STATISTICAL ANALYSIS PLAN

Study: EP0073

Product: Padsevonil (UCB0942)

AN OPEN-LABEL, MULTICENTER, EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY, TOLERABILITY, AND EFFICACY OF UCB0942 WHEN USED AS ADJUNCTIVE THERAPY FOR PARTIAL-ONSET SEIZURES IN ADULT SUBJECTS WITH HIGHLY DRUG-RESISTANT FOCAL EPILEPSY

SAP/Amendment Number	Date
Final SAP	16 Feb 2016
Amendment 1	26 Aug 2019
Amendment 2	09 Oct 2020

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LIST OF ABBREVIATIONS

50%RR	50% responder rate
75%RR	75% responder rate
AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
BPRS	Brief Psychiatric Rating Scale
BUN	blood urea nitrogen
CI	confidence interval
CIWA-B	Clinical Institute Withdrawal Assessment-Benzodiazepines
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
CSR	clinical study report
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDV	early discontinuation visit
ES	enrolled set
EV	entry visit
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEV	full evaluation visit
FV	final visit
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

ILAE	International League Against Epilepsy
IMP	investigational medicinal product
IPD	important protocol deviations
LDH	lactate dehydrogenase
LEPV	Last Evaluation Period Visit
LEV	levetiracetam
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MEV	minimal evaluation visit
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MMSE	mini-mental state examination
n	number of observations
OLE	Open Label Extension study
PCST	potentially clinical significant treatment-emergent
PDILI	potential drug-induced liver injury
PK-PPS	Pharmacokinetic Per-Protocol Set
POS	partial-onset seizure
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
SAE	serious adverse event
SAP	Statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SFU	Safety Follow-up
SOC	system organ class
SS	Safety Set

ULN	upper limit of normal
VNS	vagus nerve stimulation
WBC	white blood cell
WHODD	World Health Organization Drug Dictionary
YEV	year evaluation visit

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 EP0073. It also defines the summary tables, listings, and figures 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:

- Final Protocol: 11 June 2015
- Protocol Amendment 1: 10 December 2015
- Protocol Amendment 2: 14 November 2016
- Protocol Amendment 3: 09 November 2017

2 PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objective

The primary objective is to evaluate the long-term safety and tolerability of UCB0942 at individualized doses between 100mg/day to a maximum of 800mg/day in subjects with highly drug-resistant focal epilepsy.

2.1.2 Secondary objectives

The secondary objectives are:

- To evaluate the long-term efficacy of UCB0942.
- To evaluate the effects of UCB0942 on the subject's quality of life.

2.1.3 Exploratory Objectives

The exploratory objective is to evaluate the plasma concentrations of UCB0942 and metabolites.

2.2 Study variables

2.2.1 Safety variables

2.2.1.1 Primary safety variable

Occurrence of adverse events (AEs) reported by the subject and/or caregiver or observed by the Investigator or clinical site staff beginning at the entry visit (EV) of the Evaluation Period during the EP0073 study.

2.2.1.2 Other safety variables

- Changes from EP0069 Baseline in laboratory tests (including hematology, blood chemistry, urinalysis) at each assessment during the EP0073 study
- Changes from EP0069 Baseline in 12-lead electrocardiogram (ECG) parameters at each assessment during the EP0073 study
- Changes from EP0069 Baseline in psychiatric assessments as assessed with the BPRS at each assessment during the EP0073 study

- Changes from EP0069 baseline in memory or cognition as assessed with the Mini-Mental State Examination (MMSE) at each assessment during the EP0073 study
- Changes in withdrawal symptoms using Clinical Institute Withdrawal Assessment- Benzodiazepines (CIWA-B) from the LEPV (last visit prior to the Taper Period), at each assessment during the Taper Period (visit at the end of the Taper Period) and during the safety follow-up (SFU) Period (visits at 1 week and 30 days after administration of the final dose of UCB0942) of the EP0073 study
- Changes from EP0069 Baseline in vital sign parameters (pulse rate, blood pressure [BP], and respiratory rate) at each assessment during the EP0073 study
- Occurrence of a clinically concerning valvular or pericardial effusion change or other clinically significant abnormalities as identified by 2-dimensional Doppler echocardiography at each assessment during the EP0073 study
- Changes from EP0069 Baseline in physical examination (including body weight)
- Neurological examination findings at each assessment during the EP0073 study

2.2.2 Efficacy variables

In both this study and EP0069 only partial-onset seizures (POS) of type IA1, IB, and IC and not non-motor IA2, IA3 or IA4 seizures will be counted for the assessment of seizure frequency and responder rate. For assessment of seizure-free rate and days, all seizure types will be considered.

2.2.2.1 Primary efficacy variable

The primary efficacy variable is the 75% responder rate (75%RR) by 3-month intervals over the Evaluation Period.

A 75% responder is defined as a subject with a ≥75% reduction in POS frequency relative to the EP0069 2-week Prospective Outpatient Baseline Period (consisting of 2 to 3 weeks of prospective post-screening subject diary seizure counts).

2.2.2.2 Secondary efficacy variables

The secondary efficacy variables are:

- Median POS frequency per 28 days by 3-month intervals over the Evaluation Period of the EP0073 study.
- Median POS frequency per 28 days by seizure type by 3-month intervals over the Evaluation Period of the EP0073 study.
- Percent reduction in POS frequency relative to the EP0069 2-week Prospective Outpatient Baseline Period by 3-month intervals over the Evaluation Period of the EP0073 study.
- The 50% responder rate (50% RR) by 3-month intervals over the Evaluation Period of the EP0073 study. A 50% responder is defined as a subject with a ≥50% reduction in POS frequency relative to the EP0069 2-week Prospective Outpatient Baseline Period.
- Percentage of seizure-free days by 3-month intervals over the Evaluation Period.
- Seizure-free rate by 3-month intervals over the Evaluation Period.

- Changes in QOLIE-31-P scores from V3 of EP0069 through the assessment of the Evaluation Period.

2.2.2.3 Exploratory pharmacokinetic variable

Plasma concentrations of UCB0942 and its metabolites ([redacted] and [redacted]) will be measured during the first 13 months of treatment in EP0073 (at V3, V4, V5, V6, V7, V8, and V9).

2.3 Study design and conduct

EP0073 is a multicenter, open-label extension (OLE) study that will run throughout the clinical development period of UCB0942 and will continue for approximately 5 years or until either a marketing authorization is granted by any health authority for the adjunctive treatment for POS in adult subjects with highly drug-resistant focal epilepsy, or until UCB decides to close the study due to termination of the development program.

Subjects who experience substantial benefit from UCB0942 with acceptable tolerability in EP0069 may have the opportunity to continue UCB0942 treatment in this OLE study. The decision to enter this study must be made by the Investigator in consultation with the subject and his/her caregiver. The Investigator's decision must take into account the benefit experienced and the potential risks of long-term exposure to UCB0942, as well as the potential benefit and risks of other treatment options available. It is expected that approximately 30 subjects will be enrolled. These subjects will be dosed with UCB0942 400mg bid or a tapered UCB0942 dose of 200mg bid at the EV.

A Data Monitoring Committee (DMC) will systematically monitor and report on the progress, safety, and/or critical efficacy endpoints of the study. This includes evaluating the safety signals and benefit-risk balance for the study subjects in relationship to new data relevant for the efficacy and safety of the investigational medicinal product (IMP). The benefit-risk balance of every subject entering the study will be reviewed by the DMC within 3 months after inclusion.

The study consists of the following periods:

- **2-week Screening Period** from V13 to V15 (Days OP43 to OP57) of the 8-week Outpatient Maintenance Period of the EP0069 study. The Screening Visit will be on V13 of EP0069 and will be V1 of the current OLE study.
- **Evaluation Period of approximately 5 years**, which will start with V2, the Entry Visit (EV), which is the same as V15 (Day OP57) of the 8-week Outpatient Maintenance Period of EP0069.
- **First year**: In the first month of EP0073, subjects will have 2 telephone contacts (M1-Wk1 [TC1] and M1-Wk3 [TC2]) and 1 clinic visit (M1-Wk2 [V3]). During the second, third and fourth months, subjects will visit the clinic at M2 (V4, minimal evaluation visit, MEV), M3 (V5, full evaluation visit, FEV), and M4 (V6, MEV). Subjects will return to the clinic every 3 months for the remainder of the first year with FEV alternating with MEV: M7 (V7, FEV) and M10 (V8, MEV).
- **Second and third year**: The subjects will have clinic visits every 3 months, with MEVs alternating with FEVs/Year evaluation visit, YEVs, beginning with M13 (V9, YEV).

- **Fourth and fifth year**: The subjects will have a clinic visit every 6 months with YEVs alternating FEVs.
- **Taper Period** starting at the LEPV of the Evaluation Period; during the Taper Period, subjects will start to gradually decrease their dose of UCB0942.
- **SFU Period**: subjects must return to the clinic 1 week after administration of the final dose of UCB0942 (SFU1). A final visit (FV) will be scheduled 30 days after administration of the final dose of UCB0942 (SFU2).

The study visits by month are shown in Table 2-1 (see the schedule of study assessments in Protocol's Table 5-2).

Table 2-1: Study visit schedule

Month	Visit	Type of visit
First study year		
M0	V1 (V13 of EP0069)	Screening Visit
M1	V2 (V15 of EP0069)	EV
M1-Wk1	TC1	TC
M1-Wk2	V3	MEV
M1-Wk3	TC2	TC
M1-Wk4	-[a]	-
M2	V4	MEV
M3	V5	FEV
M4	V6	MEV
M5	-	-
M6	-	-
M7	V7	FEV
M8	-	-
M9	-	-
M10	V8	MEV
M11	-	-
M12	-	-
Second study year		
M13	V9	YEV
M16	V10	MEV
M19	V11	FEV
M22	V12	MEV

Table 2-1: Study visit schedule

Month	Visit	Type of visit
Third study year		
M25	V13	YEV
M28	V14	MEV
M31	V15	FEV
M34	V16	MEV
Fourth study year		
M37	V17	YEV
M43	V18	FEV
Fifth study year		
M49	V19	YEV
M55	V20	FEV
M58	V21	YEV and LEVP/EDV
Taper and SFU Periods[b]		
Taper Period	V22	End of Taper Visit
SFU1	V23	SFU at 1 week after last dose
SFU2	V24	SFU at 30 days after last dose (FV)

EDV=Early Discontinuation Visit; EV=Entry Visit; FEV=Full Evaluation Visit; FV=Final Visit; LEPV=Last Evaluation Period Visit; M=month; MEV=Minimal Evaluation Visit; SFU=Safety Follow-up; TC=Telephone Call; V=Visit; YEV=Yearly Evaluation Visit

[a] The "-" denotes that no visit is scheduled in that month

[b] Taper and SFU Periods to start with EDV or LEPV.

2.4 Determination of sample size

For this OLE study, no sample size calculation is needed. The sample size will depend upon recruitment into and completion of the previous study. It is estimated that about 30 subjects (75%) from EP0069 will enter this EP0073 study.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

Statistical evaluation will be performed by UCB or designee. Data may be summarized by study year, month, visit, and by timepoint, if applicable.

