the 75% responder rate (75%RR). In the active group this is defined as the proportion of subjects with a 75% or greater reduction in the focal seizure (IA1, IB, IC) frequency during the last 2 weeks of the Inpatient Period compared to the 2-week Prospective Outpatient Baseline. In the placebo group the 75%RR is defined as the proportion of subjects with a 75% or greater reduction in the focal seizure frequency during the first 2 weeks of the Inpatient Period (the 2 weeks on placebo) compared to the Prospective Outpatient Baseline Period.

2.2.1.2 Secondary efficacy variables

The 2-week Inpatient Period to be considered is the last 2 weeks of the Inpatient Period for the active group, and the first 2 weeks of the Inpatient Period for the placebo group (see Section 3.2.1.2).

The secondary efficacy variables are:

- Median percent reduction in focal seizure frequency from the Baseline Period to the 2-week Inpatient Period, the Outpatient Maintenance Period and On-UCB0942 Overall.
- Seizure-free rate during the 2-week Inpatient Period, the last 4 weeks of the Outpatient Maintenance Period, and the On-UCB0942 Overall Period (Section 3.10.2).
- The 75%RR during the last 4 weeks of the Outpatient Maintenance Period, and On-UCB0942 Overall.
- Percentage of seizure-free days during the 2-week Inpatient Period and Outpatient Maintenance Period (Section 3.10.2).

2.2.1.3 Exploratory efficacy variables

For all the exploratory efficacy variables, the Inpatient Period to be considered for the active group is the last 2 weeks and for the placebo group is the first 2 weeks of the Inpatient Period.

Exploratory efficacy variables are as follows:

- Median seizure frequency by focal seizure type (IA1, IB, IC) per study period: Baseline, 1st Inpatient Week, 2nd Inpatient Week, 3rd Inpatient Week, the 2-week Inpatient Period, Outpatient Maintenance Period, and On-UCB0942 Overall.
- The 50% responder rate (50%RR) during the 2-week Inpatient Period and during the Outpatient Maintenance Period.
- Seizure Severity Questionnaire score (SSQ, Cramer et al, 2002) change from Baseline to the end of the Inpatient Period and the end of the Outpatient Maintenance Period.

- Changes in average seizure severity as calculated by the percentage of all seizures that are type IC for the 2-week Inpatient and Outpatient Maintenance Periods.
- Change from Baseline in Quality of Life Inventory in Epilepsy-31-P (QOLIE-31-P, Cramer et al, 2003) subscales and total score for the Outpatient Visits 10, 12, 15, 17.

2.2.2 Pharmacokinetic variables

Plasma concentrations of UCB0942, [redacted] will be used to derive PK-population parameters.

The following PK variables will be calculated:

- AUC_{τ}: area under the plasma concentration-time curve over a dosing interval.
- C_{max}: maximum observed plasma drug concentration.
- t_{max}: time of occurrence of C_{max}.
- $t_{½}$: apparent terminal elimination half-life, reported in hours.
- C_{trough}: measured concentration at the end of a dosing interval at study state.

2.2.3 Other exploratory variables

Blood samples for DNA, mRNA, and lipidomics/proteomics/additional blood biomarkers will be collected during the study:

- **DNA**: One tube for DNA isolation will be collected at the beginning of the Inpatient Period of the study. The DNA may be used to assess known variants associated with drug-resistant epilepsy or AED resistance and may be used for further genetic analyses relating to epilepsy and drug response.
- **mRNA**: One tube will be collected on the day before the first dose of UCB0942/placebo, and 1 tube will be collected on the last day of the Inpatient Maintenance Dose Week. The mRNA samples may be used to identify gene expression patterns that are associated with disease etiology, that predict (Baseline sample), or that are associated with (post-treatment sample) drug response.
- **Lipidomics/proteomics/additional blood biomarkers**: One tube will be collected on the day before the first dose of UCB0942 or placebo, and 1 tube will be collected on the last day of the Inpatient Maintenance Dose Week. These samples may be used for additional blood biomarker analysis.

All subjects will be asked to provide specific consent for these samples. Refusal to provide consent for the collection of samples for DNA, mRNA, and lipidomics/proteomics will not disqualify the subject from participating in the study.

Single archive blood samples (for potential background AED assay) will be collected at the start of titration, the end of the Inpatient Period, and at the end of the Outpatient Maintenance Period (before last dose of investigational medicinal product [IMP]). These samples will be collected just before the morning dose of IMP and stored for up to 1 year after the study ends.

During the Inpatient Period, there will be video monitoring of subjects in their rooms (and in other areas depending on the infrastructure of each site) to allow detection of nocturnal seizures

and seizures not recorded by the subject and to assess seizure type, severity, duration and the duration of the postictal period. The video data will not be used to corroborate or supplement the diary data and shall not influence the diary seizure capture by the subject.

2.2.4 Safety variables

The safety of participating subjects will be closely monitored. Psychiatric assessment will be performed by a staff member trained in the identification of psychiatric symptoms, and the assessments will be performed using the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962), which assesses various psychiatric domains including:

- Changes in mood and symptoms of depression or mania.
- Changes in thinking and perception, and other symptoms of psychosis.
- Changes in behavior.

Other safety variables are:

- Adverse events (AEs) reported by the subject and/or caregiver or observed by the Investigator or inpatient staff.
- Serious AE (SAEs).
- Subject withdrawals or premature UCB0942 tapering due to AEs.
- Changes in clinical laboratory test parameters.
- Changes in vital sign parameters – pulse rate (PR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and respiratory rate.
- Changes in 12-lead electrocardiogram (ECG) parameters.
- Changes in key cardiac structures on 2-dimensional Doppler echocardiography from Baseline to after treatment (end of dosing and 6 months after last dose).
- Changes in physical examination (including body weight) and neurological examination findings.
- Changes in memory or cognition as assessed with the mini-mental state examination (MMSE; Folstein et al, 1975).
- Changes indicative of a hypersensitivity reaction including an AE or laboratory value (as defined below) suggestive of internal organ involvement (including but not limited to hepatitis, nephritis, pneumonitis, carditis, colitis, encephalitis, pancreatitis, myositis, arthritis, or hematologic system involvement) combined with at least 1 of the following: fever, rash, lymphadenopathy, or eosinophilia.
  - Treatment-emergent abnormal laboratory value criteria suggestive of internal organ involvement or eosinophilia:
    - Eosinophils % ≥10%
    - Eosinophils absolute ≥0.5G/L
    - Neutrophils absolute <1.5G/L

- Platelets ≤100G/L
- Alanine aminotransferase (ALT) ≥2x upper limit of normal (ULN)
- Aspartate aminotransferase (AST) ≥2x ULN

- Any indication of withdrawal symptoms using the Clinical Institute Withdrawal Assessment-Benzodiazepines (CIWA-B; Busto et al, 1989).
- Changes in suicidality using the Columbia-Suicide Severity Rating Scale (C-SSRS).

2.3 Study design and conduct

EP0069 is a Phase 2A, double-blind, randomized, placebo-controlled, multicenter study that will test the potential efficacy, safety/tolerability, and PK profile of UCB0942 in adult subjects with highly drug-resistant focal epilepsy.

At least 46 subjects will be randomized 1:1 to receive UCB0942 400mg bid or placebo as add-on to each subject's concomitant AED regimen. Stratified randomization will be used to ensure balance in the 2 treatment arms on the levetiracetam (LEV)-use factor (3 strata):

1. LEV prior and current use (concomitant use of LEV at study entry).
2. LEV Prior Use Only=History of prior LEV use and must have discontinued 4 weeks prior to study entry.
3. LEV Naïve=No history of prior LEV use, and no use at study entry.

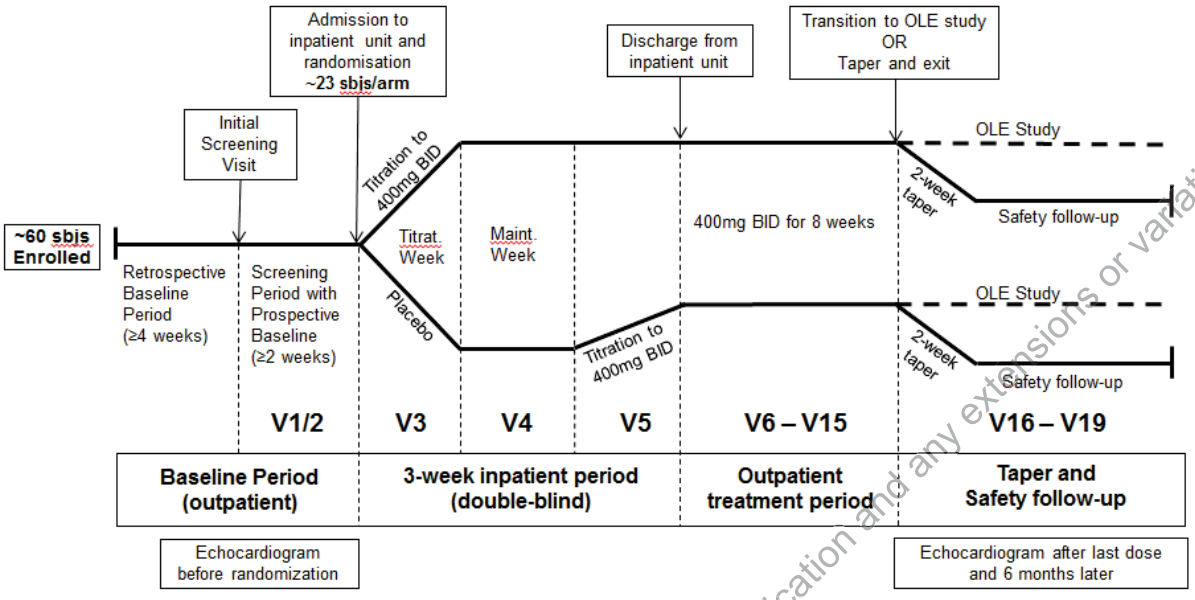
All subjects will stay in the clinical unit for a total of 3 weeks and will then be discharged for an 8-week Outpatient Period. Titration to UCB0942 400mg bid will occur over the course of 1 week in the clinical unit. Subjects in the active arm will be titrated to UCB0942 400mg bid, during the first inpatient week. Subjects who initially received placebo will be titrated to UCB0942 400mg bid during the last week of the 3-week Inpatient Period. For subjects in the active arm who do not tolerate UCB0942 400mg bid, during the third week of the Inpatient Period the dose can be tapered to UCB0942 200mg bid before starting the 8-week Outpatient Period. Similarly, for subjects in the placebo group the dose can be tapered to a tolerable dose during the Outpatient Period.

For a general presentation of the study design refer to Figure 2–1.

The total duration of the study after Screening is 20 weeks for each subject, including the Prospective Outpatient Baseline Period (2 to 3 weeks), the Inpatient Period (3 weeks), the Outpatient Period (8 weeks of treatment and 2 weeks of taper), and a Safety Follow-Up (SFU) Period (4 weeks). The total duration of exposure to UCB0942 during this study is 13 weeks.

Subjects who drop out prior to their Visit 6 may be replaced.

Figure 2–1: Study design



Maint. = maintenance; OLE = open-label extension; Sbjs=subjects; Titrat. = titration.

An echocardiogram is planed to be performed 6 months after the last dose. If not all echocardiographs are completed by the time of the initial database locks, the database will be unlocked so that the echocardiography data will be included and cleaned. These data will be reported in an addendum.

2.4 Determination of sample size

This is an exploratory pilot study to obtain a first evaluation of the efficacy (estimate and variability) of UCB0942 in this specific refractory population. The planned sample size was evaluated based on placebo results obtained in similar refractory epileptic populations from brivaracetam (BRV) and lacosamide Phase 3 studies in add-on focal epilepsy and the desired effect was based on a doubling of the effect of lacosamide and BRV in patients in the current target population.

For the primary efficacy variable, the 75%RR in the placebo group from these historical studies was estimated to be less than 5%. The response on UCB0942 was expected to be 36.5% in order to provide clear differentiation from lacosamide and BRV in this patient population. Based on a two-group Fisher's exact one-sided test with a ratio active:placebo of 1:1, the required number of subjects is 23 in each arm to detect a significant difference between the two groups with a power of 80% and a false positive rate of 5%.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

Statistical evaluation will be performed by UCB or designee and supervised by the Exploratory Statistics Department of UCB unless otherwise indicated. Data may be summarized by study period and by timepoint, if applicable.

The analysis datasets will follow the UCB analysis dataset model (ADaM) data specifications.

All analysis will be performed using SAS® version 9.3, or higher (SAS Institute, Cary, NC, USA). The PK variables will be computed by non-compartmental analysis (NCA) with Phoenix WinNonlin® (version 6.2, or higher) using the actual sampling times.

A glossary of common abbreviations will be provided and will contain abbreviations not footnoted in the tables, figures, and listings.

For continuous variables, summary statistics will include number of observations (n), mean, median, quartiles, standard deviation (SD), minimum, and maximum, and may also include 95% confidence intervals (CI). Categorical endpoints will be summarized using number of subjects, frequency, and percentages. Coefficient of variation (CV), geometric mean, and 95% CI will also be presented in the descriptive statistics for PK parameters. Missing data will not be imputed apart from the exceptions as outlined in Section 4.2.