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

All analysis will be performed using SAS® version 9.3, or higher (SAS Institute, Cary, NC, USA).

For continuous variables, summary statistics will include number of observations (n), mean, median, standard deviation (SD), minimum, and maximum, and may also include 25% and 75% quartiles. Categorical endpoints will be summarized using number of subjects, frequency, and percentages. 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.
- Minimum and maximum will be reported using the same number of decimal places as the original value.

Data collected at scheduled visits will be included in the by-visit summary. Data collected at unscheduled visits will not be included in the by-visit summary, but will be considered when determining the Last Value (Section 3.2.1.4), minimum, and maximum post-Baseline values.

Details of statistical summaries for safety are described in Section 10.

General statistical and reporting conventions are outlined in UCB Global Statistical Conventions; Version 1.1 dated 27 March 2014.

3.2 General study level definitions

3.2.1 Analysis periods

Unless noted otherwise, Baseline is the EP0069 2-week Prospective Outpatient Baseline Period. In this study, final contact date is referred to date of final contact with subject from Study Completion eCRF form.

The study is divided into 4 periods: Screening Period, Evaluation Period, Taper Period, and SFU Period. The following periods will be considered in the definition of efficacy and safety variables:

- A 2-week Screening Period from V13 to the day before V15 of the 8-week Outpatient Maintenance Period of the EP0069 study.
- Evaluation Period: Entry Visit (EV) to Last Evaluation Period Visit (LEPV) or Early Discontinuation Visit (EDV) or clinical data cutoff date if the subject is ongoing and does not have the EDV. The EV is also V15 of EP0069. Data in EP0073 database will be used in the analyses when possible. If a subject does not have a Visit 21/EDV, then the date of the final contact will be defined as the end date of the Evaluation Period.

- Taper Period: the day after the end date of evaluation period to End of Taper Visit or clinical data cutoff date if the subject is ongoing. If the end of taper period (V22) is missing, here it is the algorithm to impute it:

If EDV visit is missing then last date of evaluation period will be last contact date and taper and SFU period start/end dates will be missing.

Else if the last dose date is before EDV date, then we assume drug was not tapered and taper period start/end date will be set as missing and SFU Period start date will be EDV+1 and SFU Period end date will be final contact date.

Else if V22 is missing but SFU1 visit (V23) is not missing, then the end date of taper period be defined as max(last dose date, V23-7 days), but if this date is before the taper period start date, then taper period start/end dates will be set as missing.

Else if V23 is missing but SFU2 (V24) is not missing, the end date of taper period as min(last dose date, V24-30 days).

Else taper and SFU period start/end dates will be missing.

- SFU Period: The day after the End of Taper Visit to date of final contact or clinical data cutoff date if the subject is ongoing.

In addition, the On-Treatment Period is defined as from the date of first dose to the date of last dose of UCB0942 in EP0073 (Section 3.2.2).

At the time of a clinical cutoff prior to the study completion, a subject will be classified as "discontinued" if the Study Completion CRF is available and the date of premature study termination is provided. All other subjects will be classified as "ongoing." Only the data on or prior to the clinical cutoff date will be included in the analyses.

3.2.2 First and last dose of UCB0942

Throughout this SAP, and unless otherwise stated, the first dose (of UCB0942) refers to the first UCB0942 administration in the EP0073 study reported on First Administration of Study Medication case report form (CRF). The last dose (of UCB0942) refers to the date of last administration of study medication reported on Study Completion CRF, at any EP0073 study period, Evaluation or Taper Period.

At the time of a clinical cutoff, for subjects who are ongoing and not in the SFU Period, the last dose of UCB0942 will be set to the date of the clinical cutoff for the interim analyses. For subjects who are ongoing and in the SFU Period (ie, had the End of Taper Visit) at the time of a clinical cutoff, the last dose of UCB0942 will be set to the last dosing date on the Drug Dosing Log CRF for the interim analyses.

3.2.3 Relative day

The relative day of an event will be derived with the start date of first UCB0942 administration in EP0073 as reference date, up to and including the last day of UCB0942 administration.

Relative days for an event or measurement occurring before the reference date will have a '-' prefix and will be calculated as follows:

$$\text{Relative Day} = -[(\text{Event Date} - \text{Reference Date})]$$

Relative days for an event or measurement occurring on or after the reference date to the last day of UCB0942 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 UCB0942 administration as reference date. 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)]

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.

3.2.4 Monthly time intervals

A month is defined as 30 days and time intervals based on monthly durations are defined as a multiple of 30 days (eg, 12 months is defined as 360 days).

Interval Duration Definition:

- Months 0-3: Days 1-90
- Months >3-6: Days 91-180
- Months >6-9: Days 181-270
- Months >9-12: Days 271-360

Subsequent 3-month intervals are defined in a similar manner.

For the analysis of efficacy variables during the Evaluation Period, 3-month intervals will be derived for the Evaluation Period. For the analysis of AEs and safety variables, 3-month intervals will be derived for the On-Treatment Period.

3.2.5 Last Value during the On-Treatment Period

Last Value for safety parameters (such as clinical laboratory parameters, vital signs, ECGs) is the last available result obtained prior to or on the date of last dose of UCB0942 in EP0073. All scheduled and unscheduled assessments within this time period will be considered. Last Value will be determined separately for each laboratory parameter for hematology, chemistry, urinalysis assessments. Similarly, the minimum and maximum values are defined as the minimum and maximum values prior to or on the date of last dose of UCB0942.

3.2.6 Completer Cohort

Because the duration of the Evaluation Period varies among the subjects, each subject will be classified into one or more of the following completer cohorts based on the duration of the Evaluation Period:

≥3 months : ≥90 days

≥6 months : ≥180 days

≥12 months : ≥360 days

≥18 months : ≥540 days

≥24 months : ≥720 days

≥36 months : ≥1080 days

≥48 months : ≥1140 days

≥60 months = ≥1800 days

The duration of the Evaluation Period is calculated as the date of the end of the Evaluation Period – EV +1. Selected efficacy variables will be analyzed by completer cohorts.

3.2.7 Mapping of data from early discontinuation visits

If an EDV occurs at the day of a scheduled visit, in-clinic safety and PK assessments should correspond to that scheduled visit. Safety assessments at an EDV that occurs on a day between two scheduled visits will be assigned to the next scheduled visit. No mapping will be performed for the seizure and QOLIE-31-P data collected at the EDV.

In the by-visit summary tables, only nominal (scheduled) visits (after mapping) where the assessment is scheduled will be included. Unscheduled visits will not be mapped to scheduled visits. In the subject listing, data will be presented under the actual visits, including EDV and unscheduled visits.

3.3 Definition of Baseline values

Baseline will be based on the EP0069 Baseline. For assessments performed at scheduled and unscheduled visits, Baseline will generally be the last result obtained prior to the first randomized dose administration of the EP0069 study.

Baseline for the evaluation of seizure outcomes will be the EP0069 2-week Prospective Outpatient Baseline Period and the scores will be calculated as described in Section 3.10.

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, or key safety data for an individual subject.

The criteria for identifying important protocol deviations and the classification of important protocol deviations will be defined separately in the Specification of Important Protocol Deviations (IPD) document. To the extent feasible, rules for identifying protocol deviations will be defined without review of the data and without consideration of the frequency of occurrence of such deviations. Important protocol deviations will be reviewed as part of the ongoing data cleaning process at Data Evaluation Meetings (DEMs) prior to lock of the database.

3.5 Analysis sets

3.5.1 Enrolled Set

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

3.5.2 Safety Set

The Safety Set (SS) will consist of all enrolled subjects who took at least 1 dose of UCB0942 in the EP0073 study.

3.5.3 Full Analysis Set

The full analysis set (FAS) will consist of all enrolled subjects who took at least 1 dose of UCB0942 and completed at least 1 seizure diary during the Evaluation Period in EP0073.

3.5.4 Pharmacokinetic Per-Protocol Set

The Pharmacokinetic Per-Protocol Set (PK-PPS) will consist of subjects in the FAS who received at least 1 dose of UCB0942 in the EP0073 study and had at least 1 PK sample, and do not have a major protocol deviation impacting the PK for all the PK samples. PK-PPS exclusion should be based on the individual PK samples. Only if all PK samples are excluded, the subject will be excluded from the PK-PPS.

3.6 Treatment assignment and treatment groups

This is an uncontrolled study in which all subjects receive UCB0942 in doses that are optimally adjusted for each subject. Statistical summaries will present all subjects combined as a single treatment arm unless otherwise indicated.

3.7 Center pooling strategy

Subjects with highly drug-resistant focal epilepsy will be enrolled in approximately 25 sites. 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 Version 22.0 (or later) of the Medical Dictionary for Regulatory Activities (MedDRA®) that are available to UCB. Medications will be coded according to the Version Sep/2017 (or later) of the World Health Organization Drug Dictionary (WHODD).

The medical procedures will not be coded.

3.9 Changes to protocol-defined analyses

Not applicable.

3.10 Definition of study-specific derived variables

3.10.1 Seizure frequency related variables

3.10.1.1 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 (IC1, IC2, IC3), II, IIA (IIA1, IIA2), 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.

Observable focal-onset seizures include Type IA1, IB, and IC. Focal-onset seizures include all Type I seizures. To apply the terminology consistently, observable focal-onset seizures and all Type I seizures will be used when appropriate unless noted otherwise.

Calculation of Total Seizure Counts by Analysis Period and Interval

The total number of seizures for seizure types IA1, IB (i.e. IB1 and IB2), IC (i.e. IC1, IC2, and IC3), the total number of observable focal-onset seizures (IA1+IB+IC), the total number of all Type I seizures, and the total number of seizures for all seizure types (I+II+III) will be calculated across all diary records over a given analysis period or interval being summarized.

Calculation of Adjusted Seizure Frequency

Baseline seizure frequency will be obtained from the EP0069 2-week Prospective Outpatient Baseline Period.

Twenty-eight day adjusted seizure frequency for seizure types IA1, IB (i.e. IB1 and IB2), IC (i.e. IC1, IC2, and IC3), the observable focal-onset seizures (IA1+IB+ IC), and all Type I seizures during the Evaluation Period will be calculated overall, within each 3-month time interval, and over each completer cohort interval by dividing the number of seizures for each seizure type by the number of days for which the diary was completed during a given analysis period or interval, and multiplying the resulting value by 28.

3.10.1.2 Percent reduction in seizure frequency

Percent reduction from Baseline in seizure frequency to the corresponding interval will be calculated using the following formula:

$$\frac{\text{Reduction from Baseline in the 28 day adjusted seizure frequency}}{\text{28 day adjusted seizure frequency during the EP0069 2- week Prospective Outpatient Baseline period}} \times 100$$

The numerator is calculated by subtracting the 28-day adjusted seizure frequency during the period of interest from the 28-day adjusted seizure frequency during the EP0069 2-week Prospective Outpatient Baseline period.

3.10.1.3 XX% Responder Rate in focal 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:

$$\frac{\text{Count of XX\% responders during the period}}{\text{Number of subjects during the period}} \times 100$$

3.10.2 Seizure freedom

Subjects will be considered seizure free for a given period or time interval if the subject, completes the period or time interval, reports no seizures during the period, and has no more than 10% of days in the period for which seizure data is not available (ie, "Not Done" is reported on the Seizure Count CRF). The seizure freedom rate (%) for a specific time period will be calculated using the following formula:

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

3.10.3 Seizure-free days

The number of seizure-free days is defined as the total number of days within an analysis period or time interval for which no seizures are reported. The percentage of seizure-free days is to be computed as 100 times the number of seizure-free days divided by the number of days for which daily diary data was available in the specified analysis period. Days without the corresponding daily diary data (ie, "Not Done" is ticked) should not be used in these computations.

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 7 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 reflecting better functioning; the rescaled values for each item are defined in the scoring manual. 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 the scoring manual. 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.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

No statistical testing is planned; therefore, this section is not applicable.

4.2 Handling of dropouts or missing data

4.2.1 Seizure diary

Seizure frequency (subjects with POS) will be calculated over non missing diary days during each study period or time interval as described in Section 3.10; diary days for which seizure data were not recorded (ie, "Not Done" is ticked) will not be considered in the calculation of seizure frequency or seizure days.

If seizures are reported on a day, but the ILAE seizure code is unknown, the day will be excluded from the seizure frequency calculation for all seizure types. If seizures are reported on a day, the ILAE seizure code is known but the number of seizures is unknown, the day will be excluded from the seizure frequency calculation for the applicable seizure type. As long as seizures are reported on a day, the day will be counted as one day with seizure in the seizure free-days and seizure freedom calculations.

4.2.2 QOLIE-31-P

The QOLIE-31-P score will be summarised without any imputations, and also, only for Month 13 (V9, YEV), using the post-baseline last observation carried forward (LOCF) imputation method. For each individual, missing values for the QOLIE-31-P score will be replaced by the post-baseline last observed postbaseline value of that variable.

4.2.3 Partial/Missing Data for adverse events and concomitant medications:

For analyses of AEs and concomitant medication usage, a complete date must be established to correctly identify the AE or medication as occurring during treatment or not. In the event of completely missing dates, or if ambiguity or incomplete data makes it impossible to determine whether a medication was concomitant, or an adverse event was treatment emergent, the medication will be considered as concomitant or the adverse event will be considered treatment emergent.

For purposes of imputing missing components of partially-reported start and stop dates for AEs and for medication use, the algorithms listed below will be followed. Start and stop dates of AEs or concomitant medication will be displayed as reported in the subject data listings (i.e., no imputed values will be displayed in data listings).

Partial AE and concomitant medication start dates will be imputed as described in the following sections.

Imputation of Partial Start Dates

- If only the month and year are specified and the month and year of first dose of UCB0942 is not the same as the month and year of the start date, then use the 1st of the month
- If only the month and year are specified and the month and year of first dose of UCB0942 P is the same as the month and year of the start date, then use the date of first dose of UCB0942

- If only the year is specified, and the year of first dose of UCB0942 is not the same as the year of the start date, then use the 1st of January of the year of the start date
- If only the year is specified, and the year of first dose of UCB0942 is the same as the year of the start date, then use the date of first dose
- If the start date is completely unknown and the stop date is unknown or not prior to the date of first dose of IMP, then use the date of first dose of UCB0942.
- If the imputed start date is after the known stop date, set the start date to be the same as the stop date.

Imputation of Partial Stop Dates

- 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 31st of that year
- If the stop date is completely unknown, do not impute the stop date

4.3 Interim analyses and data monitoring

A DMC will systematically monitor and report (at least quarterly up to the timepoint when the last patient entering EP0073 reaches 1 year in the study, and less frequent thereafter) on the progress, safety, and/or critical efficacy endpoints of this study by convening to review the ongoing program safety and efficacy data. This includes evaluating the safety signals and benefit-risk balance for the study subjects in relationship to new data relevant for UCB0942 efficacy and safety. The benefit-risk balance of every subject entering the study will be reviewed by the DMC within 3 months after inclusion. Blinded data until database lock from EP0069 and data from the OLE EP0073 studies will be reviewed in order for the DMC to provide an ongoing benefit-risk evaluation with particular reference to the occurrence of psychiatric and cardiological/ cardiovascular AEs, seizure control, and any new identified safety signals. Voting members of the DMC will include external physicians with experience in treating refractory epilepsy and a cardiologist, none of whom will be involved with the conduct of the study, either by management or participation. In addition, there will be an independent reporting team, consisting of an independent statistician and independent statistical programmers, who will be completely independent from the blinded reporting team. The blinded reporting team will be responsible for all operational aspects of the study, including routine monitoring and cleaning of the data, programming, and quality control of all analyses defined in the EP0073 DMC SAP, on blinded data of EP0069, and unblinded data of EP0073 (as an open-label study). If required for monitoring of safety and benefit-risk of EP0073 patients, unblinded data from EP0069 can be reviewed by the external members of the DMC at closed sessions and provided by an independent statistician. The DMC will make recommendations to the company, which may include changes to study procedures, withdrawal of subjects with a negative risk balance, or termination of the clinical study.

A DMC Charter will define the composition, roles, and responsibilities of the DMC, specify the data to be reviewed and the periodicity of data review, and determine the procedures to be followed to maximize subject safety and ensure positive benefit-risk balance of participation in the study.

Interim analyses may be produced while this study is ongoing to support annual reports, regulatory submissions, and publications. There are no statistical concerns with such interim assessments for this study design.

4.4 Multicenter studies

Data from different centers will be pooled.

4.5 Multiple comparisons/multiplicity

No statistical testing is planned; therefore, this section is not applicable.

4.6 Use of an efficacy subset of subjects

All efficacy analyses will be performed on the FAS. No further efficacy subsets are defined for this study.

4.7 Active-control studies intended to show equivalence

Not applicable.

4.8 Examination of subgroups

Because of small number of subjects, no subgroup analyses will be performed.

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

The number of subjects screened, enrolled into the study, and subjects included in each analysis set will be summarized using ES. Subjects who completed or prematurely discontinued the study, as well as the reason for discontinuation, will be presented for the SS. The discontinuations due to AEs will be summarized in a separate table for the SS.

The number of subjects who are ongoing at the time of the clinical cutoff will be mentioned for any interim analysis.

In addition, the following listings will be provided for the ES:

- Subject disposition
- Study discontinuation
- Subject visit dates
- Subject analysis sets

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 (inclusion criteria, exclusion criteria, withdrawal criteria, prohibited concomitant medication use, incorrect treatment or dose, treatment non-compliance, procedural non-compliance), and description.

The number and percentage of subjects in the SS with important protocol deviations will be summarized overall and by category of protocol deviation. The denominator for percentages will

be the number of subjects in the SS. Protocol deviations will only be summarized for the final analysis.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics

A by-subject listing of demographic characteristics at the time of entry into the EP0073 study will be presented 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).

Baseline demographic characteristics obtained at the Entry Visit (apart from the date of birth) will be summarized for the SS for all subjects.

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 in a separate listing.

6.2 Medical history and concomitant diseases

Medical history and ongoing medical conditions for EP0073 will be listed and summarized for the SS 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.

The summary of medical history will be based on the medical history at the time of entry into EP0069 and any updates at EV.

Concomitant medical procedures carried out during the study will be listed for the SS.

6.2.1 History of epilepsy

All of the following are summarized using data collected at the time of entry into the EP0069 study. The history of epilepsy will be listed and summarized for all subjects in the SS.

Epileptic seizure profile

The number and percentage of subjects experiencing each seizure type at any time prior to the study entry will be summarized for the SS based on the ILAE Seizure Classification History EP0069 eCRF (historical seizures count).

The overall number and percentage of subjects with a history of type I seizures and the overall number and percentage of subjects with a history of type II seizures will also be summarized. A subject will be classified as having a history of type I seizures if the subject has a history of IA, IA1, IA2, IA3, IA4, IB, IB1, IB2, or IC seizures. A subject will be classified as having a history of type II seizures if the subject has a history of IIA, IIB, IIC, IID, IIE, or IIF seizures.

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 relative to the Entry Visit of EP0073 (ie, Entry Visit of EP0073 minus the date of the first epileptic seizure plus 1 divided by 365.25), age at onset of first seizure relative to the Entry Visit of EP0073, and percent of life with epilepsy relative to the Entry Visit of EP0073, will be summarized for the SS.

6.3 Other Baseline Characteristics

The following data collected at the time of entry into the EP0069 study will be summarized for the SS. The parameters derived in EP0069 will be directly used.

Number of past AEDs

The number of past AEDs taken prior to EP0069 will be summarized for the SS based on the following categorization: <4, 4 or 5, 6 or 7, 8 to 10, >10 AEDs.

Number of prior AEDs

The number of AEDs taken prior to EP0069 will be summarized for the SS based on the following categorization: <4, 4 or 5, 6 or 7, 8 to 10, >10 AEDs.

Use of vagus nerve stimulation

The number and percentage of subjects with active vagus nerve stimulation (VNS), and the number and percentage of subjects with no VNS implant or a non-active VNS implant prior to EP0069 will be summarized for the SS.

Number of AEDs taken at EP0069 study entry

The number and percentage of subjects taking 1, 2, and ≥3 AEDs at the time of EP0069 study entry will be summarized for the SS.

Levetiracetam use at EP0069 study entry

The number and percentage of subjects in each LEV-use category at EP0069 study entry will be summarized for the SS:

LEV prior and current use (concomitant use of LEV at study entry).

LEV Prior Use Only=History of prior LEV use and must have discontinued 4 weeks prior to study entry.

LEV Naïve=No history of prior LEV use, and no use at study entry.

6.4 Concomitant medications

The medications will be classified as AEDs or non-AEDs. For interim analyses, any non-coded terms will report the levels as UNCODED in the listing and table.

Medications will be considered as concomitant if

- the start date of the medication is on or after the date of first dose of UCB0942 in EP0073 and the start date is not after the date of last dose in EP0073
- Or the start date is prior to the first dose of UCB0942 in EP0073 but the stop date is after the first dose in EP0073 or ongoing.

6.4.1 Non- Antiepileptic drugs

All concomitant non-AED medications will be listed for the SS by WHODD Anatomical Main Group [Level 1], Therapeutic Subgroup [Level 2], PT and reported term.

The number and percentage of subjects taking concomitant non-AED medications during EP0073will be summarized separately for the SS by WHODD Anatomical Main Group [Level 1], Therapeutic Subgroup [Level 2], and PT for the whole study period.

6.4.2 Concomitant AEDs

Concomitant AED medications will be listed separately for the SS by WHODD Therapeutic Subgroup [Level 2], Chemical [Level 4], PT and reported term.

The number and percentage of subjects taking concomitant AED medications will be summarized by chemical/therapeutic/pharmacological subgroup (ATC classification level 4), and preferred drug name for the SS.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Information reported on the CRF regarding tablets/bottles dispensed and returned will be reported in subject data listings. Treatment compliance will be evaluated through the review of important protocol deviations.

8 EFFICACY ANALYSES

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

The derivations of 28-day adjusted seizure frequency are described in detail in Section 3.10.1. All summaries of efficacy data are descriptive. No statistical testing will be performed.