When reporting relative frequencies or other percentage values, the following rules apply:

- For values where all subjects fulfill certain criteria, the percentage value will be displayed as 100.
- For values where the absolute frequency is 0, there will be no percentage presented at all.
- All other percentage displays will use 1 decimal place.

When reporting descriptive statistics, the following rules will apply in general:

- n will be an integer.
- Mean, SD, and median will use 1 decimal place more than the original data.
- The CV will be reported as a percentage to 1 decimal place.
- Minimum and maximum will be reported using the same number of decimal places as the original value.
- If no subjects have data at a given timepoint, for example, then only n=0 will be presented. However, if n<3, present the n, minimum and maximum only. If n=3, n, mean, median, minimum and maximum will be presented only. The other descriptive statistics will be left blank.

Details of statistical summaries for safety are described in Section 9.

General statistical and reporting conventions are outlined in UCB Global Statistical Conventions; Version 1.0 dated 26 June 2013.

For PK calculations the User guide for Clinical Pharmacokinetics Modeling and Simulation; Version 8.0, dated 4 July 2012 of UCB will be considered as guideline.

3.2 General study level definitions

3.2.1 Analysis timepoints

3.2.1.1 Relative day

The relative day of an event will be derived with the start date of first IMP administration as reference date, up to and including the last day of the IMP administration:

- Active group: Date of the first/last UCB0942 administration (including the tapering period, where applicable)
- Placebo group: Date of the first Placebo administration /last Placebo administration (before the first UCB0942 administration).

Relative days for an event or measurement occurring before the reference date are calculated as follows:

Relative Day=(Event Date-Reference Date)

Relative days for an event or measurement occurring on or after the reference date to the last day of IMP administration are calculated as follows:

Relative Day=(Event Date-Reference Date)+1

For events or measurements occurring after the date of last dosing (as defined above), the relative day will be calculated with the date of last IMP administration as reference. Relative day in this case will be prefixed with '+' in the data listings and will be calculated as follows:

Relative Day=+(Event Date-Reference Date)

Therefore, for the active group, every relative day post the tapering period will be presented with a prefix, and for the placebo group, every day since the first UCB0942 dose (2nd Inpatient Week) be presented with a prefix.

There is no relative Day 0. Relative day is not calculated for partial dates in cases where relative day is shown in a subject data listing. In such cases, relative day should be presented as '--' in the subject data listings.

3.2.1.2 Study periods

The following periods, and their combinations will be considered in the definition of efficacy and safety variables:

- Baseline Period: Prospective Outpatient Baseline Period consisting of 2 to 3 weeks of prospective post-screening subject diary seizure counts.
- Inpatient Period: The Double-Blind Inpatient Treatment Period, with the following sub-periods.
  - 1st Inpatient Week: Double-Blind Titration Week (active group on UCB0942 titration; placebo group on placebo)
  - 2nd Inpatient Week: Double-Blind Maintenance-Dose Week (active group on UCB0942 maintenance; placebo group on placebo)

  - 3nd Inpatient Week: Transition to Outpatient Week (active group on UCB0942 maintenance; placebo group on UCB0942 titration).
  - 2-week Inpatient Period: For the active treatment group this is the last 2 weeks of the Inpatient Treatment Period and for the placebo treatment group this is the first 2 weeks of the Inpatient Treatment Period.
- Outpatient Maintenance Period: 8 week Outpatient open-label (active group on UCB0942 maintenance; placebo group on UCB0942 maintenance).
- Last 4 weeks of Outpatient Maintenance Period.
- On-UCB0942 Overall: This is the whole period while the subjects have been taking UCB0942 (from the 1st Week of the Inpatient period for the active group and from the 3rd week of the Inpatient period for the Placebo group, until the end of Outpatient period or Tapering).
- Tapering Period.
- SFU Period.
- Overall: Whole study duration (start of 1st inpatient week through end of SFU).

3.3 Definition of Baseline values

Baseline for seizure frequency will be based on the seizure frequency over the Baseline Period. This calculation is described in detail in Section 3.10.

The Baseline for other efficacy and safety variables will be the last available scheduled or unscheduled assessment (see Table 3–1).

Table 3–1: Measurement-specific Baseline timepoints

Category	Parameter	Baseline
Efficacy	QOLIE-31-P, SSQ	Pre-dose T1
Safety	Clinical laboratory assessments (chemistry, hematology, urinalysis), echocardiogram	Screening Day -1
	Vital signs (SBP, DBP, PR, and respiratory rate), temperature, weight, 12-lead ECG, physical examination	Pre-dose T1, or, if missing, the Screening Day -1
	C-SSRS, psychiatric and cognitive assessments (BPRS, MMSE), neurological examination,	Pre-dose T1, or if missing, the Screening Day -1
Other	DNA, mRNA, lipodomics/ proteonomics	Pre-dose T1

BPRS=Brief Psychiatric Rating Scale; C-SSRS=Columbia Suicide Severity Rating Scale; DBP=diastolic blood pressure; ECG=electrocardiogram; MMSE=mini-mental state examination; mRNA=messenger RNA; QOLIE-31-P=Quality of Life Inventory in Epilepsy-31-P; SBP=systolic blood pressure; SSQ=seizure severity questionnaire; T1 = Titration Day 1.

In addition, the change from the last pre-UCB0942 administration measurement may be calculated for the placebo subjects for safety and efficacy variables.

3.4 Protocol deviations

Important protocol deviations are deviations from the protocol which could potentially have a meaningful impact on the study conduct or on the primary efficacy outcome, secondary efficacy variables, PK data or key safety data for an individual subject. Important protocol deviations will be reviewed as part of the data cleaning process and all important deviations will be identified and documented to confirm exclusion from the analysis sets.

After all data have been verified/coded/entered into a database, all protocol deviations will be classified according to their impact on study objectives during the database pre-lock data evaluation meeting (DEM). The purpose of this meeting will be to check all protocol deviations, define the analysis sets, and check the quality of the data. The review will also help decide how to manage problems in the subjects' data (e.g., missing values, withdrawals, dropouts, and protocol deviations). After the classification of all deviations, Statistical Programming will then incorporate the definition of the analysis populations into the analysis files for statistical evaluation. If necessary, appropriate actions will be implemented in the SAP before locking the database. After the pre-analysis review, resolution of all issues, and documentation of all decisions, the database will be locked.

3.5 Analysis sets

3.5.1 Enrolled Set

The Enrolled Set (ES) will consist of all subjects who have signed the informed consent form (ICF).

3.5.2 Randomized Set

The Randomized Set (RS) will consist of all enrolled subjects randomized into the study.

3.5.3 Safety Set

The Safety Set (SS) will consist of all subjects in the RS who have received at least 1 dose of IMP.

3.5.4 Full Analysis Set

The FAS will consist of all subjects in the RS who received at least 1 dose of IMP, and have at least 1 post-Baseline seizure diary.

3.5.5 Per Protocol Set

The Per-Protocol Set (PPS) will consist of subjects in the FAS Population who do not have a major protocol deviation impacting the primary efficacy variable.

3.5.6 Other analysis sets

The Pharmacokinetic Per-Protocol Set (PK-PPS) will consist of subjects in the RS who received at least 1 dose of IMP who do not have a major protocol deviation impacting the PK variables. The evaluable population for the PK analysis will consist of those subjects in the PK-PPS for whom a sufficient number of samples are available to determine at least 1 PK parameter. At the discretion of the pharmacokineticist, a subject may be excluded from this set.

3.6 Treatment assignment and treatment groups

Incorrectly-treated subjects will be evaluated during the DEM to assess the potential impact of such cases and any special analysis considerations. The treatment assignment for the SS, PK-PPS will be according to the actual treatment received, whereas the treatment assignment for the PPS and the FAS will be based on the randomized treatment.

Listings and summaries will be presented by the most appropriate treatment group and for the most appropriate period and all outputs will use the conventions outlined in Table 3–2.

Table 3–2: Table conventions

	Label used in outputs	Description
By Arm	**Placebo/UCB0942**	Subjects randomized to Placebo; period: whole study
	UCB0942/UCB0942	Subjects randomized to UCB0942; period: whole study
	All UCB0942 Subjects	All subjects; period: whole study
By Period	**Placebo only**	Subjects randomized to Placebo; period: 1st+ 2nd Inpatient week
	UCB0942 Titration	Subjects randomized to UCB0942; period: 1st Inpatient week Subjects randomized to Placebo; period: 3rd Inpatient week
	UCB0942 Maintenance	Subjects randomized to UCB0942; period: 2nd Inpatient week to the end of Outpatient Period Subjects randomized to Placebo; period: whole Outpatient Period
	UCB0942 Taper	Subjects randomized to UCB0942; period: 2- week Taper Period Subjects randomized to Placebo; period: 2- week Taper Period
	SFU	Subjects randomized to UCB0942; period: SFU Subjects randomized to Placebo; period: SFU
	On-UCB0942 Overall	Subjects randomized to UCB0942; period: 1st Inpatient week to end of the Outpatient Maintenance Period Subjects randomized to Placebo; period: 3rd Inpatient week to end of the Outpatient Maintenance Period

3.7 Center pooling strategy

Subjects with highly drug-resistant focal epilepsy will be enrolled at up to 10 [redacted] clinical centers. The data from all centers will be pooled. The data summaries and statistical analyses will not be performed by center, unless otherwise is stated.

3.8 Coding dictionaries

Adverse events and medical history will be coded according to the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Medications will be coded according to the latest available version of the World Health Organization Drug Dictionary (WHODD).

The medical procedures will not be coded.

3.9 Changes to protocol-defined analyses

The protocol states that all analyses will be based on the randomized treatment. However, the PK and safety analyses will be performed on the actual treatment received.

The Change in time to recovery (protocol, section 4.1.3) will not be analyzed in this study.

The efficacy endpoints will be reported and analyzed in the periods specified in the protocol, and also at additional periods if deemed appropriate.

3.10 Definition of study-specific derived variables

3.10.1 Seizure frequency related variables

- **Seizure frequency**

Initial Processing of Diary Data

Each seizure code in the clinical database will be mapped to exactly 1 of the following codes based on the 1981 International League Against Epilepsy (ILAE) classification: I, IA, IA1, IA2, IA3, IA4, IB, IB1, IB2, IC, II, IIA, IIB, IIC, IID, IIE, IIF, or III.

With regard to cluster seizures, investigator sites are to report the number of cluster episodes rather than reporting the estimated number of individual seizures. Therefore, no imputation will be applied for the seizure counts corresponding to reports of cluster seizures.

Calculation of Total Seizure Counts by Study Period

The total number of seizures for seizure types IA1 (not IA2-4), IB (i.e. IB1 and IB2), IC (i.e. IC1, IC2, and IC3), and the total number of focal seizures (IA1, IB, IC), and the total number of seizures for all seizure types (I+II+III) will be calculated across all diary records over the study period being summarized.

Calculation of Adjusted Seizure Frequency

Weekly adjusted seizure frequency for seizure types IA1 (not IA2-4), IB (i.e. IB1 and IB2), IC (i.e. IC1, IC2, and IC3), and the total number of focal seizures (IA1, IB, IC) will be calculated for the period of interest by dividing the number of seizures for each seizure type by the number of days for which the diary was completed for each study period, and multiplying the resulting value by 7.

The 28-day adjusted seizure frequency will be calculated in a similar way as above.

Calculation of Log-Transformed Values

The above values for each study period of interest will be transformed using the function ln(x+1), where ln represents the natural logarithm function.

- **Percent reduction in seizure frequency**

Percent reduction from Baseline in seizure frequency to the corresponding evaluation Period will be calculated using the following formulae:

$$\frac{\text{Change from Baseline in the weekly adjusted seizure frequency}}{\text{Weekly adjusted seizure frequency during the Baseline period}} \times 100$$

The change from Baseline is calculated subtracting the weekly adjusted seizure frequency during the period of interest from the weekly adjusted seizure frequency during the Baseline period.

The following categories of percent reduction in seizure frequency from Baseline to the corresponding Treatment Period will be computed: <-25%, -25% to <25%, 25% to <50%, 50% to <75%, 75% to <100%, and 100%.

- **XX% Responder Rate in seizure frequency**

A subject is defined as a responder if s/he has a reduction in seizure frequency of at least XX% from their Baseline seizure frequency. The XX%RRs that will be calculated include, but are not limited to 50%, 75%, and will be calculated as follows:

$$\frac{\text{Count of responders during the period}}{\text{Count of responders during the period} + \text{Count of non responders during the period}} \times 100$$

3.10.2 Seizure freedom

A subject is defined as seizure free over a specific time period if they meet all of the following criteria:

1. The subject completed this specific time period.
2. The subject did not have any missing diary days over the time period.
3. The subject did not report any seizure of any type over the time period. Period-specific algorithm rules will be added for the seizure freedom evaluation.