8.1 Statistical analysis of the primary efficacy variable

A 75% responder is defined as a subject with a ≥75% reduction in observable focal-onset seizure (Type IA1, IB, and IC) frequency relative to the EP0069 2-week Prospective Outpatient Baseline Period. Seizure frequency will be standardized to a 28-day duration.

The primary efficacy variable is the 75%RR and will be summarized by 3-month intervals over the Evaluation Period and by complete cohort using descriptive statistics.

8.1.1 Supportive analysis

The 75% RR will be calculated using all Type I seizures and will be summarized by 3-month intervals over the Evaluation Period using descriptive statistics.

The primary analysis described in Section 8.1 will be repeated for the 75% RR, calculated using all Type I seizures.

8.2 Statistical analysis of the secondary efficacy variables

8.2.1 Observable focal-onset seizure frequency

Twenty-eight day adjusted observable focal-onset seizure frequency (Type IA1+IB+IC) will be summarized with quantitative descriptive statistics for all subjects for the EP0069 2-week Prospective Outpatient Baseline Period by 3-month time intervals and by completer cohort over the Evaluation Period.

8.2.2 Focal-onset seizure frequency by seizure type

The summaries described in Section 8.2.1 will be repeated for all Type I seizures and by seizure types IA1, IB, IC.

8.2.3 Percent reduction in focal-onset seizure frequency

The percent reduction in observable focal-onset seizure (Type IA1+IB+IC) and All Type I seizure frequency from the 2-week Prospective Outpatient Baseline Period to 3-month time intervals over the Evaluation Period will be computed as defined in Section 3.10.1.

Percent reduction from the 2-week Prospective Outpatient Baseline for observable focal-onset seizure and All Type I seizure frequency will be summarized using quantitative descriptive statistics by 3-month time intervals and by completer cohort over the Evaluation Period.

8.2.4 50%RR on percent reduction in 28-day observable focal-onset seizure frequency

A 50% responder is defined as a subject with a ≥50% reduction in observable focal-onset seizure and all Type I seizure frequency relative to the EP0069 2-week Prospective Outpatient Baseline Period. Seizure frequency will be standardized to a 28-day duration.

The 50% responder rate (50%RR) will be calculated for 3-month time intervals over the Evaluation Period and by completer cohort and will be summarized using descriptive statistics.

8.2.5 Percentage of seizure free days

The percentage of seizure free days will be listed and tabulated by 3-month intervals over the Evaluation Period and by complete cohort in frequency tables.

8.2.6 Seizure freedom

The seizure freedom rate will be calculated and summarized over the Evaluation Period and by completer cohort.

8.2.7 Quality of Life

The observed value and the change from Baseline for the QOLIE-31-P total score and its sub-scores (Seizure Worry, Daily Activities/Social Function, Energy/Fatigue, Emotional Well-Being, Cognitive Function, Medication Effects, Overall Quality of Life, and Health Status)

will be summarized for all available visits (Month 3, 7, 13, 19, 25, 31, 37, 43, 49, 55 and 58) for the FAS. Only subjects with a non-missing change from the EP0069 Baseline will be summarized at each timepoint.

The observed ranks for the prioritization items (Seizure Worry, Daily Activities/Social Function, Energy/Fatigue, Emotional Well-Being, Cognitive Function, Medication Effects, and Overall Quality of Life) will be summarized at all available timepoints as above and for all subjects and by study visit cohort as defined above in separate tables. Changes from Baseline will not be summarized, and only the numbers of subjects and sample means will be presented.

The QOLIE-31-P mean change from Baseline for the total score and the sub-scores will be plotted in line plots with 95% CIs (assuming normally distributed data) for the whole study period.

The observed value and the change from Baseline for the post-baseline LOCF imputed values for the QOLIE-31-P total score and its sub-scores at Month 13 (V9, YEV) will be summarized for the FAS.

8.2.8 Time to discontinuation

Kaplan-Meier estimates of the percentage of subjects completing 3, 6, 12, 18, 24, 36, 48, and 60 months of treatment will be provided. The corresponding Kaplan-Meier plot will also be provided. For subjects who discontinued from the study, the event date is set to the date of last dose of UCB0942 and the time to event will be calculated as the date of last dose minus the date of first dose of UCB0942 in EP0073 plus 1. Subjects who completed the study will be censored as of the date of last dose of UCB0942. At a clinical cutoff, subjects who are ongoing will be censored as of the date of last dose of UCB0942 defined for the interim analyses (Section 3.2.2).

9 PHARMACOKINETICS

This data may be used for any refinement of the UCB0942 population PK modeling. The population PK analysis is outside the scope of this SAP.

Individual PK data will be reported for the FAS and the analyses will be reported for the PK-PPS.

9.1 Plasma concentrations

Plasma concentrations of UCB0942, [redacted], and [redacted] will be determined from blood samples obtained in the study during the first year (V3, V4, V5, V6, V7, V8, V9).

The individual concentrations of UCB0942, [redacted], and [redacted] will be listed for the FAS with blood sampling dates/times and elapsed time from last administration. Unless otherwise stated, measured values below the limit of quantification (BLQ) will be reported as LLOQ/2.

9.2 Population pharmacokinetics

If appropriate, a population PK analysis of UCB0942 and identified active metabolites, may be performed using non-linear mixed effects modeling within the population software (NONMEM) aimed at identifying relevant covariates (demographic variables, other AEDs). An evaluation of longer term (up to 1 year) exposure-response relationships to support the understanding of the

clinical efficacy profile of UCB0942 may be undertaken. These population analyses 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.

10 SAFETY ANALYSES

Safety is assessed with AEs, laboratory tests (blood chemistry, hematology, urinalysis, and pregnancy test), vital signs, body weight, ECGs, physical examination, psychiatric assessment using the BPRS, cognition/memory assessment using the MMSE, withdrawal symptoms using CIWA-B, echocardiography and neurological examination. Summary tables will be provided for AEs; blood chemistry, hematology, urinalysis, and vital signs, body weight, ECGs, and echocardiography. No summary tables will be provided for pregnancy testing, physical examination, and neurological examination.

All safety summaries will be based on the SS.

10.1 Extent of exposure

All UCB0942 administration information will be listed by subject.

A daily dose will be calculated for each study day from the day of first dose of UCB0942 to the day of last dose of UCB0942 for the purposes of calculating modal dose. Daily dose will be calculated as the sum of the AM and PM dose for each day.

Modal daily doses will be calculated across all study days on or after the day of first dose of UCB0942 and up to and including the day of last dose of UCB0942. Modal daily dose is the most frequently taken daily dose during this period. In the event of a tie, the modal dose will be set to the lower of the tied doses. Modal daily dose will be categorized as ≤200mg/day, >200mg/day to ≤400mg/day, >400mg/day to ≤600mg/day, >600mg/day to ≤800mg/day, and >800mg/day.

For subjects who completed or discontinued from the study, the overall duration of exposure will be calculated as the date of last dose of UCB0942 minus the date of first dose of UCB0942 in EP0073 plus 1 day. For ongoing subjects at a clinical cutoff, the duration of exposure will be calculated based on the date of last dose of UCB0942 defined for the interim analyses (Section 3.2.2). Subject years of exposure will be calculated by summing the exposure duration in days for all subjects being summarized and dividing the resulting value by 365.25.

The number and percentage of subjects exposed to UCB0942 will be summarized overall and by modal dose category. The number and percentage of subjects exposed for ≥3, ≥6, ≥12, ≥18, ≥24, ≥36, ≥48, and ≥60 months will be summarized.

10.2 Adverse events

Adverse events that occurred up to the first EP0073 UCB0942 administration will be recorded in the EP0069 database. Adverse events that occurred from the first EP0073 UCB0942 administration until study completion or study termination will be captured in the EP0073 database. All AEs will be coded using the latest available version of MedDRA and will be categorized by intensity (mild/moderate/severe).

10.2.1 Definition of treatment-emergent AE

A treatment-emergent adverse event (TEAE) is defined as AEs that started on or after the first dose of UCB0942 in EP0073 or AEs whose intensity worsened on or after the date of first dose of UCB0942 in EP0073.

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. AEs with an incomplete onset date will be classified as TEAEs if the month and year of onset (when only the month and year are specified) is the same as the month and year of the first UCB0942 dose or the year of onset (when only year is specified) is the same as the year of first UCB0942 dose. TEAEs are assigned into an analysis period or time interval based on the onset date.

10.2.2 General summaries of TEAEs

Listings will be provided for all AEs, SAEs, AEs leading to discontinuation (ie, drop out), and AEs leading to death by subject for the SS.

Unless noted otherwise, TEAEs during the study (including the Taper and SFU Periods) will be summarized. At the time of a clinical cutoff, TEAEs with onset date prior to or on the clinical cutoff date will be summarized.

The following tabular summaries will be presented for the SS:

- Ongoing AEs at EP0073 study entry. Of note, this table will not be included in the interim analyses.
- Incidence of TEAEs during the Study - Overview
- Incidence of TEAEs by 3-month time interval during the On-Treatment Period. TEAEs with onset date prior to or on the date of last dose of UCB0942 will be included in the summary.
- Incidence of TEAEs by Period (Entire Study, Evaluation, Taper, SFU)
- Incidence of Serious TEAEs
- Incidence of TEAEs by Relationship
- Incidence of SAEs by Relationship. Of note, this table is needed for data transparency reporting and will not be included in the interim analyses.
- Incidence of Fatal TEAEs by Relationship. Of note, this table is needed for data transparency reporting and will not be included in the interim analyses.
- Incidence of TEAEs by Maximum Intensity
- Incidence of TEAEs leading to discontinuation (ie, drop out)
- Incidence of TEAEs occurring in at least 5% of Subjects
- Incidence of TEAEs by Dose at Onset during the On-Treatment Period. TEAEs with onset date prior to or on the date of last dose of UCB0942 will be included in the summary.
- Incidence of Non-Serious TEAEs above the Threshold of 5% of Subjects. Of note, this table is needed for data transparency reporting and will not be included in the interim analyses.

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 of relationship to study treatment per the investigator, the following relationships will be summarized: 'Not related', 'Related'. 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 of maximum 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 alphabetically by SOC and by decreasing frequency for the PT within SOC.

10.3 Clinical laboratory evaluations

Clinical laboratory parameters (clinical chemistry, hematology, urinalysis) are assessed at all FEVs, YEVs, EDVs, and at FV and may also be assessed at Unscheduled Visits.

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 10-1), and changes from the EP0069 Baseline for numeric parameters will be listed and summarized by visit, including Last Value, minimal, and maximum value. Laboratory values will be grouped according to the laboratory function panel shown in Table 10-1) and flagged based on the possibly clinically significant treatment emergent (PCST) criteria (see Section 12.1), if applicable. Treatment-emergent values are those occurring any time after the first dose of UCB0942 in EP0073. The number and percentage of subjects with a PCST value will be summarized for the overall On-Treatment Period and by 3-month. Percentages will be relative to the number of subjects with an assessment during the interval. Subject numbers for those meeting the PCST will also be presented.

Possibly clinically significant treatment emergent criteria are based on FDA Division of Neuropharmacologic Drug Products guidelines with some UCB-defined additions (Section 12.1).

Additional laboratory tests performed will be listed, but will not be summarized.

Table Error! No text of specified style in document.**–1: Clinical laboratory measurements**

Category	Panel	Variable
Hematology	Red blood cell	RBC count, hemoglobin, hematocrit, MCH, MCHC, MCV
	White blood cell	WBC count, basophils, eosinophils, lymphocytes, monocytes, neutrophils
	Platelet	Platelet count
Clinical Chemistry	Electrolytes	Sodium, chloride, potassium
	Minerals	Calcium, magnesium
	Metabolic	Glucose
	Liver function	ALP, ALT, AST, total bilirubin, LDH
	Kidney function	BUN or urea, creatinine
Urinalysis	Dipstick	Total protein, pH, glucose, WBC, RBC

ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; WBC=white blood cell.

10.3.1 Subjects with potential drug-induced liver injury (PDILI)

There are specific criteria described in the protocol Section 11.6.1 to evaluate subjects for potential drug-induced liver injury (PDILI). A summary of number and percent of subjects meeting PDILI criteria will be provided along with the subject numbers. Data collected for PDILI subjects will be listed.

A summary table highlighting the potential cases of Hy's Law will be presented. Potential cases of Hy's Law is defined as:

- AST >3xULN or ALT >3xULN and
- Total Bilirubin >2xULN

In order to meet the above criteria, a subject must experience the elevation in bilirubin and ALT or AST at the same visit. For example, a subject who experiences a >=2 x ULN elevation of bilirubin at one visit and a 3 x ULN elevation in ALT (or AST) at a subsequent visit has not fulfilled the Hy's law criteria.

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

10.4.1 Vital signs

Vital signs (including weight) are assessed at all FEVs, MEVs, YEVs, EDVs, and at FV, and may also be assessed at Unscheduled Visits.

A by-subject listing of all observed vital measurements (including systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate [PR], respiratory rate, weight) and changes from

EP0069 Baseline will be listed. This listing will include a flag for measurements identified as being abnormal by the criteria outlined in Section 12.2.

Measured values, and changes from Baseline for all vital sign measurements (excluding temperature) will be summarized by visit, including Last Value, maximum value, and minimal value.

The number and percentage of subjects with abnormal vital signs will be summarized for the overall On-Treatment Period and by 3-month interval. Percentages will be relative to the number of subjects with an assessment during the interval. Subject numbers meeting the abnormal criteria will also be presented.

10.4.2 Electrocardiograms

Observed ECG data (heart rate, PR, QT, QTcB [QT using Bazett's], QTcF [QT using Fridericia's formula], and QRS) and changes from EP0069 Baseline will be listed. The listing will include a flag for measurements identified as being abnormal by the criteria outlined in Section 12.3.

Measured values, and changes from Baseline for all vital sign measurements will be summarized by visit, including Last Value, maximum value, and minimal value. 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 visit. Percentages will be relative to the number of subjects with an ECG result at each visit.

The number and percentage of subjects with an abnormal ECG value will be summarized for the overall On-Treatment Period and by 3-months interval. Percentages will be relative to the number of subjects with an assessment during the interval. Subject numbers meeting the abnormal criteria will also be presented.

ECG findings will be listed and summarized by visit.

10.4.3 Doppler echocardiography

Doppler echocardiography results (including valvular and other cardiac abnormalities) will be listed and summarized by visit.

10.4.4 Physical examination

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

10.4.5 Columbia-Suicide Severity Rating Scale

C-SSRS data will be provided in subject listing for subjects with suicidal ideation and suicide behavior.

10.4.6 Neurological examination

A listing of abnormal neurological examination findings will be provided; 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) observed results and changes from EP0069 Baseline will be listed. The changes from EP0069 Baseline in the total scores will be summarized.

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

10.4.8 Employment and living status and epilepsy surgery status

Employment and living status and epilepsy surgery status data at Visit 2 will be listed.

11 REFERENCES

Cramer JA, Perrine K, Devinsky O, Bryant-Comstock L, Meador K, Hermann B. Development and cross-cultural translations of a 31-item quality of life in epilepsy inventory. Epilepsia. 1998:39(1):81-8.

12 APPENDICES

12.1 PCST Criteria for Hematology, Serum Chemistry and Urinalysis Parameters

12.1.1 Hematology

PARAMETER	*AGE RANGE*	*UNIT (conventional)*	*ABNORMALITY CRITERIA (conventional)*	*UNIT (standard)*	*ABNORMALITY CRITERIA (standard)*
Hematocrit	<2y	%	≤27 >45	%	≤27 >45
	2y - <18y		≤29 >47		≤29 >47
	≥18y		≤85% of LLN ≥115% of ULN)		≤85% of LLN ≥115% of ULN
Hemoglobin	<2y	g/dL	≤9.0 >15.0	g/L	≤90 >150
	2y - <18y		≤9.5 >16.0		≤95 >160
	≥18y		≤85% of LLN ≥115% of ULN		≤85% of LLN ≥115% of ULN
WBC/Leukocytes	<12y	10^9/L	<3.5 >15.0	G/L	<3.5 >15.0
	≥12y		<3.0 >12.0		<3.0 >12.0

PARAMETER	*AGE RANGE*	*UNIT (conventional)*	*ABNORMALITY CRITERIA (conventional)*	*UNIT (standard)*	*ABNORMALITY CRITERIA (standard)*
Neutrophils Absolute	>1m	10^9/L	<1.5	G/L	<1.5
Lymphocytes	<6m	%	≤30.0	%	≤30.0
	6m - <6y		≤22.0		≤22.0
	6y - <18y		≤12.0 ≥80.0		≤12.0 ≥80.0
	≥18y		≤10.0 ≥80.0		≤10.0 ≥80.0
Basophils	>1m	%	≥3.0	%	≥3.0
Eosinophils	>1m	%	≥10.0	%	≥10.0
Monocytes	>1m	%	≥20.0	%	≥20.0
Platelets	>1m	10^9/L	≤100 >600	G/L	≤100 >600
RBC/ Erythrocytes	<2y	10^{12}/L	<3.0	T/L	<3.0
	≥2y		<3.5		<3.5

Abbreviations: F=female; M=male; m=month; y= year. A month is defined as 30 days; a year is defined as 365.25 days.

12.1.2 Blood chemistry

PARAMETER	*AGE RANGE*	*UNIT (conventional)*	*ABNORMALITY CRITERIA (conventional)*	*UNIT (standard)*	*ABNORMALITY CRITERIA (standard)*
AST (SGOT)	<14y	U/L	>180	U/L	>180
	≥14y		>144		>144
ALT (SGPT)	1y - <18y	U/L	>90	U/L	>90
	≥18y		>123		>123
Alkaline Phosphatase	<4y	U/L	>690	U/L	>690
	4y - <10y		>834		>834
	10y - <18y		>1174		>1174
	≥18y		>432 (F) >933 (M)		>432 (F) >933 (M)
GGT	<6m	U/L	>522	U/L	>522
	6m - <1y		>279		>279
	1y - <13y		>66		>66

PARAMETER	*AGE RANGE*	*UNIT (conventional)*	*ABNORMALITY CRITERIA (conventional)*	*UNIT (standard)*	*ABNORMALITY CRITERIA (standard)*
	13y - <18y		>126		>126
	≥18y		>255		>255
Total Bilirubin	>1m	mg/dL	≥1.5	umol/L	≥25.656
Total Protein	2m-<1y	g/dL	<3.0 >10.0	g/L	<30 >100
	≥1y		<4.3 >10.0		<43 >100
Albumin	<1y	g/dL	<1.6 >6.0	g/L	<16 >60
	≥1y		<2.4 >7.0		<24 >70
BUN	<1y	mg/dL	>21	mmol/L	>7.497
	≥1y		>30		>10.71
Urea	<1y	mg/dL	>42	mmol/L	>7.014
	≥1y		>60		>10.02

PARAMETER	*AGE RANGE*	*UNIT (conventional)*	*ABNORMALITY CRITERIA (conventional)*	*UNIT (standard)*	*ABNORMALITY CRITERIA (standard)*
Creatinine	1y - <10y	mg/dL	>0.9	umol/L	>79.56
	10y - <16y		>1.4		>123.76
	≥16y		>1.6		>141.44
Creatinine Clearance*	All	mL/min	<70	mL/s	<1.169
Calcium	<1y	mg/dL	<6.9 >12.2	mmol/L	<1.725 >3.05
	1y - <18y		<7.4 >11.7		<1.85 >2.925
	≥18y		<7.9 >11.1		≤1.975 ≥2.775
Phosphorous	<1y	mg/dL	<1.8 >8.2	mmol/L	<0.5814 >2.6486
	≥1y		<1.8 >7.4		<0.5814 >2.3902
Potassium	<1y	mEq/L	<3.0 >6.5	mmol/L	<3.0 >6.5

PARAMETER	*AGE RANGE*	*UNIT (conventional)*	*ABNORMALITY CRITERIA (conventional)*	*UNIT (standard)*	*ABNORMALITY CRITERIA (standard)*
	≥1y		<3.0 >5.8		<3.0 >5.8
Sodium	>1m	mEq/L	≤130 ≥150	mmol/L	≤130 ≥150
Glucose	>1m	mg/dL	<50 >180	mmol/L	<2.775 >9.99
Total Cholesterol	1y - <18y	mg/dL	>250	mmol/L	>6.475
	≥18y		>300		>7.77
LDL (calculated)	1y - <18y	mg/dL	>140	mmol/L	>3.626
	≥18y		>200		>5.18
HDL	≤2y	mg/dL	<10	mmol/L	<0.259
	>2y		<20		<0.518
Triglycerides	<1y	mg/dL	>750	mmol/L	>8.475
	≥1y		>250		>2.825
Uric Acid	<1y	mg/dL	>7.7	umol/L	>457.996

PARAMETER	*AGE RANGE*	*UNIT (conventional)*	*ABNORMALITY CRITERIA (conventional)*	*UNIT (standard)*	*ABNORMALITY CRITERIA (standard)*
	1y - <13y		>6.5		>386.62
	13y - <18y		>8.6		>511.528
	≥18y		>6.8 (F) >9.6 (M)		>404.464 (F) >571.008 (M)
Thyroxine (T4)	<1y	ug/dL	≤4.3 ≥18.4	nmol/L	≤55.3453 ≥236.8264
	≥1y		≤3.8 ≥13.5		≤48.9098 ≥173.7585
Globulin	<1y	g/dL	<1.0 >3.8	g/L	<10 >38
	≥1y		<1.2 >4.4		<12 >44

Abbreviations: ALT= alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; dL = deciliter; F=female; GGT: gamma-glutamyltransferase; HDL = high density lipoprotein; LDL = low density lipoprotein; L = liter; M=male; m = month (a month is defined as 30 days) mg = milligram; mmol = millimoles; µg = microgram; U = unit; ULN = upper limit of normal; y = years (a year is defined as 365.25 days). *Schwartz equation (patients <12): Cr Cl ml/min = [Height (cm) * 0.55] / serum creatinine 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

12.1.3 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 two 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

12.2 VITAL SIGN ASSESSMENTS - ABNORMAL

Abnormality criteria to be applied in the assessment of vital signs parameter values are given below.