- **Seizure-free rate**

The seizure-free rate (%) for a specific time period will be calculated using the following formula:

$$\frac{\text{Count of seizure free subjects during the period}}{\text{Count of seizure free subjects during the period} + \text{Count of non seizure free subjects during the period}} \times 100$$

3.10.3 Seizure-free days

The percentage of seizure-free days for a specific time period will be calculated using the following formula:

$$\frac{\text{Count of seizure free days during the time interval}}{\text{Count of days of the time interval will available seizure diary data}} \times 100$$

3.10.4 Patient Weighted Quality of Life in Epilepsy Inventory

The Patient Weighted QOLIE-31-P is an adaptation of the original QOLIE-31 (Cramer et al, 1998). The QOLIE-31-P includes 30 items grouped into 7 multi-item subscales (seizure worry [5 items], overall quality of life [2 items], emotional well-being [5 items], energy/fatigue [4 items], cognitive functioning [6 items], medication effects [3 items], and social function [5 items]) and a health status item. The QOLIE-31-P total score, subscale scores, and health status item score are calculated according to the scoring algorithm described below, with scores ranging from 0 to 100 and higher scores indicating better functioning. In addition to these 31 items, the QOLIE-31-P includes seven items assessing the degree of "distress" associated with the topic of each subscale (ie, distress items) and 1 item asking about the relative importance of each subscale topic (ie, prioritization item).

Subscale Scores

As a first step to calculating the subscale scores, the individual responses for the 30 subscale items are rescaled to a 0 to 100 scale with higher scores reflects better functioning; the rescaled values for each item are defined in Section 13.3. Each subscale score is then calculated by summing the rescaled responses for that subscale and dividing by the number of items with a non-missing response. A subscale score will be calculated only if at least 50% of the items within the subscale are present.

Total Score

Total score is calculated as a weighted sum of the subscale scores based on the weighting in Section 13.3. Total score will be missing if at least 1 subscale score is missing. Total score will range from 0 to 100 with a higher score reflecting better functioning.

Health Status Item

Responses for the health status item are a multiple of 10 ranging from 0 to 100 with a higher score corresponding to a better health status. The health status item response is analyzed without rescaling.

Distress Items

Each subscale includes 1 distress item. The response for each distress item is an integer ranging from 1 to 5. The response for each distress item will be converted to a 0 to 100 scale (ie, 0, 25, 50, 75, and 100) with a higher score corresponding to greater distress.

Prioritization Item

The response for each subscale for the prioritization item is an integer ranging from 1 to 7. The prioritization ranking is analyzed without rescaling.

3.10.5 Medications

Each medication will be classified as either an AED or a non-AED. Medications recorded on the Prior and Concomitant AED case report form (CRF) will be classified as AEDs. Medications recorded on the Prior and Concomitant Non-AED CRF can be classified as either AEDs or Non-AEDs based on the following rules and based on manual review of such medications.

Benzodiazepines taken more than once per week for non-epilepsy indications will generally be classified as AEDs. Generally, benzodiazepines taken with a frequency of QD, BID, TID, QID, 5XD, 6XD, QOD, QAM, or QPM will be classified as AEDs. With regard to PRN use, each individual intake of a benzodiazepine is to be recorded on the CRF and the classification of such benzodiazepines as an AED will generally be assessed on an individual basis. In general, all benzodiazepines will be reviewed during pre-lock meeting to ensure the appropriate classification as AEDs or non-AEDs.

Other medications which pharmacologically can be classified as an AED but which were taken for non-epilepsy indications may also be classified as AEDs. The classification of such medications will be determined during the database pre-lock meeting and prior unblinding.

There may be medications recorded on the Prior and Concomitant Medications CRF which are taken for seizure rescue. These medications will be classified as AEDs. The identification of such medications will be based on a manual evaluation of the indication and other CRF fields.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

The primary analysis will be conducted using adjustment for the stratification variable; the LEV-use factor (3 strata):

1. LEV prior and current use (concomitant use of LEV at study entry).
2. LEV Prior Use Only=History of prior LEV use and must have discontinued 4 weeks prior to study entry.
3. LEV Naïve=No history of prior LEV use, and no use at study entry.

4.2 Handling of dropouts or missing data

Missing data will not be imputed with the following exceptions:

Seizure diary:

Seizure frequency will be computed over non-missing diary days as described in Section 3.10; missing seizure diary days will not be considered in the calculation of seizure frequency. Generally, compliance with the daily seizure diary is expected to be high in a refractory population and, therefore, the impact of missing diary data is expected to be minimal. However, the impact of missing diary data cannot be ruled out, and missing data will be assessed as part of the database pre-lock meeting to ensure an acceptable level of compliance with the seizure diary across the study population.

For subjects who prematurely discontinue, or have missing diary days, the calculation of the seizure frequency over a specified period will be based on available seizure diary up to the last diary entry. This effectively imputes the unobserved seizures after discontinuation with the seizure frequency observed prior to discontinuation.

Times and Dates:

Times and partial dates may be imputed for statistical analyses for specific outcomes according to the following rules. Imputed times and dates should not be shown in the listing.

Imputation of Start Times and Partial Start Dates:

- If only the date is specified and it is the date of the first dose, then use the time of the first dose, otherwise, use 00:00.
- If only the month and year are specified and the month and year of first dose is not the same as the month and year of the start date, then use the 1st of the month and 00:00.
- If only the month and year are specified and the month and year of first dose is the same as the month and year of the start date, then use the date and time of first dose.
- If only the year is specified, and the year of first dose is not the same as the year of the start date, then use January 1st and 00:00 of the year of the start date.
- If only the year is specified, and the year of first dose is the same as the year of the start date, then use the date and time of the first dose.

- If the start date is completely unknown and end date is unknown or not prior to first dose, then use the date and time of first dose.
- If the start date is completely unknown and end date is known to be prior to first dose, then set start date equal to end date.

Imputation of End Times and Partial End Dates:

- If only the date is specified, then use 23:59 as end time.
- If only the month and year are specified, then use the last day of the month.
- If only the year is specified, then use December 31 of that year.
- If the stop date is completely unknown, do not impute the stop date.

4.3 Interim analyses and data monitoring

4.3.1 Safety Review Group

In order to monitor the safety data, a Safety Review Group (SRG) will be established prior to the start of the study with the intention of protecting the safety, health, and wellbeing of each participating subject. The precise membership, scope, and responsibilities of the SRG are described in the SRG Charter.

The SRG will meet once the first 4 subjects have completed the Transition-to-Outpatient Period (Visit 6) or withdrawn from the study before Visit 6. Subsequent meetings will occur when the first 10 subjects, the first 16 subjects, and the first 22 subjects have completed Visit 6 or withdrawn from the study before Visit 6. Thereafter, SRG meetings will be held on an as required/ad hoc basis, in response to emerging data, and at the request of any member of the SRG.

The SRG will remain blinded through the first database lock (see Protocol; Section 12.3.3) unless emergent safety information requires unblinding of individual drug allocation for optimal assessment and response to AEs of concern. At the time of the first database lock, the Study Physician(s), clinical pharmacologist, DS representative, biostatistician, and other UCB personnel will be unblinded as to all subjects' treatment allocation at the beginning of the Inpatient Period.

4.3.2 Blinded Interim Analysis

An interim analysis will be performed if needed for purposes of planning and designing of future studies. If performed, this analysis will be conducted when at least 75% of patients have been randomized and completed through the Inpatient Period (completed through Visit 5).

All subjects who have completed through Visit 5 at the time of the data snapshot will be included in the interim analysis.

All statistical analyses will be described in detail in a separate interim SAP or appropriate charter document.

For the interim analysis, the primary efficacy variable (75%RR) will be analyzed using the methods described for the primary efficacy analysis. In addition, seizure-free rate, 50%RR, and percent reduction in focal seizure frequency will be analyzed as described for the secondary/exploratory analyses.

The 75%RR, Seizure-free rate, and 50%RR variables may also be analyzed using Bayesian logistic regression. If Bayesian analysis is peformed, the percent reduction in focal seizure frequency from the Baseline will be estimated using Bayesian analysis of variance (ANOVA) and/or ANCOVA. For these analyses, posterior medians, 95% credible intervals for the treatment effect, and additional posterior probabilities will be presented. Non informative and informative priors will be considered, and sensitivity to different prior settings will be assessed. Other efficacy variables may also be analyzed in the Bayesian framework.

The following safety data will also be presented:

- Treatment emergent AEs
- AEs leading to drop-out or withdrawal
- SAEs
- Laboratory assessments out of normal range
- BPRS

The study will not be terminated early for either efficacy or futility based on the results of this interim analysis and therefore, an alpha penalty may not assessed. At a maximum, an alpha penalty of 0.001 may be assessed on the primary efficacy variable.

The study is not expected to be stopped due to safety reasons during this interim analysis, since there are ongoing quarterly Safety Review Group meetings already planned for this purpose. Therefore, no criteria for evaluation of early stopping due to safety are included.

An unblinded team will be established at both the Sponsor and CRO and will include the following roles (all unblinded): Statistician, Statistical Programmer, and Project Lead. All staff involved in the conduct of the study, including staff at UCB, the CRO, participating vendors, and the participating sites will remain blinded to individual treatment identity and will not be informed of the results of the interim analysis until final unblinding.

4.4 Multicenter studies

The data from different centers will be pooled.

4.5 Multiple comparisons/multiplicity

No adjustments for multiplicity will be made as the statistical analyses will be exploratory in nature.

4.6 Use of an efficacy subset of subjects

All efficacy analyses will be performed for the FAS. The primary analysis will be performed for the PPS as well. No further efficacy subsets are planned.

4.7 Active-control studies intended to show equivalence

Not applicable.

4.8 Examination of subgroups

Descriptive analysis may be performed by the 3 LEV-use levels for some variables, including, but not limited to the primary efficacy variable, and the seizure-freedom.

Descriptive analysis will performed for subjects requiring dose reduction from study medication at any point during the study prior to the protocol-defined taper. The following tables will be repeated for these subjects:

- 75%, 50% Responder Rate in Focal Seizure Frequency Summary
- Incidence of TEAEs - Overview
- Incidence of TEAEs

4.9 End of Study Analyses

The database lock and unblinding may occur in a tiered approach, as described in the protocol. Details regarding the tiered database lock will be described in the Data Management Plan (DMP).

Data analysis and production of TFLs will occur as follows:

After the final subject has completed through Visit 15 (end of Outpatient Maintenance Period) and the corresponding database lock has occurred, all TFLs will be produced and analyses of all data at time points through Visit 15 will be considered final. Note that unblinding of the placebo-controlled portion of the study (Visits 3-5) will occur prior to this analysis, as described in the protocol and DMP. TFLs will include all study visits as planned in the SAP. However, only those time points through Visit 15 will be considered final. TFLs will be annotated with a header to display which visits are considered final.

After the final subject has completed through Visit 20 (End of Taper and Safety Follow Up Period) and the corresponding database lock has occurred, all TFLs will be produced and analyses of all data at time points through Visit 20 will be considered final.

After the final subject has completed the echocardiogram required at 6 months (±1 month) after the last dose, and the corresponding database lock has occurred, the echocardiogram TFLs will be produced and considered final.

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

The number of subjects screened, enrolled into the study, subjects included in each analysis set, and subjects who completed or prematurely discontinued the study, as well as the reason for discontinuation, will be presented for the RS by treatment group, and for All Subjects using frequency counts and percentages. The discontinuations due to AEs will be summarized in a separate table. Screen failure reasons will be summarized.

In addition, the following listings will be provided by treatment group:

- Subject disposition (ES)
- Study discontinuation (RS)
- Subject visit dates (RS)
- Subject analysis sets (ES)

5.2 Protocol deviations

A listing of all important protocol deviations identified at the database pre-lock meeting will be presented for all subjects in the FAS, and will include the deviation type and description. The number and percentage of subjects in the FAS with important protocol deviations will be summarized by period and overall if appropriate. The denominator for percentages will be the number of subjects in the FAS.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics

A by-subject listing of Baseline demographic characteristics will be presented by treatment group for the ES. This will include the date of birth, age (in years), sex, race, ethnicity, height (in cm), weight (in kg), and body mass index (BMI, in kg/m²).

All Baseline demographic characteristics obtained at the Screening Visit will be summarized for the FAS by treatment group, and for All Subjects (apart from the date of birth).

BMI (in kg/m²) is calculated based on the following formula:

$$\text{BMI}\left(\frac{\text{kg}}{\text{m}^2}\right) = \frac{\text{Weight (kg)}}{\text{Height (m)}^2}$$

Body mass index will be reported to 1 decimal place.

The following age groups will be summarized in the same table:

- 12 - <18 years
- 18 - <65 years
- 65 - <85 years
- ≥ 85 years
- ≤18 years
- 19 - <65 years
- ≥65 years

Childbearing potential will be listed for the RS.

Lifestyle information (alcohol, tobacco, caffeinated beverage, and illicit drug use) will be listed and summarized by treatment group and for the RS.

6.2 Medical history and concomitant diseases

Medical history and ongoing medical conditions will be listed and summarized for the SS by treatment group and MedDRA® system organ class (SOC) and preferred term (PT). The start date (month and year only) and end date (or ongoing if applicable) will also be included in the listing. Epilepsy history will not be included in these tables.