PARAMETER	*AGE RANGE*	*ABNORMALITY CRITERIA*
Pulse Rate (beats/minute)	<6m	<100 >180
	6m - <3y	<90 >150
	3y - <12y	<60 >130
	12y - <17y	<50 >120
	≥17y	<50 and a decrease from Baseline of ≥15 >120 and an increase from Baseline of ≥15
Systolic Blood Pressure (mmHg)	<6m	<60 >100
	6m - <3y	<70 >120
	3y - <12y	<80 >140
	12y - <17y	<90 >160
	≥17y	≤ 90 and a decrease from Baseline of ≥20 ≥ 180 and an increase from Baseline of ≥20
Diastolic Blood Pressure (mmHg)	<6m	<40 >65
	6m - <3y	<45 >75
	3y - <12y	<50 >80
	12y - <17y	<50 >105

	≥17y	<50 and a decrease from Baseline of ≥15 >105 and an increase from Baseline of ≥ 15
Respiratory Rate (breaths/minute)	<6m	<25 >55
	6m - <3y	<20 >45
	3y - <12y	<15 >35
	≥12y	<10 >25
Body Weight	1m - <17y	<3% or >97% of the normal body weight growth curve ranges based on gender and the age of subject on date of weight assessment[a]
	≥17y	≥ 10% change from Baseline (an increase or a decrease)[a]

Abbreviations: m = month, y = year. A month is defined as 30 days; a year is defined as 365.25 days.

[a]source: http://www.cdc.gov/growthcharts/

12.3 ELECTROCARDIOGRAM (ECG) – ABNORMAL

Abnormality criteria to be applied in the assessment of ECG parameter values are given below:

Parameter	Age	Abnormality Criteria
QT interval (ms)	1m-<12y	>500
	>12y	>500 or ≥60ms increase from Baseline
QTc(F) (ms)	<6m	>490, or >15% increase from Baseline
	6m-<3y	>440, or >15% increase from Baseline
	3y-<12y	>440, or >15% increase from Baseline
	>12y- <17y	>440, or >15% increase from Baseline
	≥17y	>500 or ≥60ms increase from Baseline
QTc(B) (ms)	<6m	>490, or >15% increase from Baseline
	6m-<3y	>450, or >15% increase from Baseline
	3m-<12y	>450, or >15% increase from Baseline
	>12y- <17y	>450, or >15% increase from Baseline
	≥17y	>500 or ≥60ms increase from Baseline
PR interval (ms)	<6m	>150, or >25% increase from Baseline
	6m-<3y	>170, or >25% increase from Baseline
	3y-<12y	>180, or >25% increase from Baseline
	>12y - <17y	>200, or >25% increase from Baseline
	≥17y	Treatment-emergent value >200, >220, >250
QRS interval (ms)	<6m	>90, or >25% increase from Baseline
	6m-<3y	>90, or >25% increase from Baseline
	3y-<12y	>100, or >25% increase from Baseline
	>12y - <17y	>110, or >25% increase from Baseline
	≥17y	Treatment-emergent value >100, >120, >140
Heart rate (bpm)	<6m	<100, >180
	6m-<3y	<90, >150
	3y-<12y	<60, >130
	>12y	<50, >120

Abbreviations: bpm = beats per minute; m = months; ms = milliseconds; QTc = corrected QT interval; y = years. A month is defined as 30 days; a year is defined as 365.25 days.

Note: Treatment-emergent is defined as meeting the criteria at any post-Baseline visit and not meeting the same criteria during Baseline

13 AMENDMENT(S) TO THE SAP

13.1 Amendment 1

Rationale for the amendment

The primary purpose of this amendment is to add the analyses for Potentially Drug Induced Liver Injury (PDILI) and provide clarifications to the planned analyses according to the current program standards.

Modifications and Changes

Major specific changes

Change #1

3.2.1 Analysis timepoints

3.2.1.1 First and last dose of UCB0942

Throughout this SAP, and unless otherwise stated, the "first dose of UCB0942" refers to the first UCB0942 administration in the EP0073 study. This is the first administration after the subject has filled in the EP0069 completion form and has returned the unused EP0069 UCB0942 tablets and empty containers. The first UCB0942 administration is planned to be the evening dose of the Entry Visit (V2; ie, not the first UCB0942 administration from any previous studies that subjects might have participated). Throughout this SAP, the "last dose of UCB0942" refers to the last dose of UCB0942 that was administered at any EP0073 study period; Evaluation or Taper Period.

3.2.1.2 Relative day

The relative day of an event will be derived with the start date of first UCB0942 administration in EP0073 as reference date, up to and including the last day of UCB0942 administration.

Relative days for an event or measurement occurring before the reference date will have a '-' prefix and will be 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 UCB0942 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 UCB0942 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)]

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.

3.2.1.3 Study periods

For seizure endpoints and safety parameters, the Baseline used is the EP0069 2 week Prospective Outpatient Baseline Period.

The study is divided into 4 periods: Screening Period, Evaluation Period, Taper Period, and SFU Period. The following periods and sub-periods will be considered in the definition of efficacy and safety variables (for details see Section 2.2.2.3):

- A 2-week Screening Period from V13 to V15 (Days OP43 to OP57) of the 8-week Outpatient Maintenance Period of the EP0069 study.
- Evaluation Period: The approximate five-year Treatment Period, with the following sub periods.
  - 1st Year
  - 2nd Year
  - 3nd Year
  - 4th Year
  - 5th Year
- Taper Period.
- SFU Period.

3.2.1.4 Monthly time intervals

A month is defined as 30 days and time intervals based on monthly durations are defined as a multiple of 30 days (eg, 12 months is defined as 360 days). The following definitions of 3-month and 6-month intervals are based on 30-day months where the date of first dose of UCB0942 in EP0073 is Day 1:

Interval Duration Definition:

- Months 1-3 Days 1-90
- Months 4-6 Days 91-180
- Months 7-9 Days 181-270
- Months 10-12 Days 271-360

Subsequently, 3- and 6-month intervals are defined in a similar manner. Three-month intervals will be used for analysis of efficacy outcomes and AEs.

For the analysis of efficacy outcomes, a subject is included in the analysis for a 3-month interval if the subject remained in the study for at least 83 days of the 3-month interval and the subject diary was completed for at least 1 day during the 3-month interval.

For the analysis of AEs, a subject is included in the analysis for a 3-month interval if the subject is ongoing for at least one (whole or partial) day of the interval.

3.2.1.5 Last Value on UCB0942 Treatment

Last Value for safety parameters (such as clinical laboratory parameters, vital signs, ECGs) is the last available result obtained after the first dose of UCB0942 and prior to or on the date of last dose of UCB0942. All scheduled and unscheduled assessments within this time period will be considered. Last Value will be determined separately for each laboratory parameter for hematology, chemistry, urinalysis assessments. A similar definition applies for summaries based on regulatory submission interim cutoffs for subjects who have discontinued the study prior to the clinical cutoff date. For subjects who are ongoing at the time of the clinical cutoff date, Last Value will be the last result obtained from any scheduled or unscheduled visit prior to or on the date of the clinical cutoff.

3.2.1.6 Exposure duration and exposure duration cohorts

At the final analysis, the overall duration of exposure (or On Treatment Period) will be calculated as the date of last dose of UCB0942 minus the date of first dose of UCB0942 in EP0073 plus 1 day. The following rules apply for analyses based on clinical cutoffs. For subjects who have discontinued prior to or on the date of the clinical cutoff, the overall duration of exposure will be calculated as the date of last dose of UCB0942 on or prior to the date of the clinical cutoff minus the date of first dose of UCB0942 plus 1 day. For subjects who are ongoing at the time of the clinical cutoff, the overall duration of exposure will be calculated as the date of last scheduled or unscheduled visit on or prior to the date of the clinical cutoff minus the date of first dose of UCB0942 plus 1 day.

Each subject will be classified into one or more of the following exposure duration cohorts based on the duration of UCB0942 exposure as calculated above:

All Subjects: ≥1 day

≥3 months = ≥90 days

≥6 months = ≥180 days

≥12 months = ≥360 days

≥18 months = ≥540 days

≥24 months = ≥720 days

and then yearly ≥ 3, 4, 5 years

For summaries based on clinical cutoffs, this categorization will continue in 6-month increments past 12 months up to a timepoint that will be determined based on cumulative exposure at the time of the clinical cutoff.

3.2.1.7 Study visit cohorts

Study visit cohorts are defined for summaries of QOLIE-31-P. Six-month, 12-month, 18-month, and 24-month, 3-, 4-, 5 year cohorts are defined. Subjects will be classified into a study visit cohort if they attend the scheduled visit at the timepoint defined by the cohort. For example, subjects will be included in the 18-month study visit cohort if they attend the scheduled visit at 3 months (i.e., FEV at Month 3, V5). Subjects may be classified in more than 1 cohort. Generally, subjects included in a cohort for a later visit will be included in all earlier study visit cohorts (e.g., 6-month and 12-month study visit cohorts for subjects in the 18-month study visit cohort), although this may not be the case in the event of a missed visit or if an unscheduled visit is conducted in lieu of a scheduled visit.

Has been changed to:

3.2.1 Analysis periods

Unless noted otherwise, Baseline is the EP0069 2 week Prospective Outpatient Baseline Period.

The study is divided into 4 periods: Screening Period, Evaluation Period, Taper Period, and SFU Period. The following periods will be considered in the definition of efficacy and safety variables:

- A 2-week Screening Period from V13 to the day before V15 of the 8-week Outpatient Maintenance Period of the EP0069 study.
- Evaluation Period: Entry Visit (EV) to Last Evaluation Period Visit (LEPV) or Early Discontinuation Visit (EDV) or clinical data cutoff date if the subject is ongoing and does not have the EDV. The EV is also V15 of EP0069. Data in EP0073 database will be used in the analyses when possible.
- Taper Period: the day after LEPV or EDV to End of Taper Visit or clinical data cutoff date if the subject is ongoing.
- SFU Period: The day after the End of Taper Visit to date of final contact or clinical data cutoff date if the subject is ongoing.

In addition, the On-Treatment Period is defined as from the date of first dose to the date of last dose of UCB0942 in EP0073 (Section 3.2.2).

At the time of a clinical cutoff prior to the study completion, a subject will be classified as "discontinued" if the Study Completion CRF is available and the date of premature study termination is provided. All other subjects will be classified as "ongoing." Only the data on or prior to the clinical cutoff date will be included in the analyses.

3.2.2 First and last dose of UCB0942

Throughout this SAP, and unless otherwise stated, the first dose (of UCB0942) refers to the first UCB0942 administration in the EP0073 study reported on First Administration of Study Medication case report form (CRF). The last dose (of UCB0942) refers to the date of last administration of study medication reported on Study Completion CRF, at any EP0073 study period, Evaluation or Taper Period.

At the time of a clinical cutoff, for subjects who are ongoing and not in the SFU Period, the last dose of UCB0942 will be set to the date of the clinical cutoff for the interim analyses. For subjects who are ongoing and in the SFU Period (ie, had the End of Taper Visit) at the time of a clinical cutoff, the last dose of UCB0942 will be set to the last dosing date on the Drug Dosing Log CRF for the interim analyses.

3.2.3 Relative day

The relative day of an event will be derived with the start date of first UCB0942 administration in EP0073 as reference date, up to and including the last day of UCB0942 administration.

Relative days for an event or measurement occurring before the reference date will have a '-' prefix and will be 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 UCB0942 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 UCB0942 administration as reference date. 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)]

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.

3.2.4 Monthly time intervals

A month is defined as 30 days and time intervals based on monthly durations are defined as a multiple of 30 days (eg, 12 months is defined as 360 days).

Interval Duration Definition:

- Months 0-3: Days 1-90
- Months >3-6: Days 91-180
- Months >6-9: Days 181-270

- Months >9-12: Days 271-360

Subsequent 3-month intervals are defined in a similar manner.

For the analysis of efficacy variables during the Evaluation Period, 3-month intervals will be derived for the Evaluation Period. For the analysis of AEs and safety variables, 3-month intervals will be derived for the On-Treatment Period.

3.2.5 Last Value during the On-Treatment Period

Last Value for safety parameters (such as clinical laboratory parameters, vital signs, ECGs) is the last available result obtained prior to or on the date of last dose of UCB0942 in EP0073. All scheduled and unscheduled assessments within this time period will be considered. Last Value will be determined separately for each laboratory parameter for hematology, chemistry, urinalysis assessments. Similarly, the minimum and maximum values are defined as the minimum and maximum values prior to or on the date of last dose of UCB0942.

3.2.6 Completer Cohort

Because the duration of the Evaluation Period varies among the subjects, each subject will be classified into one or more of the following completer cohorts based on the duration of the Evaluation Period:

≥3 months : ≥90 days

≥6 months : ≥180 days

≥12 months : ≥360 days

≥18 months : ≥540 days

≥24 months : ≥720 days

≥36 months : ≥1080 days

≥48 months : ≥1140 days

≥60 months = ≥1800 days

The duration of the Evaluation Period is calculated as the date of the end of the Evaluation Period – EV +1. Selected efficacy variables will be analyzed by completer cohorts.

3.2.7 Mapping of data from early discontinuation visits

If an EDV occurs at the day of a scheduled visit, in-clinic safety and PK assessments should correspond to that scheduled visit. Safety assessments at an EDV that occurs on a day between two scheduled visits will be assigned to the next scheduled visit. No mapping will be performed for the seizure and QOLIE-31-P data collected at the EDV.

In the by-visit summary tables, only nominal (scheduled) visits (after mapping) where the assessment is scheduled will be included. Unscheduled visits will not be mapped to scheduled

visits. In the subject listing, data will be presented under the actual visits, including EDV and unscheduled visits.

Change #2

6.2 Medical history and concomitant diseases

Medical history and ongoing medical conditions for EP0073 will be listed and summarized for the SS 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 at the time of entry into the EP0073 study will be listed separately by the procedure reported term for the SS.

Concomitant medical procedures carried out during the study will be listed for the SS.

6.2.1 History of epilepsy

All of the following are summarized using data collected at the time of entry into the EP0069 study.

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

Etiology of epilepsy

The number and percentage of subjects with each type of etiology as specified in the EP0069 eCRF (genetic, congenital, etc) will be summarized for the FAS.

Epileptic seizure profile

The number and percentage of subjects experiencing each seizure type at any time prior to the study entry will be summarized for the FAS based on the ILAE Seizure Classification History EP0069 eCRF (historical seizures count).

The overall number and percentage of subjects with a history of type I seizures and the overall number and percentage of subjects with a history of type II seizures will also be summarized. A subject will be classified as having a history of type I seizures if the subject has a history of IA, IA1, IA2, IA3, IA4, IB, IB1, IB2, or IC seizures. A subject will be classified as having a history of type II seizures if the subject has a history of IIA, IIB, IIC, IID, IIE, or IIF seizures.

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.

Seizure types experienced during Baseline

The number and percentage of subjects experiencing each seizure type during the EP0069 2 week Prospective Outpatient 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 IV.

Subjects will be counted for all higher levels of seizure type categories corresponding to the seizure types or seizure sub-types reported on the EP0069 eCRF. For example, subjects with an IA1 seizure will be counted for types I and IA.

The Baseline 28 day adjusted POS frequency will also be summarized at Baseline.

6.3 Prior and concomitant medications

The medications will be classified as AEDs or non AEDs during the DEM.

For interim analyses, any non coded terms will report the levels as UNCODED in the listing.

Prior medication definition

'Prior medication' is any medication that started prior to the date of first UCB0942 administration in EP0073.

Concomitant medication definition

'Concomitant medication' is any medication that has been taken for at least 1 day between the first UCB0942 administration in EP0073 and the end of study. This definition includes the following:

- Prior medication not stopped before the date of the first UCB0942 administration in EP0073
- When the start date is between the date (including the date) of the first UCB0942 administration in EP0073 and the final study visit or, in case of early termination, on the date of the subject's last visit

Medications may be both prior and concomitant.

6.3.1 Non- Antiepileptic drugs

All non-AED medications will be listed for the SS by WHODD Anatomical Main Group [Level 1], Therapeutic Subgroup [Level 2], PT and reported term.

The number and percentage of subjects taking non-AED medications at entry into EP0069 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 at entry into EP0073 will be summarized separately for the SS by WHODD Anatomical Main Group [Level 1], Therapeutic Subgroup [Level 2], and PT for the whole study period.

6.3.2 Antiepileptic drugs

Prior and concomitant AED medications will be listed separately for the SS by WHODD Therapeutic Subgroup [Level 2], Chemical [Level 4], PT and reported term.

Prior AED Medications

The number and percentage of subjects taking AED medications prior to EP0073 will be summarized for the SS by PT. These are prior and concomitant AED medications from the EP0069 study.

Number of prior AEDs

The number of AEDs taken prior to EP0073 will be summarized for the SS based on the following categorization: <4, 4 or 5, 6 or 7, 8 to 10, >10 AEDs.

Previous AEDs by reason for AED discontinuation

The number and percentage of subjects by reason for discontinuation of previous AEDs prior to EP0073 will be summarized for the SS. Percentages for each reason for discontinuation will be relative to the number of subjects taking each AED.

Use of vagus nerve stimulation

The number and percentage of subjects with active vagus nerve stimulation (VNS), and the number and percentage of subjects with no VNS implant or a non active VNS implant prior to EP0073 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 EP0073 study entry

The number and percentage of subjects taking 1, 2, and ≥3 AEDs at the time of EP0073 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 EP0073 study entry

The number and percentage of subjects in each LEV use category at EP0073 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 during EP0073 will be summarized separately for the SS by PT for the whole study period.

Has been changed to:

6.2 Medical history and concomitant diseases

Medical history and ongoing medical conditions for EP0073 will be listed and summarized for the SS 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.

The summary of medical history will be based on the medical history at the time of entry into EP0069 and any updates at EV.

Concomitant medical procedures carried out during the study will be listed for the SS.

6.2.1 History of epilepsy

All of the following are summarized using data collected at the time of entry into the EP0069 study. The history of epilepsy will be listed and summarized for all subjects in the SS.

Epileptic seizure profile

The number and percentage of subjects experiencing each seizure type at any time prior to the study entry will be summarized for the SS based on the ILAE Seizure Classification History EP0069 eCRF (historical seizures count).

The overall number and percentage of subjects with a history of type I seizures and the overall number and percentage of subjects with a history of type II seizures will also be summarized. A subject will be classified as having a history of type I seizures if the subject has a history of IA, IA1, IA2, IA3, IA4, IB, IB1, IB2, or IC seizures. A subject will be classified as having a history of type II seizures if the subject has a history of IIA, IIB, IIC, IID, IIE, or IIF seizures.

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 relative to the Entry Visit of EP0073 (ie, Entry Visit of EP0073 minus the date of the first epileptic seizure plus 1 divided by 365.25), age at onset of first seizure relative to the Entry Visit of EP0073, and percent of life with epilepsy relative to the Entry Visit of EP0073, will be summarized for the SS.

6.3 Other Baseline Characteristics

The following data collected at the time of entry into the EP0069 study will be summarized for the SS. The parameters derived in EP0069 will be directly used.

Number of past AEDs

The number of past AEDs taken prior to EP0069 will be summarized for the SS based on the following categorization: <4, 4 or 5, 6 or 7, 8 to 10, >10 AEDs.

Number of prior AEDs

The number of AEDs taken prior to EP0069 will be summarized for the SS based on the following categorization: <4, 4 or 5, 6 or 7, 8 to 10, >10 AEDs.

Use of vagus nerve stimulation

The number and percentage of subjects with active vagus nerve stimulation (VNS), and the number and percentage of subjects with no VNS implant or a non active VNS implant prior to EP0069 will be summarized for the SS.

Number of AEDs taken at EP0069 study entry

The number and percentage of subjects taking 1, 2, and ≥3 AEDs at the time of EP0069 study entry will be summarized for the SS.

Levetiracetam use at EP0069 study entry

The number and percentage of subjects in each LEV use category at EP0069 study entry will be summarized for the SS:

LEV prior and current use (concomitant use of LEV at study entry).

LEV Prior Use Only=History of prior LEV use and must have discontinued 4 weeks prior to study entry.

LEV Naïve=No history of prior LEV use, and no use at study entry.

6.4 Concomitant medications

The medications will be classified as AEDs or non AEDs. For interim analyses, any non coded terms will report the levels as UNCODED in the listing and table.

Medications will be considered as concomitant if

- the start date of the medication is on or after the date of first dose of UCB0942 in EP0073 and the start date is not after the date of last dose in EP0073

- Or the start date is prior to the first dose of UCB0942 in EP0073 but the stop date is after the first dose in EP0073 or ongoing.

6.4.1 Non- Antiepileptic drugs

All concomitant non-AED medications will be listed for the SS by WHODD Anatomical Main Group [Level 1], Therapeutic Subgroup [Level 2], PT and reported term.

The number and percentage of subjects taking concomitant non-AED medications during EP0073will be summarized separately for the SS by WHODD Anatomical Main Group [Level 1], Therapeutic Subgroup [Level 2], and PT for the whole study period.

6.4.2 Concomitant AEDs

Concomitant AED medications will be listed separately for the SS by WHODD Therapeutic Subgroup [Level 2], Chemical [Level 4], PT and reported term.

The number and percentage of subjects taking concomitant AED medications will be summarized by chemical/therapeutic/pharmacological subgroup (ATC classification level 4), and preferred drug name for the SS.

Change #3

7 MEASUREMENTS OF TREATMENT COMPLIANCE

At each visit after UCB0942 is dispensed, subjects must return all unused UCB0942 and empty UCB0942 containers. 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. The number and percentage of subjects with compliance levels <75%, 75% to 120%, and >120% will be summarized for the first year.

Has been changed to:

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Information reported on the CRF regarding tablets/bottles dispensed and returned will be reported in subject data listings. Treatment compliance will be evaluated through the review of important protocol deviations.