Procedure history will be listed separately by the procedure reported term for the SS by treatment group. Concomitant medical procedures carried out during the study will be listed for the SS. For this listing, concomitant is defined in Section 6.3 as for concomitant medications.

6.2.1 History of epilepsy

The history of epilepsy will be listed for all subjects in the ES.

Etiology of epilepsy

The number and percentage of subjects with each type of etiology as specified in the CRF (genetic, congenital, etc) will be summarized for the FAS and listed for the RS.

Epileptic seizure profile

The number and percentage of subjects experiencing each seizure type during the last 4 weeks prior to the screening visit will be summarized for the FAS based on the ILAE Seizure Classification History CRF.

The overall number and percentage of subjects with a history of type I, II, III seizures will be summarized. In addition, the overall number and percentage of subjects with a history of type IA, IB, IC will be summarized.

Focus localization

The number and percentage of subjects with each category of focus localization (unknown, frontal, temporal, parietal, occipital) will be summarized for the FAS. Subjects may be counted in more than 1 category of focal localization.

History of epileptic seizures

History of epileptic seizures, including the number and percentage of subjects with a history of status epilepticus, the number and percentage of subjects with a history of withdrawal seizures, and quantitative summaries of epilepsy duration, age at onset of first seizure, and percent of life with epilepsy, will be summarized for the FAS and listed for the RS.

Historical seizure count

The Historical Seizure Count CRF records the number of seizures experienced by the subject during the 4 weeks prior to study entry. These data will only be provided in subject data listing for the RS and will not be summarized.

Seizure types experienced during baseline

The number and percentage of subjects experiencing each seizure type during the Baseline Period will be summarized for the FAS based on data from the subjects' seizure diaries. The following seizure types will be summarized: I, IA, IB, IC, II, IIA through IIF, III, and clusters.

Subjects will be counted for all higher levels of seizure type categories corresponding to the seizure types or seizure sub-types reported on the CRF. For example, subjects with an IA1 seizure will be counted for types I and IA.

Baseline focal seizure frequency

Baseline weekly adjusted weight frequency will be summarized with descriptive statistics for the FAS. Additionally, baseline weekly adjusted frequency will be summarized for the FAS for seizure types IA, IB, and IC.

6.3 Prior and concomitant medications

The medications will be classified as AEDs or non-AEDs based on coded terms. The list of coded terms considered AEDs will be finalized prior to database lock and unblinding. Prior and concomitant non-AED medications will be listed for the SS by treatment group and by WHODD

Anatomical Main Group [Level 1], Therapeutic Subgroup [Level 2], PT and reported term. This listing will be repeated for all AED medications.

Any non-coded terms will report Level 1 and Level 2 as UNCODED in the listing.

Prior medications include any medications that started prior to the date of first dose of study drug. Concomitant medications are medications taken at least one day in common with the study medication dosing period. Medications may be both prior and concomitant. Past medications are a subset of prior medications, and include prior medications with a stop date before the date of first study medication administration.

6.3.1 Non- Antiepileptic drugs

The number and percentage of subjects taking prior non-AED medications will be summarized for the SS by WHODD Anatomical Main Group [Level 1], Therapeutic Subgroup [Level 2], and PT.

The number and percentage of subjects taking concomitant non-AED medications will be summarized separately for the SS by WHODD Anatomical Main Group [Level 1], Therapeutic Subgroup [Level 2], and PT, and by treatment group for the whole study period. In the same table, the number and percentage of subjects taking concomitant non-AED medications will be summarized by the following treatment periods as defined in Section 3.2.1.2: Placebo Only, UCB0942 Titration, UCB0942 Maintenance, UCB0942 Taper, and UCB0942 Overall.

6.3.2 Antiepileptic drugs

Previous AED Medications

The number and percentage of subjects taking prior or concomitant AED medications will be summarized for the SS by PT.

Number of previous AEDs

The number of AEDs taken prior to study entry will be summarized for the SS based on the following categorization: <4, 4 or 5, 6 or 7, 8-10,>10 AEDs.

Previous AEDs by reason for AED discontinuation

The number and percentage of subjects by reason for discontinuation of previous AEDs will be summarized for the SS. Percentages for each reason for discontinuation will be relative to the number of subjects taking each AED.

Since reason for discontinuation is collected as free text field, a medical review will be conducted prior to database lock and unblinding to combine like terms. The combined terms only will be presented in the summary table. Both the reported and combined terms will be listed.

Use of vagal nerve stimulation at study entry

The number and percentage of subjects with active vagal nerve stimulation (VNS), and the percentage of subjects with no VNS implant or a non-active VNS implant will be summarized for the SS.

All other VNS data (eg, use of magnet, VNS settings) will be listed but will not be summarized.

Number of AEDs taken at study entry

The number and percentage of subjects taking 1, 2, and 3, 4, 5, >5 AEDs at the time of study entry will be summarized for the SS. The same summary will be reported separately by VNS use at study entry (no VNS or VNS not active versus currently active VNS).

Levetiracetam use at study entry

The number and percentage of subjects in each LEV-use category at study entry will be summarized for the SS:

1. LEV prior and current use (concomitant use of LEV at study entry).
2. LEV Prior Use Only=History of prior LEV use and must have discontinued 4 weeks prior to study entry.
3. LEV Naïve=No history of prior LEV use, and no use at study entry.

Concomitant AED Medications

The number and percentage of subjects taking concomitant AED medications will be summarized separately for the SS by PT, and by treatment group for the whole study period. In the same table, the number and percentage of subjects taking concomitant non-AED medications will be summarized by the following treatment periods as defined in Section 3.2.1.2: Placebo Only, UCB0942 Titration, UCB0942, UCB0942 Taper, and UCB0942 Overall.

Changes to Concomitant AEDs

All concomitant AEDs will be listed for subjects requiring a dose change to any concomitant AED during the study. A change is defined as any of the following occurring after randomization through the end of the Outpatient Maintenance period:

- Initiation of a new AED
- Termination of an existing AED
- Dose change for an existing AED (increase or decrease)
- Change in frequency of an existing AED

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Study drug compliance will be assessed from the day of first IMP administration to the day of last dose during the taper period, or up to the end of the outpatient period for the subjects who will continue to the open label extension (OLE). Compliance will be calculated as 100 times the dose (tablets) taken divided by the planned dose (tablets) that should have been taken. If a subject withdraws from the study during a treatment period, their compliance will be calculated up to the time that they dropped out. After a subject has dropped out, the compliance should not be set to zero. Compliance will be listed and summarized for the SS.

Compliance will be included in the study drug administration listing. In addition, the mean compliance will be listed for each subject, for each of the following treatment periods: 1st Inpatient Week, 2nd Inpatient Week, 3rd Inpatient Week, Outpatient Maintenance Period, Tapering Period, SFU Period, UCB0942 Overall.

Compliance will be summarized by treatment group for the following treatment periods: 1st Inpatient Week, 2nd Inpatient Week, 3rd Inpatient Week, Outpatient Maintenance Period, Tapering Period, SFU Period, and UCB0942 Overall. The compliance for the subjects randomized to placebo will be summarized separately for the Placebo and UCB0942 compliance. Additionally, the number and percentage of subjects with compliance levels <80%, 80% to 120%, and >120% will be summarized by treatment group for the overall UCB0942 treatment period.

8 EFFICACY ANALYSES

All seizure diary data will be listed for the RS. The summaries will include the statistics for continuous or categorical variables as specified in Section 3.1.

For the efficacy analyses the term "by treatment group" corresponds to the UCB0942/Placebo group, the UCB0942/UCB0942 group, and the All UCB0942 Subjects group.

8.1 Statistical analysis of the primary efficacy variable

The primary outcome measure is the 75%RR which is defined as the proportion of subjects with a 75% or greater reduction in focal seizure frequency during the 2-week Inpatient Period (as defined in Section 3.2.1.2) compared to the Baseline Period.

The 75%RR will be analyzed using a logistic regression with effects for treatment, for the 3 levels of LEV use, and the log-transformed Baseline seizure frequency as a continuous covariate.

The frequency and percentage of 75%RR will be reported with the estimated odds-ratios and two-sided Wald 95% CI for UCB0942 versus placebo.

The primary analysis will be performed for the FAS but also for the PPS.

8.2 Statistical analysis of the secondary efficacy variables

All analyses of the secondary efficacy analyses will be done for the FAS.

Median percent reduction in weekly focal seizure frequency

The percent reduction in focal seizure (Type IA1+IB+IC) frequency from Baseline Period to the 2-week Inpatient Period will be compared between the UCB0942 and placebo arms using a Wilcoxon-Mann-Whitney test. The Hodges-Lehmann non-parametric estimator will be used to estimate the median percent reduction in seizures between groups and its corresponding 95% CI will be provided.

Percent reduction in focal seizure frequency from the Baseline Period to the Outpatient Maintenance Period and On-UCB0942 Overall will be assessed using summary tables by treatment group.

The percent reduction in focal seizure frequency from the Baseline Period to the 2-week Inpatient Period, the Outpatient Maintenance Period and the On-UCB0942 Overall period will be presented graphically with box-plots.

75%RR on percent reduction in weekly focal seizure frequency

This score will be calculated during the last 4 weeks of the Outpatient Maintenance Period, and On-UCB0942 Overall, and will be compared to the Baseline Period by treatment group using summary statistics.

Seizure free rate

The seizure free rate for the 2-week Inpatient Period will be analyzed using a logistic regression with effects for treatment and log-transformed Baseline seizure frequency as a continuous covariate, if applicable. Odds-ratio of UCB0942 versus placebo groups and its 95% CIs will be estimated.

The seizure freedom will also be evaluated by treatment group for the last 4 weeks of the Outpatient Period and for the On-UCB0942 Overall period using summary statistics.

Percentage of seizure free days

The percentage of seizure free days will be assessed during the 2-week Inpatient and the Outpatient Maintenance periods using summary statistics by treatment group. 95% Hodges-Lehmann CIs for the median will be estimated.

8.3 Analysis of exploratory efficacy variables

All analyses of the exploratory efficacy analyses will be done for the FAS.

50%RR on percent reduction in weekly focal seizure frequency

The 50%RR on percent reduction in weekly focal seizure frequency for the 2-week Inpatient Period (see Section 2.2.1.3) will be analyzed only for the FAS using a logistic regression with effects for treatment, for the 3 levels of LEV-use, and the log-transformed Baseline seizure frequency as a continuous covariate. The 50%RR at the Outpatient Maintenance Period will be summarized by treatment group.

Median seizure frequency by focal seizure type

An analysis of covariance (ANCOVA) will be performed on the log-transformed weekly seizure frequency during the 2-week Inpatient Period. Specifically, ln(1+weekly seizure frequency during the 2-week Inpatient Period) will be modeled with treatment group as factor and ln(1+weekly seizure frequency during the Baseline Period) as covariate. Contrasts will be estimated to compare UCB0942 to placebo results observed. Transformation of efficacy data could be envisaged given the data distribution. This analysis will be repeated for all the subtypes of focal seizures (Type IA1, IB, IC, and disabling [IB+ IC]).

The seizure frequency for the focal seizures (Type IA1+ IB +IC) and focal seizure subtypes (Type IA1, IB, IC, and disabling [IB+ IC]) will also be summarized by treatment group and UCB0942 Overall for the following study periods: Baseline, 1st Inpatient Week, 2nd Inpatient Week, 3rd Inpatient Week, 2-week Inpatient, Outpatient Maintenance Period, and On-UCB0942 Overall.

The mean 28-day adjusted seizure frequency by focal seizure subtype (Type IA1, IB, IC, and disabling [IB+ IC]) will be displayed graphically as stacked bar charts for the following study periods: Baseline, 1st Inpatient Week, 2nd Inpatient Week, 3rd Inpatient Week, 2-week Inpatient, Outpatient Maintenance Period, and On-UCB0942 Overall. This will also be presented by subject.

The mean percent reduction in seizure frequency from baseline to each of the following study periods will be presented as a bar chart: 1st Inpatient Week, 2nd Inpatient Week, 3rd Inpatient

Week, 2-week Inpatient, Outpatient Maintenance Period, and On-UCB0942 Overall. This will also be presented by subject

Change in seizure severity

Seizure severity is calculated as the percentage of seizures that are type IC out of the total number of focal seizures during a given period. Change from Baseline in seizure severity is the seizure severity in the period of interest minus the seizure severity during the 2-week prospective baseline period. Seizure severity and its change from baseline will be listed and summarized by treatment group for the 2-week Inpatient and Outpatient Maintenance Periods. For subjects not experiencing IC seizures during the observed period, severity is considered to be 0%.

Seizure severity questionnaire

Changes in SSQ will be summarized by treatment group for the Inpatient Period (V3, 4, 5), the Outpatient Period (V10, 15) and for the Tapering and SFU periods (V15, 17, 18, 20) using summary statistics. Mean change from baseline in SSQ total and subscores will be presented graphically.

The SSQ total score (TS) is derived using the algorithm in Appendix x.

Quality of life

The observed values, and changes from Baseline for the QOLIE-31-P total score and the subscales will be listed for all subjects for visits 3, 10, 12, 15, 17. The prioritization item will be listed separately.

The QOLIE-31-P change from Baseline will be summarized by treatment group using descriptive statistics for visits 10, 12, 15, 17.

The QOLIE-31-P mean change from Baseline for the total score and the sub-scores will be presented in line plots with 95% Hodges-Lehmann CIs for the whole study period.

Exploratory analyses for efficacy

Median 28-day seizure frequency by focal seizure type: An analysis of covariance (ANCOVA) will be performed on the log-transformed weekly seizure frequency during the 2-week Inpatient Period. Specifically, ln(1+weekly seizure frequency during the 2-week Inpatient Period) will be modeled with treatment group as factor and ln(1+weekly seizure frequency during the Baseline Period) as covariate. Contrasts will be estimated to compare UCB0942 to placebo results observed. Transformation of efficacy data could be envisaged given the data distribution. This analysis will be repeated for all the subtypes of focal seizures (Type IA1, IB, IC, and disabling [IB+ IC]).

The seizure frequency for the focal seizures (Type IA1+ IB +IC) and focal seizure subtypes (Type IA1, IB, IC, and disabling [IB+ IC]) will also be summarized by treatment group and UCB0942 Overall for the following study periods: Baseline, 1st Inpatient Week, 2nd Inpatient Week, 3rd Inpatient Week, 2-week Inpatient, Outpatient Maintenance Period, and On-UCB0942 Overall.

Exploratory analysis will be performed on the seizure count and SSQ data collected during the tapering and SFU periods. The focal seizure frequency will be summarized by treatment group for the tapering and SFU periods.

The relationship between QOLIE-31-P parameters and efficacy parameters will be evaluated graphically. Plots may include, but are not limited to, scatterplots of the QOLIE-31-P subscales and total score versus the focal seizure reduction at the end of the Outpatient Maintenance Period. This plot will be repeated for the 75%RR.

All video data recorded in the CRF will be listed.

9 PHARMACOKINETICS

All PK analyses will be performed for the PK-PPS.

9.1 Non compartmental PK analysis

Plasma concentrations of UCB0942, [redacted] will be determined from blood samples obtained in the study, during the Titration and Maintenance Periods in order to investigate the population PK of UCB0942 and its major metabolites.

Individual concentrations of UCB0942, [redacted] will be listed by treatment group for the FAS and will include the actual and nominal sampling times and the deviation between them. All deviations will be calculated relative to the IMP administration.

Individual concentrations will be summarized by treatment group, and sampling times for the PK-PPS using n, mean, median, SD, minimum, maximum, geometric mean, and geoCV and 95% CI (assuming log-normally distributed data). This table will be repeated for UCB0942, [redacted].

The following plots will be produced for UCB0942, [redacted] for the PK-PPS:

- All individual concentration time profiles will be displayed graphically on a linear and semi-logarithmic scale.
- Spaghetti plots with the individual plasma concentrations over time profiles for each treatment group will be displayed for all subjects (linear and semi-logarithmic scale).
- Geometric mean profiles (with and without corresponding lower and upper limit of the 95% CI) for the treatment groups will be displayed on the same plot.

The figures will include the LLOQ on the semi-logarithmic plots only.

The following PK parameters will be calculated for UCB0942 and its metabolites:

- AUC_{τ}: area under the plasma concentration-time curve over a dosing interval, as determined using the linear trapezoidal rule.
- C_{max}: maximum observed plasma concentration.
- t_{max}: time of C_{max}.
- $t_{½}$: apparent terminal elimination half-life, reported hours, as determined via simple linear regression (slope = $-\lambda_z$) of natural log (ln) concentration vs time for data points in the terminal phase of the concentration-time curve. $t_{½}$ is calculated as $\ln(2)/\lambda_z$.
- C_{trough}: measured concentration at the end of a dosing interval at steady state.

The PK parameters will be calculated via NCA methods using Phoenix WinNonlin (version 6.2 or higher) using the actual sampling times by PRA with UCB's supervision. Actual sampling times relative to dosing rather than nominal times will be used in the calculation of all derived PK parameters.

The PK parameters of UCB0942 and its metabolites will be listed and summarized using the following descriptive statistics: n, geometric mean, lower and upper 95% CI, geometric CV, arithmetic mean, SD, median, and minimum and maximum values.

Graphical outputs over time will be produced on the trough plasma drug concentrations.

9.2 Population pharmacokinetics

If appropriate, a population PK analysis of UCB0942 and identified active metabolites, will be performed using non-linear mixed effects modeling within the population software (NONMEM) aimed at identifying relevant covariates (demographic variables, other AEDs). The population PK analysis will be performed by UCB and will be described in a separate data analysis plan (DAP), and it will be reported in a separate report.

9.3 Pharmacokinetic/pharmacodynamic analysis

Exploratory population PK-PD analysis may be performed if needed to characterize the relationship between exposure to UCB0942 and the clinical and/or safety clinical outcome. A separate DAP will describe the analysis, which will be reported in a separate report.

10 SAFETY ANALYSES

10.1 Extent of exposure

All study drug administration information will be listed by treatment group.

The duration of study drug will be calculated as the date of last dose of study drug minus the date of first dose of study drug plus 1 day. The duration will be listed for each subject for the following treatment periods: 1st Inpatient Week, 2nd Inpatient Week, 3rd Inpatient Week, Outpatient Maintenance Period, Tapering Period, SFU Period, UCB0942 Overall.

The duration of study drug exposure will be calculated as the date of last dose of study drug during the Period of interest minus the date of first dose of study drug plus 1 day.

The duration of study drug exposure (in days) will be summarized by treatment group. The exposure for the subjects randomized to placebo will be summarized separately for the Placebo and UCB0942 exposure. The number and percentage of subjects with the following categories of durations of study drug exposure will also be summarized: ≤1 week, >1 to ≤2 weeks, >2 to ≤4 weeks; 4 to ≤6 weeks; >6 to ≤8 weeks; >8 to ≤9 weeks; >9 to ≤11 weeks; >11 weeks.

10.2 Adverse events

Adverse events will be recorded from the time informed consent is granted until study completion or study termination (end of the SFU period). All AEs will be coded using the latest available version of MedDRA and will be categorized by intensity (mild/moderate/severe).

Listings will be provided for all AEs, SAEs, AEs leading to tapering, AEs leading to withdrawal, and AEs leading to death by treatment group for the SS.

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to the initiation of the first dose of study treatment or any unresolved event already present before initiation of the first dose that worsens in intensity following exposure to the treatment.

The number and percentage of subjects who experience TEAEs will be summarized by SOC and PT, and by treatment group. In the same table, the number and percentage of subjects will be summarized by the following treatment periods as defined in Section 3.2.1.2: Placebo Only, UCB0942 Titration, UCB0942 Maintenance, UCB0942 Taper, and On-UCB0942 Overall.

The following tabular summaries will be presented for the SS:

- Incidence of AEs - Overview
- Incidence of TEAEs
- Incidence of Serious TEAEs
- Incidence of TEAEs by Relationship
- Incidence of SAEs by Relationship
- Incidence of Non-Serious TEAEs by Relationship
- Incidence of Fatal TEAEs by Relationship
- Incidence of TEAEs by Maximum Relationship
- Incidence of TEAEs by Maximum Intensity
- Incidence of TEAEs leading to Tapering
- Incidence of TEAEs leading to Withdrawal
- Incidence of Non-Serious TEAEs above the Threshold of 5% of Subjects
- Incidence of Non-Serious TEAEs above the Threshold of 5% of Subjects by Relationship

Where dates are missing or partially missing, AEs will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates, see Section 4.2) to suggest that the AE started prior to the first dose of study treatment.

Summary tables will contain counts of subjects, percentages of subjects in parentheses and the number of events where applicable. A subject who has multiple events in the same SOC and PT will be counted only once in the subject counts but all events will be included.

In summaries including relationship to study treatment, the following relationships will be summarized: ‘Not related’, ‘Related’. Subjects who experience the same event multiple times will be included in the most related category. Events with missing relationship will be considered as ‘Related’ to the last given study product for summary purposes but recorded as missing in the listings.

In summaries including intensity, the following intensity categories will be summarized: ‘Mild’, ‘Moderate’, ‘Severe’. Subjects who experience the same event multiple times will be included in the most severe category. Events with missing intensity will be considered as ‘Severe’ events for summary purposes but recorded as missing in the listings.

Adverse event summaries will be ordered in terms of decreasing frequency for SOC, and PT within SOC, in the UCB0942 overall column.

10.3 Clinical laboratory evaluations

All summaries of laboratory parameters will only summarize parameters planned based on the protocol; however, both planned and unplanned laboratory parameters will be provided in subject data listings.

Observed laboratory data (chemistry, hematology, urinalysis measurements as listed in Table 8–1), and changes from Baseline for numeric parameters will be listed and summarized for the SS by treatment group. The change from the last pre-UCB0942 administration measurement will be listed and summarized for the placebo group. Laboratory values will be grouped according to the laboratory function panel shown in Table 8–1 and flagged as high or low based on the possibly clinically significant treatment emergent (PCST) criteria, if applicable. The number and percentage of subjects with a PCST low or high value will be summarized by treatment group. In the same table, the number and percentage of subjects will be summarized by the following treatment periods as defined in Section 3.2.1.2: Placebo Only, UCB0942 Titration, UCB0942 Maintenance, UCB0942 Taper, and UCB0942 Overall.

Possibly clinically significant treatment emergent criteria are based on FDA Division of Neuropharmacologic Drug Products guidelines with some UCB-defined additions (Section 13.2).

For the laboratory parameters that are identified in Table 8–1, the change in category (normal range: low, normal, high) at the end of Maintenance from Baseline will be presented in shift tables.

Additional laboratory tests (including serology—only at Screening-, drugs and alcohol, pregnancy) performed will be listed, but will not be summarized.

Table 8–1: Clinical laboratory measurements

Category	Panel	Variable
Serology		HBsAg, HCV Ab, HIV1 Ab, HIV2 Ab
Hematology	Red blood cell	RBC count, hemoglobin[a], hematocrit, MCH, MCHC, MCV
	White blood cell	WBC count[a], basophils, eosinophils, lymphocytes, monocytes, neutrophils[a]
	Platelet	Platelet count
Clinical chemistry	Electrolytes	Sodium, chloride, potassium
	Minerals	Calcium, magnesium
	Metabolic	Glucose
	Liver function	ALP[a], ALT[a], AST[a], total bilirubin[a], LDH
	Kidney function	BUN or urea
	Other	Creatinine[a]
Urinalysis	Dipstick	Total protein, pH, glucose, WBC, RBC

ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, HBsAg=hepatitis B surface antigen, HCV-Ab=hepatitis C virus antibody, HIV=human immunodeficiency virus, LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; WBC=white blood cell.

[a]Shift tables will be presented for these variables.

10.4 Vital signs, physical findings, and other observations related to safety

10.4.1 Vital signs

A by-subject listing of all observed vital measurements (including SBP, DBP, PR, respiratory rate, weight, oral body temperature) and changes from Baseline will be listed. This listing will include a flag for measurements identified or as being PCST as calculated by the criteria outlined in Section 13.2.

Measured values, and changes from Baseline for all vital sign measurements (excluding weight and temperature) will be summarized by treatment group and timepoint. The change from the last pre-UCB0942 administration measurement will be listed and summarized for the placebo group.

The number and percentage of subjects with a PCST value, PCST low values, and PCST high value will be summarized for SBP, DBP, PR, and body weight by treatment group. In the same table, the number and percentage of subjects will be summarized by the following treatment periods as defined in Section 3.2.1.2: Placebo Only, UCB0942 Titration, UCB0942 Maintenance, UCB0942 Taper, and On-UCB0942 Overall. Percentages will be relative to the number of subjects with an assessment within each period.

Potentially clinical significant treatment-emergent criteria are based on FDA Division of Neuropharmacologic Drug Products guidelines with some UCB-defined additions.

10.4.2 Electrocardiograms

Observed ECG data (ventricular rate, PR, QT, QTcB [QT corrected for heart rate using Bazett's formula], and QTcF [QT corrected for heart rate using Fridericia's formula], and QRS) and changes from Baseline will be listed and summarized by treatment group and period. The change from the last pre-UCB0942 administration measurement will be listed and summarized for the placebo group. A separate listing will report the ECG findings. QTcB and QTcF will be calculated for all subjects as below:

$QTcB = \frac{QT}{\sqrt{60/HR}}$ and $QTcF = \frac{QT}{\sqrt[3]{60/HR}}$, where QT is the QT interval as reported in the ECG transfer and HR is the heart rate as reported in the ECG transfer.

The number and percentage of subjects with no abnormality, an abnormal but not clinically significant finding, and a clinically significant finding will be summarized by treatment group. The number and percentage of subjects will be summarized by the following treatment periods as defined in Section 3.2.1.2: Placebo Only, UCB0942 Titration, UCB0942 Maintenance, UCB0942 Taper, and On-UCB0942 Overall. Percentages will be relative to the number of subjects with an ECG result at each timepoint. Subjects will be counted at most once within each time point based on the worst observed outcome across all abnormalities at that timepoint.

Summaries of shift from Baseline will also be provided based on the categories normal and abnormal by treatment group. In the same table, the number and percentage of subjects will be summarized by the following treatment periods as defined in Section 3.2.1.2: Placebo Only, UCB0942 Titration, UCB0942 Maintenance, UCB0942 Taper, and On-UCB0942 Overall.

10.4.3 Doppler echocardiography

Doppler echocardiography abnormalities at Baseline and subsequent visits will be listed and summarized by treatment group and period. All available echocardiography data will be reported in the CSR and its addendum.

10.4.4 Physical examination

A listing of abnormal physical examination findings at will be provided; no summaries of physical examination findings are planned.

10.4.5 Columbia-Suicide Severity Rating Scale

All C-SSRS data obtained at Screening and subsequent visits will be listed for the FAS.

10.4.6 Neurological examination

A listing of abnormal neurological examination findings at will be provided for the FAS; no summaries of neurological examination findings are planned.

10.4.7 Psychiatric and cognition assessment and withdrawal monitoring

Psychiatric and cognitive assessments (BPRS and MMSE throughout the study) as well as the changes from Baseline will be listed. The changes from Baseline will be summarized by treatment group for the FAS.

Any symptoms of withdrawal reactions will be monitored using the CIWA-B questionnaire. The CIWA-B scores will listed and summarized by treatment group.

10.4.8 Other safety variables

Treatment-emergent abnormal laboratory value criteria suggestive of internal organ involvement or eosinophilia will be listed by the following treatment periods as defined in Section 3.2.1.2: Placebo Only, UCB0942 Titration, UCB0942 Maintenance, UCB0942 Taper, and On-UCB0942 Overall.

11 OTHER ANALYSES

The analyses for blood samples for DNA, mRNA, and lipidomics/proteomics/additional blood biomarkers, and other exploratory variables will be described in a separate DAP.

If there is a high number of missing observations (>15%), due to withdrawals or missing measurements, further post-hoc analyses may be performed, for example for the QOLIE-31-P, and other questionnaires.

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13 APPENDICES

13.1 Treatment groups in TFL outputs

TFL Group	By Arm			By Period				
	Placebo/ UCB0942	UCB0942/ UCB0942	All UCB0942 Subjects	Placebo only	UCB0942 Titration	UCB0942 Maintenance	UCB0942 Taper	On-UCB0942 Overall
Subject disposition	X	X	X					
Protocol Deviations	X	X	X					
Demographics	X	X	X					
Epilepsy history	X	X	X					
Prior Medications	X	X	X					
Concomitant Medications	X	X		X	X	X	X	X
Study Medication Exposure / Compliance	X	X		X	X	X	X	X
PK	X	X						
AEs	X	X		X	X	X	X	X
Labs, Vitals, ECG, Other Safety	X	X	X					
PCST Incidence	X	X		X	X	X	X	X
Efficacy	X	X	X					

AE=adverse event; ECG=electrocardiogram; PCST=potentially clinical significant treatment-emergent; PK=pharmacokinetics.

13.2 PCST criteria

13.2.1 Hematology

Parameter	Conventional Units	SI Units	CF
Hematocrit	For 1 m to < 6 m: ≤ 25% For 6 m to < 2 y: ≤ 27% For 2 y to < 4 y: ≤ 29% For 4 y to < 12 y: ≤ 32% (F); ≤ 35% (M) For ≥ 12 y: ≤ 32% (F); ≤ 37% (M)	For 1 m to < 6 m: ≤ 025% For 6 m to < 2 y: ≤ 027% For 2 y to < 4 y: ≤ 029% For 4 y to < 12 y: ≤ 032% (F); ≤ 035% (M) For ≥ 12 y: ≤ 032% (F); ≤ 037% (M)	1
Hemoglobin	For < 6 m: ≤ 9.7 g/dL For 6 m to < 12 y: ≤ 10.0 g/dL For ≥ 12 y: ≤ 9.5 g/dL (F); ≤ 11.5 g/dL (M)	For < 6 m: ≤ 97 g/L For 6 m to < 12 y: ≤ 100 g/L For ≥ 12 y: ≤ 95 g/L (F); ≤ 115 g/L (M)	10
Platelets	≤ 75 x 10^9/L or ≥ 700 x 10^9/L	≤ 75 x 10^9/L or ≥ 700 x 10^9/L	N/A
WBC	For < 17 y: ≤ 3.0 x 10^9/L or ≥ 20 x 10^9/L; For ≥ 17 y: ≤ 2.8 x 10^9/L or ≥ 16 x 10^9/L;	For < 17 y: ≤ 3.0 x 10^9/L or ≥ 20 x 10^9/L; For ≥ 17 y: ≤ 2.8 x 10^9/L or ≥ 16 x 10^9/L;	N/A
RBC	For < 17 y: ≤ 2.5 x 10^6/mm^3 For ≥ 17 y: ≤ 2.0 x 10^6/mm^3 (F); ≤ 2.5 x 10^6/mm^3 (M)	For < 17 y: ≤ 2.5 x 10^{12}/L For ≥ 17 y: ≤ 2.0 x 10^{12}/L (F); ≤ 2.5 x 10^{12}/L (M)	1
Eosinophils	≥ 10% or ≥ 0.7 x 10^9/L	≥ 0.10 or ≥ 0.7 x 10^9/L	0.01 or N/A
Neutrophils	≤ 15% or ≤ 1.0 x 10^9/L	≤ 0.15 or ≤ 1.0 x 10^9/L	0.01 or N/A
Basophils	≥ 5% or ≥ 0.4 x 10^9/L	≥ 0.05 or ≥ 0.4 x 10^9/L	0.01 or N/A
Monocytes	≥ 20% or ≥ 1.5 x 10^9/L	≥ 0.20 or ≥ 1.5 x 10^9/L	0.01 or N/A
Lymphocytes	For 1 m to < 6 m: ≤ 22% or ≥ 80% ≤ 2.1 x 10^9/L or ≥ 8.5 x 10^9/L For 6 m to < 2 y: ≤ 15% or ≥ 80% ≤ 1.5 x 10^9/L or ≥7.5 x 10^9/L For 2 y to < 12 y: ≤ 12% or ≥ 80% ≤ 1.0 x 10^9/L or ≥ 7.5 x 10^9/L For 12 y to < 17 y: ≤ 10% or ≥ 80% ≤ 0.5 x 10^9/L or ≥ 5.5 x 10^9/L For ≥ 17 y: ≤ 10% or ≥ 80% ≤ 0.5 x 10^9/L or ≥ 4.5 x 10^9/L	For 1 m to < 6 m: ≤ 0.22 or ≥ 0.80 ≤ 2.1 x 10^9/L or ≥ 8.5 x 10^9/L For 6 m to < 2 y: ≤ 0.15 or ≥ 0.80 ≤ 1.5 x 10^9/L or ≥7.5 x 10^9/L For 2 y to < 12 y: ≤ 0.12 or ≥ 0.80 ≤ 1.0 x 10^9/L or ≥ 7.5 x 10^9/L For 12 y to < 17 y: ≤ 0.10 or ≥ 0.80 ≤ 0.5 x 10^9/L or ≥ 5.5 x 10^9/L For ≥ 17 y: ≤ 0.10 or ≥ 0.80 ≤ 0.5 x 10^9/L or ≥ 4.5 x 10^9/L	0.01 N/A 0.01 N/A 0.01 N/A 0.01 N/A 0.01 N/A

13.2.2 Blood chemistry

Parameter	Conventional Units	SI Units	CF
AST (SGOT)	≥ 3 times of ULN	≥ 3 times of ULN	N/A
ALT (SGPT)	≥ 3 times of ULN	≥ 3 times of ULN	N/A
ALP	For < 17 y: ≥ 2 times of ULN, if normal range adjusted to the age range; For ≥ 17 y: ≥ 3 times of ULN	For < 17 y: ≥ 2 times of ULN, if normal range adjusted to the age range; For ≥ 17 y:≥ 3 times of ULN	N/A
GGT	≥ 3 times of ULN, if baseline value ≤ 3 times of ULN	≥ 3 times of ULN, if baseline value ≤ 3 times of ULN	N/A
BUN	≥ 30 mg/dL	≥ 10.71 mmol/L	0.357
Urea	≥ 60 mg/dL	≥ 10.02 mmol/L	0.167
Creatinine	For < 17 y: ≥ 1.5 mg/dL; For ≥ 17 y: ≥ 2.0 mg/dL	For < 17 y: ≥ 132.6 umol/L; For ≥ 17 y: ≥ 176.8 umol/L	88.4
Creatinine clearance (calc)	For < 12 y: < 70 ml/min (Schwartz)[a] For ≥ 12 y: < 70 ml/min (Cockroft)[b]	For < 12 y: < 70 ml/min (Schwartz)[a] For ≥ 12 y: < 70 ml/min (Cockroft)[b]	N/A
Total bilirubin	≥ 2.0 mg/dL	≥ 34.2 umol/L	17.1
Glucose	≤ 50 mg/dL or ≥ 180 mg/dL	≤ 2.775 mmol/L or ≥ 9.99 mmol/L	0.0555
Total Protein	For ≥ 1 m to < 6 m: ≤ 3.6 g/dL or ≥ 7.8 g/dL For ≥ 6 m to < 17 y: ≤ 4.7 g/dL or ≥ 9.5 g/dL For ≥ 17 y: ≤ 4.5 g/dL or ≥ 9.0 g/dL	For ≥ 1 m to < 6 m: ≤ 36 g/L or ≥ 78 g/L For ≥ 6 m to < 17 y: ≤ 47 g/L or ≥ 95 g/L For ≥ 17 y: ≤ 45 g/L or ≥ 90 g/L	10
Albumin	For < 17 y: ≤ 2.4 g/dL or ≥ 6.5 g/dL For ≥ 17 y: ≤ 2.5 g/dL or ≥ 6.5 g/dL	For < 17 y: ≤ 24 g/L or ≥ 65 g/L For ≥ 17 y: ≤ 25 g/L or ≥ 65 g/L	10
Globulin	For < 17 y: ≤ 1.2 g/dL or ≥ 5.0 g/dL For ≥ 17 y: ≤ 1.5 g/dL or ≥ 5.0 g/dL	For < 17 y: ≤ 12 g/L or ≥ 50 g/L For ≥ 17 y: ≤ 15 g/L or ≥ 50 g/L	10
Sodium	For < 17 y: ≤ 120 mEq/L or ≥ 155 mEq/L For ≥ 17 y: ≤ 115 mEq/L or ≥ 155 mEq/L	For < 17 y: ≤ 120 mmol/L or ≥ 155 mmol/L For ≥ 17 y: ≤ 115 mmol/L or ≥ 155 mmol/L	1
Potassium	For < 17 y: ≤ 3.0 mEq/L or ≥ 6.5 mEq/L For ≥ 17 y: ≤ 3.0 mEq/L or ≥ 5.8 mEq/L	For < 17 y: ≤ 3.0 mmol/L or ≥ 6.5 mmol/L For ≥ 17 y: ≤ 3.0 mmol/L or ≥ 5.8 mmol/L	1
Calcium	For < 17 y: ≤ 7 mg/dL or ≥ 11.5 mg/dL For ≥ 17 y: ≤ 7 mg/dL or ≥ 15.5 mg/dL	For < 17 y: ≤ 1.75 mmol/L or ≥ 2.875 mmol/L For ≥ 17 y: ≤ 1.75 mmol/L or ≥ 3.875 mmol/L	0.25
Uric Acid	For < 12 y: ≥ 8 mg/dL For ≥ 12 y: ≥ 8 mg/dL (F); ≥ 9.5 mg/dL (M)	For < 12 y: ≥ 475.84 umol/L For ≥ 12 y: ≥ 475.84 umol/L (F); ≥ 565.06 umol/L (M)	59.48
Cholesterol	≥ 300 mg/dL	≥ 7.77 mmol/L	0.0259
HDL	≤ 25 mg/dL	≤ 0.65 mmol/L	0.0259
LDL	≥ 200 mg/dL	≥ 5.18 mmol/L	0.0259
Triglycerides	≥ 300 mg/dL	≥ 3.42 mmol/L	0.0114

[a] Schwartz equation (patients <12): Cr Cl ml/min = [Height (cm) * 0.55] / serum creatinine
[b] Cockroft equation (patients ≥12): Male: Cr Cl ml/min = [(140-age) x body weight (kg)] / (72 x serum creatinine);
Female: Cr Cl ml/min = [(140-age) x body weight (kg)] / (72 x serum creatinine)] x 0.85
CF=correction factor.

13.2.3 Urinalysis

Qualitative urine parameters are generally reported by a descriptive score, which differs among laboratories. For data analysis purpose, a four-point scale is used. Five-point, six-point, or seven-point scales will be collapsed into a four-point scale first. A value is considered possibly clinically significant treatment-emergent abnormal if an upward shift of at least 2 degrees from the baseline occurs under investigational treatment. To collapse the results in a five-point scale into a four-point scale, the lowest 2 positive results will be combined (see example below). For results reported with a scale of more than five-point, please consult your study physician for how to collapse into four-point scale.

Original Five-point Scale	**Four-point Scale**
Negative/None	Negative/None
Trace/Rare/Mild/A Few	Trace/1+/Rare/Mild/A Few
1+	
2+/Mod	2+/Mod
3+/Sev	3+/Sev

13.2.4 Vital signs and body weight

Pulse rate	For 1 m to < 12 m: ≤110 bpm and a decrease of ≥ 20 bpm from baseline or ≥ 180 bpm and an increase of ≥ 20 bpm from baseline For 12 m to < 3 y: ≤ 90 bpm and a decrease of ≥ 20 bpm from baseline or ≥ 150 bpm and an increase of ≥ 20 bpm from baseline For 3 y to < 12 y: ≤ 65 bpm and a decrease of ≥ 20 bpm from baseline or ≥ 130 bpm and an increase of ≥ 20 bpm from baseline For 12 y to < 17 y: ≤ 60 bpm and a decrease of ≥ 20 bpm from baseline or ≥ 120 bpm and an increase of ≥ 20 bpm from baseline For ≥ 17 y: ≤ 50 bpm and a decrease of ≥ 30 bpm from baseline or ≥ 120 bpm and an increase of ≥ 30 bpm from baseline
Systolic blood pressure	For 1 m to < 12 m: < 60 mmHg and a decrease of > 20 mmHg from baseline or > 110 mmHg and an increase of > 30 mmHg from baseline For 12 m to < 6 y: < 70 mmHg and a decrease of > 20 mmHg from baseline or > 120 mmHg and an increase of > 30 mmHg from baseline For 6 y to < 13 y: < 70 mmHg and a decrease of > 20 mmHg from baseline or > 130 mmHg and an increase of > 30 mmHg from baseline For 13 y and < 17 y: < 90 mmHg and a decrease of > 20 mmHg from baseline or > 140 mmHg and an increase of > 30 mmHg from baseline For ≥ 17 y: < 90 mmHg and a decrease of > 30 mmHg from baseline or > 180 mmHg and an increase of > 40 mmHg from baseline

Diastolic blood pressure	For 1 m to < 12 m: < 40 mmHg and a decrease of > 15 mmHg from baseline or > 60 mmHg and an increase of > 20 mmHg from baseline For 12 m to < 6 y: < 45 mmHg and a decrease of > 15 mmHg from baseline or > 80 mmHg and an increase of > 20 mmHg from baseline For 6 y to < 13 y: < 50 mmHg and a decrease of > 15 mmHg from baseline or > 85 mmHg and an increase of > 20 mmHg from baseline For 13 y to < 17 y: < 55 mmHg and a decrease of > 20 mmHg from baseline or > 90 mmHg and an increase of > 30 mmHg from baseline For ≥ 17 y: < 50 mmHg and a decrease of > 20 mmHg from baseline or > 105 mmHg and an increase of > 30 mmHg from baseline
Weight	For < 17 y: < 3% or > 97% of the normal body weight growth curve ranges for the age at date of weight assessment [(a)] and gender; For ≥ 17 y: change of ≥ 7% of baseline weight

(a) Once the subject reaches 17 years of age use the body curve criteria of a 17 year old regardless of their age in the study.

13.3 QOLIE-31-P total and subscale score calculations

The following outlines the calculation of the subscale scores for the QOLIE 31 P. The rescaled responses are provided for each item. The subscale scores are calculated by summing the rescaled responses for that subscale and dividing by the number of items with a non-missing response. Note that the divisors shown assume that all items for each subscale have a response; the divisor will differ if there are missing responses. A subscale score will be calculated only if at least 50% of the items within the subscale are present.

Scale/Item Numbers	Response 1	2	3	4	5	6	Subtotal	Final Score 0-100 point scale
Seizure Worry								
30.	0	20	40	60	80	100	_____	
31.	0	33.3	66.7	100	—	—	_____	
32.	0	50	100		—	—	_____	
33.	0	33.3	66.7	100	—	—	_____	
34.	100	75	50	25	0	—	_____	
						TOTAL :	_____	÷ 5 = _____
Overall Quality of Life								
1.	Multiply each response by 10						_____	
36.	100	75	50	25	0	—	_____	
						TOTAL :	_____	÷ 2 = _____
Emotional Well-Being								
7.	0	20	40	60	80	100	_____	
8.	0	20	40	60	80	100	_____	
9.	100	80	60	40	20	0	_____	
10.	0	20	40	60	80	100	_____	
11.	100	80	60	40	20	0	_____	
						TOTAL :	_____	÷ 5 = _____
Energy/Fatigue								
2.	100	80	60	40	20	0	_____	
3.	100	80	60	40	20	0	_____	
4.	0	20	40	60	80	100	_____	
5.	0	20	40	60	80	100	_____	
						TOTAL :	_____	÷ 4 = _____
Cognitive Functioning								
19.	0	20	40	60	80	100	_____	
20.	0	33.3	66.7	100	—	—	_____	
21.	0	20	40	60	80	100	_____	
22.	0	20	40	60	80	100	_____	
23.	0	20	40	60	80	100	_____	
24.	100	75	50	25	0	—	_____	
						TOTAL :	_____	÷ 6 = _____

Medication Effects								
28.	0	33.3	66.7	100	—	—	_____	
26.	100	75	50	25	0	—	_____	
27.	100	75	50	25	0	—	_____	
						TOTAL :	_____	÷ 3 = _____
Daily Activities/Social Functioning								
13.	0	20	40	60	80	100	_____	
14.	0	25	50	75	100	—	_____	
15.	0	25	50	75	100	—	_____	
16.	100	75	50	25	0	—	_____	
17.	100	75	50	25	0	—	_____	
						TOTAL :	_____	÷ 5 = _____

Total score is calculated as a weighted sum of the subscale scores based on the weighting shown below. Total score will be missing if at least 1 subscale score is missing. Total score will range from 0 to 100 with a higher score reflecting better functioning.

QOLIE-31-P Scale		**Final Scale Score**		**Weight**		**Subtotal**
Seizure worry	(a)	_____	×	0.08	=	_____
Overall quality of life	(b)	_____	×	0.14	=	_____
Emotional well-being	(c)	_____	×	0.15	=	_____
Energy/fatigue	(d)	_____	×	0.12	=	_____
Cognitive functioning	(e)	_____	×	0.27	=	_____
Medication effects	(f)	_____	×	0.03	=	_____
Daily activities/Social functioning	(g)	_____	×	0.21	=	_____
TOTAL SCORE : Sum subtotals (a) through (g)						

13.4 SSQ Scoring Algorithm

Items	Scoring Algorithm	Label
A. Before Seizures	**A. Before Seizures**	
1. Warning	Score =1a	Warning score
1a. Helpful Score	1-7	
B. During Seizures	**B. During Seizures**	
2. Movements	Score = 2a+2b÷ 2 or 3a (mutually exclusive sections)	Movement during seizures score
2a. Severe Score	1-7	
2b. Bothersome Score	1-7	
3. Altered Consciousness	Score = 2a+2b÷ 2 or 3a (mutually exclusive sections)	Altered consciousness score
3a. Bothersome Score	1-7	
C. After Seizures	**C. After Seizures**	
4. Recover After Seizures	If no, Component C=0; if yes, score q. 5, 6, 7	Recovery duration score
5. Cognitive Effects	Recovery Cognitive= Total 5a, 5b, 5c ÷ 3	Cognitive effects score
5a. Frequency Score	1-7	
5b. Severe Score	1-7	
5c. Bothersome Score	1-7	
6. Emotional Effects	Recovery Emotional = Total 6a, 6b, 6c ÷ 3	Emotional effects score
6a. Frequency Score	1-7	
6b. Severe Score	1-7	
6c. Bothersome Score	1-7	
7. Physical Effects	Recovery Physical = Total 7a, 7b, 7c ÷ 3	Physical effects score
7a. Frequency Score	1-7	
7b. Severe Score	1-7	

7c. Bothersome Score	1-7	
Recovery Frequency = 5a +6a + 7a ÷ 3		Recovery Frequency score
Recovery Severity = 5b +6b +7b ÷ 3		Recovery Severity score
Recovery Bother = 5c +6c +7c ÷ 3		Recovery Bother score
Recovery Composite	Recovery Overall = [mean 5a,b,c] + [mean 6a,b,c] + [mean 7a,b,c] ÷ 3	Recovery composite score
D. Severity & Bother	Severity & Bother score = 8+9 ÷ 2	Severity & bother score
8. Severity Score 1-7	Global Severity score = 8	Global severity score
9. Bothersome Score 1-7	Global Bother score = 9	Global bother score
10. Most Bothersome	Not scored; calculate proportion designating each category	
Total SSQ score	Mean of: (Warning score, Movement during seizures score OR Altered consciousness score, Recovery composite score, Severity & bother score)	Total SSQ score

Note: items 2 and 3 are meant to be mutually exclusive. In case both are present, the worst score (ie the lowest score) will be used to calculate composite scores.

13.5 SAP Amendment 1

Rationale for the Amendment

The SAP was amended for consistency wit hProtocol Amendment 4 and for clarity.

Modifications and Changes

Change #1

Section 2.2.1.1. Primary Efficacy Variable

The primary outcome measure is the 75% responder rate (75%RR). In the active group this is defined as the proportion of subjects with a 75% or greater reduction in the focal seizure frequency during the last 2 weeks of the Inpatient Period compared to the 2-week Prospective Outpatient Baseline.

Has been changed to

The primary outcome measure is the 75% responder rate (75%RR). In the active group this is defined as the proportion of subjects with a 75% or greater reduction in the focal seizure (IA1, IB, IC) frequency during the last 2 weeks of the Inpatient Period compared to the 2-week Prospective Outpatient Baseline.

Change #2

Section 2.2.1.3 Exploratory Efficacy Variables, 4th bullet

- Changes in average seizure severity as calculated by the percentage of seizures that are type IC for the 2-week Inpatient and Outpatient Maintenance Periods.

Has changed to

- Changes in average seizure severity as calculated by the percentage of all seizures that are type IC for the 2-week Inpatient and Outpatient Maintenance Periods.

Change #3

Section 2.3 Study design and conduct, last paragraph

An echocardiogram is planed to be performed 6 months after the last dose. If not all echocardiographs are completed by the time of the database lock, the database will be unlocked so that the echocardiography data will be included and cleaned. These data will be reported in an addendum.

Has changed to

An echocardiogram is planed to be performed 6 months after the last dose. If not all echocardiographs are completed by the time of the initial database locks, the database will be unlocked so that the echocardiography data will be included and cleaned. These data will be reported in an addendum.

Change #4

Section 3.1 General presentation of summaries and analyses

A glossary of common abbreviations will be provided and will contain abbreviations not footnoted in the tables, figures, and listings.

Was added.

Change #5

Section 3.2.1.2 Study periods, last bullet

- Overall: Whole study duration

Was changed to

- Overall: Whole study duration (start of 1st inpatient week through end of SFU).

Change #6

Section 4.2 Handling of dropouts or missing data

- If the start date is completely unknown, then use the date and time of first dose.

Was changed to

- If the start date is completely unknown and end date is unknown or not prior to first dose, then use the date and time of first dose.
- If the start date is completely unknown and end date is known to be prior to first dose, then set start date equal to end date.

Change #7

Section 4.3 Interim analyses and data monitoring

Was renamed as:

4.3.1 Safety Review Group

Change #8

Section 4.3.1 Safety Review Group

The SRG will remain blinded during the study unless emergent safety information requires unblinding of individual drug allocation for optimal assessment and response to AEs of concern.

Was changed to

The SRG will remain blinded through the first database lock (see Protocol; Section 12.3.3) unless emergent safety information requires unblinding of individual drug allocation for optimal assessment and response to AEs of concern. At the time of the first database lock, the Study Physician(s), clinical pharmacologist, DS representative, biostatistician, and other UCB personnel will be unblinded as to all subjects' treatment allocation at the beginning of the Inpatient Period.

Change #9

Section 4.3.2 Blinded Interim Analysis

Was added.

Change #10

Section 4.8 Examination of Subgroups

Descriptive analysis will performed for subjects requiring dose reduction from study medication at any point during the study prior to the protocol-defined taper. The following tables will be repeated for these subjects:

- 75%, 50% Responder Rate in Focal Seizure Frequency Summary
- Incidence of TEAEs - Overview
- Incidence of TEAEs

Was added.

Change #11

Section 4.9 End of Study Analyses

Was added.

Change #12

Section 5.2 Protocol Deviations

A listing of all important protocol deviations identified at the database pre-lock meeting will be presented for all subjects in the SS, and will include the deviation type and description. The number and percentage of subjects in the SS with important protocol deviations will be summarized by period and overall if appropriate. The denominator for percentages will be the number of subjects in the SS.

Was changed to

A listing of all important protocol deviations identified at the database pre-lock meeting will be presented for all subjects in the FAS, and will include the deviation type and description. The number and percentage of subjects in the FAS with important protocol deviations will be summarized by period and overall if appropriate. The denominator for percentages will be the number of subjects in the FAS.

Change #13

Section 6.1 Demographics

Childbearing potential and lifestyle will be listed in separate listings
Lifestyle information (alcohol, tobacco, caffeinated beverage, and illicit drug use) will be listed and summarized by treatment group and for All Subjects.

Was changed to

Childbearing potential will be listed for the RS.

Lifestyle information (alcohol, tobacco, caffeinated beverage, and illicit drug use) will be listed and summarized by treatment group and for the RS.

Change #14

Section 6.2 Medical history and concomitant diseases

For this listing, concomitant is defined in Section 6.3 as for concomitant medications.

Was added.

Change #15

Section 6.2.1 History of Epilepsy

Classification of epileptic syndrome
The number and percentage of subjects with each epileptic syndrome will be summarized for the FAS based on the Classification of Epileptic Syndrome CRF. This summary will include the number and percentage of subjects within the following categories: localization-related epilepsy; idiopathic, symptomatic, and cryptogenic localization-related epilepsy; generalized epilepsy; epilepsies undetermined whether focal or generalized including the sub-categories for both generalized and focal seizures and without unequivocal generalized or focal seizures; and situation-related seizures.

Was removed.

Change #16

Section 6.3 Prior and concomitant medications

The medications will be classified as AEDs or non-AEDs in the CRF, and will be reviewed during the DEM. Prior and concomitant non-AED medications will be listed for the SS by treatment group and by WHODD Anatomical Main Group [Level 1], Therapeutic Subgroup [Level 2], PT and reported term. This listing will be repeated for all AED medications.
Any non-coded terms will report Level 1 and Level 2 as UNCODED in the listing.
Prior medication definition
If a subject takes a medication between the Screening date and before the date of study drug administration, this medication will be classified as 'prior medication'. With this definition, any medication recorded that has been taken for at least 1 day and has been stopped before the Inpatient Period will be considered as prior.
Concomitant medication definition
Prior medication not stopped before the study drug administration date will be classified as 'concomitant medication'. Medication will be labeled as 'concomitant medication' when the start date is between the date (including the date) of study drug administration and the final study visit or, in case of early termination, on the date of the subject's last visit. With this definition, any medication that has been taken for at least 1 day during the study period will be considered as concomitant.

Was changed to

The medications will be classified as AEDs or non-AEDs based on coded terms. The list of coded terms considered AEDs will be finalized prior to database lock and unblinding. Prior and concomitant non-AED medications will be listed for the SS by treatment group and by WHODD Anatomical Main Group [Level 1], Therapeutic Subgroup [Level 2], PT and reported term. This listing will be repeated for all AED medications.

Any non-coded terms will report Level 1 and Level 2 as UNCODED in the listing.

Prior medications include any medications that started prior to the date of first dose of study drug. Concomitant medications are medications taken at least one day in common with the study medication dosing period. Medications may be both prior and concomitant. Past

medications are a subset of prior medications, and include prior medications with a stop date before the date of first study medication administration.

Change #17

Section 6.3.2 Antiepileptic drugs

Since reason for discontinuation is collected as free text field, a medical review will be conducted prior to database lock and unblinding to combine like terms. The combined terms only will be presented in the summary table. Both the reported and combined terms will be listed.

Was added.

Change #18

Section 6.3.2 Antiepileptic drugs

Changes to Concomitant AEDs

All concomitant AEDs will be listed for subjects requiring a dose change to any concomitant AED during the study. A change is defined as any of the following occurring after randomization through the end of the Outpatient Maintenance period:

- Initiation of a new AED
- Termination of an existing AED
- Dose change for an existing AED (increase or decrease)
- Change in frequency of an existing AED

Was added.

Change #19

Section 8.3 Analysis of Exploratory Efficacy Variables

Median seizure frequency by focal seizure type
An analysis of covariance (ANCOVA) will be performed on the log-transformed weekly seizure frequency during the 2-week Inpatient Period. Specifically, ln(1+weekly seizure frequency during the 2-week Inpatient Period) will be modeled with treatment group as factor and ln(1+weekly seizure frequency during the Baseline Period) as covariate. Contrasts will be estimated to compare UCB0942 to placebo results observed. Transformation of efficacy data could be envisaged given the data distribution. This analysis will be repeated for all the subtypes of focal seizures (Type IA1, IB, IC).
The seizure frequency for the focal seizures (Type IA1+ IB +IC) and focal seizure subtypes (Type IA1, IB, IC) will also be summarized by treatment group and UCB0942 Overall for the following study periods: Baseline, 1st Inpatient Week, 2nd Inpatient Week, 3rd Inpatient Week, 2-week Inpatient, Outpatient Maintenance Period, and On-UCB0942 Overall.
Change in seizure severity
The change in seizure severity is calculated as the change from Baseline in the percentage of seizures that are type IC out of the total number of focal seizures. It will be listed and summarized by treatment group for the 2-week Inpatient and Outpatient Maintenance Periods.

Seizure severity questionnaire
Changes in SSQ will be summarized by treatment group for the Inpatient Period (V3, 4, 5), the Outpatient Period (V10, 15) and for the Tapering and SFU periods (V15, 17, 18, 20) using summary statistics.
Quality of life
The observed values, and changes from Baseline for the QOLIE-31-P total score and the subscales will be listed for all subjects for visits 3, 10, 12, 15, 17. The prioritization item will be listed separately.
The QOLIE-31-P change from Baseline will be summarized by treatment group using descriptive statistics for visits 10, 12, 15, 17.
The QOLIE-31-P mean change from Baseline for the total score and the sub-scores will be presented in line plots with 95% CIs for the whole study period.
Exploratory analyses for efficacy
Median 28-day seizure frequency by focal seizure type: An analysis of covariance (ANCOVA) will be performed on the log-transformed weekly seizure frequency during the 2-week Inpatient Period. Specifically, ln(1+weekly seizure frequency during the 2-week Inpatient Period) will be modeled with treatment group as factor and ln(1+weekly seizure frequency during the Baseline Period) as covariate. Contrasts will be estimated to compare UCB0942 to placebo results observed. Transformation of efficacy data could be envisaged given the data distribution. This analysis will be repeated for all the subtypes of focal seizures (Type IA1, IB, IC).
The seizure frequency for the focal seizures (Type IA1+ IB +IC) and focal seizure subtypes (Type IA1, IB, IC) will also be summarized by treatment group and UCB0942 Overall for the following study periods: Baseline, 1st Inpatient Week, 2nd Inpatient Week, 3rd Inpatient Week, 2-week Inpatient, Outpatient Maintenance Period, and On-UCB0942 Overall.
Exploratory analysis will be performed on the seizure count and SSQ data collected during the tapering and SFU periods. The focal seizure frequency will be summarized by treatment group for the tapering and SFU periods.
The relationship between QOLIE-31-P parameters and efficacy parameters will be evaluated graphically. Plots may include, but are not limited to, scatterplots of the QOLIE-31-P subscales and total score versus the focal seizure reduction at the end of the Outpatient Maintenance Period. This plot will be repeated for the 75%RR.
All video data recorded in the CRF will be listed.

Was changed to

Median seizure frequency by focal seizure type

An analysis of covariance (ANCOVA) will be performed on the log-transformed weekly seizure frequency during the 2-week Inpatient Period. Specifically, ln(1+weekly seizure frequency during the 2-week Inpatient Period) will be modeled with treatment group as factor and ln(1+weekly seizure frequency during the Baseline Period) as covariate. Contrasts will be estimated to compare UCB0942 to placebo results observed. Transformation of efficacy data could be envisaged given the data distribution. This analysis will be repeated for all the subtypes of focal seizures (Type IA1, IB, IC, and disabling [IB+ IC]).

The seizure frequency for the focal seizures (Type IA1+ IB +IC) and focal seizure subtypes (Type IA1, IB, IC, and disabling [IB+ IC]) will also be summarized by treatment group and UCB0942 Overall for the following study periods: Baseline, 1st Inpatient Week, 2nd Inpatient

Week, 3rd Inpatient Week, 2-week Inpatient, Outpatient Maintenance Period, and On-UCB0942 Overall.

The mean 28-day adjusted seizure frequency by focal seizure subtype (Type IA1, IB, IC, and disabling [IB+ IC]) will be displayed graphically as stacked bar charts for the following study periods: Baseline, 1st Inpatient Week, 2nd Inpatient Week, 3rd Inpatient Week, 2-week Inpatient, Outpatient Maintenance Period, and On-UCB0942 Overall. This will also be presented by subject.

The mean percent reduction in seizure frequency from baseline to each of the following study periods will be presented as a bar chart: 1st Inpatient Week, 2nd Inpatient Week, 3rd Inpatient Week, 2-week Inpatient, Outpatient Maintenance Period, and On-UCB0942 Overall. This will also be presented by subject

Change in seizure severity

Seizure severity is calculated as the percentage of seizures that are type IC out of the total number of focal seizures during a given period. Change from Baseline in seizure severity is the seizure severity in the period of interest minus the seizure severity during the 2-week prospective baseline period. Seizure severity and its change from baseline will be listed and summarized by treatment group for the 2-week Inpatient and Outpatient Maintenance Periods. For subjects not experiencing IC seizures during the observed period, severity is considered to be 0%.

Seizure severity questionnaire

Changes in SSQ will be summarized by treatment group for the Inpatient Period (V3, 4, 5), the Outpatient Period (V10, 15) and for the Tapering and SFU periods (V15, 17, 18, 20) using summary statistics. Mean change from baseline in SSQ total and subscores will be presented graphically.

The SSQ total score (TS) is derived using the algorithm in Appendix x.

Quality of life

The observed values, and changes from Baseline for the QOLIE-31-P total score and the subscales will be listed for all subjects for visits 3, 10, 12, 15, 17. The prioritization item will be listed separately.

The QOLIE-31-P change from Baseline will be summarized by treatment group using descriptive statistics for visits 10, 12, 15, 17.

The QOLIE-31-P mean change from Baseline for the total score and the sub-scores will be presented in line plots with 95% Hodges-Lehmann CIs for the whole study period.

Exploratory analyses for efficacy

Median 28-day seizure frequency by focal seizure type: An analysis of covariance (ANCOVA) will be performed on the log-transformed weekly seizure frequency during the 2-week Inpatient Period. Specifically, ln(1+weekly seizure frequency during the 2-week Inpatient Period) will be modeled with treatment group as factor and ln(1+weekly seizure frequency during the Baseline Period) as covariate. Contrasts will be estimated to compare UCB0942 to placebo results observed. Transformation of efficacy data could be envisaged given the data distribution. This

analysis will be repeated for all the subtypes of focal seizures (Type IA1, IB, IC, and disabling [IB+ IC]).

The seizure frequency for the focal seizures (Type IA1+ IB +IC) and focal seizure subtypes (Type IA1, IB, IC, and disabling [IB+ IC]) will also be summarized by treatment group and UCB0942 Overall for the following study periods: Baseline, 1st Inpatient Week, 2nd Inpatient Week, 3rd Inpatient Week, 2-week Inpatient, Outpatient Maintenance Period, and On-UCB0942 Overall.

Exploratory analysis will be performed on the seizure count and SSQ data collected during the tapering and SFU periods. The focal seizure frequency will be summarized by treatment group for the tapering and SFU periods.

The relationship between QOLIE-31-P parameters and efficacy parameters will be evaluated graphically. Plots may include, but are not limited to, scatterplots of the QOLIE-31-P subscales and total score versus the focal seizure reduction at the end of the Outpatient Maintenance Period. This plot will be repeated for the 75%RR.

All video data recorded in the CRF will be listed.

Change #20

Section 10.2 Adverse Events

Adverse events will be recorded from the time informed consent is granted until study completion or study termination. All AEs will be coded using the latest available version of MedDRA and will be categorized by intensity (mild/moderate/severe).

Has changed to

Adverse events will be recorded from the time informed consent is granted until study completion or study termination (end of the SFU period). All AEs will be coded using the latest available version of MedDRA and will be categorized by intensity (mild/moderate/severe).

Change #21

Section 10.4.2 Electrocardiograms

Formulas for QTcB and QTcF have been added.

Change #22

Section 10.4.3 Dopper Echocardiography

Doppler echocardiography results at Baseline and subsequent visits, and changes from baseline will be listed and summarized by treatment group and period. All available echocardiography data will be reported in the CSR and its addendum.

Has changed to

Doppler echocardiography abnormalities at Baseline and subsequent visits will be listed and summarized by treatment group and period. All available echocardiography data will be reported in the CSR and its addendum.

Change #23

Appendix 13.4 SSQ Scoring Algorithm

Has been added.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

This document has been reviewed and approved per the Review and Approval of Clinical Documents Standard Operating Procedures. Signatures indicate that the final version of the Statistical Analysis Plan (SAP) or amended SAP is released for execution.

EP0069 SAP Amendment 1

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
[redacted]	Clinical Approval	07-Oct-2016 12:25 GMT+02
[redacted]	Clinical Approval	07-Oct-2016 12:32 GMT+02