Change #4

The following has been added:

8.2.8 Time to discontinuation

Kaplan-Meier estimates of the percentage of subjects completing 3, 6, 12, 18, 24, 36, 48, and 60 months of treatment will be provided. The corresponding Kaplan-Meier plot will also be provided. For subjects who discontinued from the study, the event date is set to the date of last dose of UCB0942 and the time to event will be calculated as the date of last dose minus the date of first dose of UCB0942 in EP0073 plus 1. Subjects who completed the study will be censored as of the date of last dose of UCB0942. At a clinical cutoff, subjects who are ongoing will be censored as of the date of last dose of UCB0942 defined for the interim analyses (Section 3.2.2).

Change #5

9.1 Non compartmental pharmacokinetics analyses

Plasma concentrations of UCB0942, [redacted], and [redacted] will be determined from blood samples obtained in the study during the first year (V3, V4, V5, V6, V7, V8, V9).

The individual concentrations of UCB0942, [redacted], and [redacted] will be listed for the FAS.

Individual concentrations will be summarized by visit 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], and [redacted]

Has been changed to:

9.1 Plasma concentrations

Plasma concentrations of UCB0942, [redacted], and [redacted] will be determined from blood samples obtained in the study during the first year (V3, V4, V5, V6, V7, V8, V9).

The individual concentrations of UCB0942, [redacted], and [redacted] will be listed for the FAS with blood sampling dates/times and elapsed time from last administration. Unless otherwise stated, measured values below the limit of quantification (BLQ) will be reported as LLOQ/2.

The concentrations of UCB0942 from samples taken 1-3 hours and 10-12 hours after the most recent UCB0942 administration will be summarized by visit using n, mean, median, SD, minimum, maximum, geometric mean, and geoCV and 95% CI of the geometric mean. This table will be repeated for UCB0942, [redacted] and [redacted] PK samples taken at other timepoints will be included in the subject listing but not summarized.

Change #6

10.1 Extent of exposure

All UCB0942 administration information will be listed by subject.

A daily dose will be calculated for each study day from the day of first dose of UCB0942 to the day of last dose of UCB0942 for the purposes of calculating modal dose. Daily dose will be calculated as the sum of the AM and PM dose for each day.

Modal daily doses will be calculated across all study days on or after the day of first dose of UCB0942 and up to and including the day of last dose of UCB0942. Modal daily dose is the most frequently taken daily dose during this period. In the event of a tie, the modal dose will be set to the lower of the tied doses. Modal daily dose will be categorized as follows:

Category	Definition
200mg/day	≤ 200mg/day
400mg/day	>200mg/day to ≤400mg/day
600mg/day	>400mg/day to ≤600mg/day
800mg/day	>600mg/day

Subject years of exposure will be calculated by summing the exposure duration in days for all subjects being summarized, and dividing the resulting value by 365.25.

The number and percentage of subjects exposed to UCB0942 will be summarized overall and by modal dose category. The number and percentage of subjects in each Exposure Duration Cohort (≥3 months, ≥6 months, ≥12 months, and so forth) will be summarized.

The number and percentage of subjects within each modal dose category will be summarized for each Exposure Duration Cohorts; percentages will be relative to the total number of subjects in each Exposure Duration Cohort.

Has been changed to:

10.1 Extent of exposure

All UCB0942 administration information will be listed by subject.

A daily dose will be calculated for each study day from the day of first dose of UCB0942 to the day of last dose of UCB0942 for the purposes of calculating modal dose. Daily dose will be calculated as the sum of the AM and PM dose for each day.

Modal daily doses will be calculated across all study days on or after the day of first dose of UCB0942 and up to and including the day of last dose of UCB0942. Modal daily dose is the most frequently taken daily dose during this period. In the event of a tie, the modal dose will be set to the lower of the tied doses. Modal daily dose will be categorized as ≤200mg/day, >200mg/day to ≤400mg/day, >400mg/day to ≤600mg/day, >600mg/day to ≤800mg/day, and >800mg/day.

For subjects who completed or discontinued from the study, the overall duration of exposure will be calculated as the date of last dose of UCB0942 minus the date of first dose of UCB0942 in EP0073 plus 1 day. For ongoing subjects at a clinical cutoff, the duration of exposure will be calculated based on the date of last dose of UCB0942 defined for the interim analyses (Section 3.2.2). Subject years of exposure will be calculated by summing the exposure duration in days for all subjects being summarized, and dividing the resulting value by 365.25.

The number and percentage of subjects exposed to UCB0942 will be summarized overall and by modal dose category. The number and percentage of subjects exposed for ≥3, ≥6, ≥12, ≥18, ≥24, ≥36, ≥48, and ≥60 months will be summarized.

Change #7

10.2.1 Definition of treatment-emergent AE

Adverse events will be classified as either prior, concomitant, or treatment-emergent.

A prior AE is defined as any AE which had onset prior to the date of the first dose of UCB0942 in EP0073. A concomitant AE is defined as any AE which is ongoing at any time between the first dose of UCB0942 in EP0073 and prior to the end of the study.

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to the first dose of UCB0942 in EP0073 or any unresolved event already present before administration of UCB0942 that worsens in intensity following exposure to the treatment.

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. AEs with an incomplete onset date will be classified as TEAEs if the month and year of onset (when only the month and year are specified) is the same as the month and year of the first UCB0942 dose or the year of onset (when only year is specified) is the same as the year of first UCB0942 dose.

10.2.2 General summaries of TEAEs

Listings will be provided for all AEs, SAEs, AEs leading to taper, AEs leading to withdrawal, and AEs leading to death by subject for the SS.

The number and percentage of subjects who experience TEAEs will be summarized by SOC and PT, overall and by 3-month time intervals.

The following tabular summaries will be presented for the SS:

- Incidence of AEs - Overview
- Incidence of TEAEs
- Incidence of TEAEs by Period (Evaluation, Taper, SFU)
- 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 Intensity
- Incidence of TEAEs by Maximum Intensity
- Incidence of TEAEs leading to Taper
- Incidence of TEAEs leading to Withdrawal
- Incidence of TEAEs occurring in at least 2% of Subjects
- Incidence of TEAEs by Dose at Onset
- 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

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.

Has been changed to:

10.2.1 Definition of treatment-emergent AE

A treatment-emergent adverse event (TEAE) is defined as AEs that started on or after the first dose of UCB0942 in EP0073 or AEs whose intensity worsened on or after the date of first dose of UCB0942 in EP0073.

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. AEs with an incomplete onset date will be classified as TEAEs if the month and year of onset (when only the month and year are specified) is the same as the month and year of the first UCB0942 dose or the year of onset (when only year is specified) is the same as the year of first UCB0942 dose. TEAEs are assigned into an analysis period or time interval based on the onset date.

10.2.2 General summaries of TEAEs

Listings will be provided for all AEs, SAEs, AEs leading to discontinuation (ie, drop out), and AEs leading to death by subject for the SS.

Unless noted otherwise, TEAEs during the study (including the Taper and SFU Periods) will be summarized. At the time of a clinical cutoff, TEAEs with onset date prior to or on the clinical cutoff date will be summarized.

The following tabular summaries will be presented for the SS:

- Ongoing AEs at EP0073 study entry. Of note, this table will not be included in the interim analyses.
- Incidence of TEAEs during the Study - Overview
- Incidence of TEAEs by 3-month time interval during the On-Treatment Period. TEAEs with onset date prior to or on the date of last dose of UCB0942 will be included in the summary.
- Incidence of TEAEs by Period (Entire Study, Evaluation, Taper, SFU)
- Incidence of Serious TEAEs
- Incidence of TEAEs by Relationship
- Incidence of SAEs by Relationship. Of note, this table is needed for data transparency reporting and will not be included in the interim analyses.
- Incidence of Fatal TEAEs by Relationship. Of note, this table is needed for data transparency reporting and will not be included in the interim analyses.
- Incidence of TEAEs by Maximum Intensity
- Incidence of TEAEs leading to discontinuation (ie, drop out)
- Incidence of TEAEs occurring in at least 5% of Subjects

- Incidence of TEAEs by Dose at Onset during the On-Treatment Period. TEAEs with onset date prior to or on the date of last dose of UCB0942 will be included in the summary.

- Incidence of Non-Serious TEAEs above the Threshold of 5% of Subjects. Of note, this table is needed for data transparency reporting and will not be included in the interim analyses.

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 of relationship to study treatment per the investigator, the following relationships will be summarized: 'Not related', 'Related'. 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 of maximum 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 alphabetically by SOC and by decreasing frequency for the PT within SOC.

Change#8

The following has been added:

10.3.1 Subjects with potential drug-induced liver injury (PDILI)

There are specific criteria described in the protocol Section 11.6.1 to evaluate subjects for potential drug-induced liver injury (PDILI). A summary of number and percent of subjects meeting PDILI criteria will be provided along with the subject numbers. Data collected for PDILI subjects will be listed.

A summary table highlighting the potential cases of Hy's Law will be presented. Hy's Law is defined as:

- AST >3xULN or ALT >3xULN and
- Total Bilirubin >2xULN

In order to meet the above criteria, a subject must experience the elevation in bilirubin and ALT or AST at the same visit. For example, a subject who experiences a >=2 x ULN elevation of bilirubin at one visit and a 3 x ULN elevation in ALT (or AST) at a subsequent visit has not fulfilled the Hy's law criteria.

Change #9

Section 12 has been updated to the current standards.

13.2 Amendment 2

Rationale for the amendment

The primary purpose of this amendment is to update SAP because of the PSL program termination.

Modifications and Changes

Major specific changes

Change #1

3.2.1 Analysis periods

Unless noted otherwise, Baseline is the EP0069 2-week Prospective Outpatient Baseline Period.

The study is divided into 4 periods: Screening Period, Evaluation Period, Taper Period, and SFU Period. The following periods will be considered in the definition of efficacy and safety variables:

- A 2-week Screening Period from V13 to the day before V15 of the 8-week Outpatient Maintenance Period of the EP0069 study.
- Evaluation Period: Entry Visit (EV) to Last Evaluation Period Visit (LEPV) or Early Discontinuation Visit (EDV) or clinical data cutoff date if the subject is ongoing and does not have the EDV. The EV is also V15 of EP0069. Data in EP0073 database will be used in the analyses when possible.
- Taper Period: the day after LEPV or EDV to End of Taper Visit or clinical data cutoff date if the subject is ongoing.
- SFU Period: The day after the End of Taper Visit to date of final contact or clinical data cutoff date if the subject is ongoing.

Has been changed to:

3.2.1 Analysis periods

Unless noted otherwise, Baseline is the EP0069 2-week Prospective Outpatient Baseline Period. In this study, final contact date is referred to date of final contact with subject from Study Completion eCRF form.

The study is divided into 4 periods: Screening Period, Evaluation Period, Taper Period, and SFU Period. The following periods will be considered in the definition of efficacy and safety variables:

- A 2-week Screening Period from V13 to the day before V15 of the 8-week Outpatient Maintenance Period of the EP0069 study.

- Evaluation Period: Entry Visit (EV) to Last Evaluation Period Visit (LEPV) or Early Discontinuation Visit (EDV) or clinical data cutoff date if the subject is ongoing and does not have the EDV. The EV is also V15 of EP0069. Data in EP0073 database will be used in the analyses when possible. If a subject does not have a Visit 21/EDV, then the date of the final contact will be defined as the end date of the Evaluation Period.
- Taper Period: the day after the end date of evaluation period to End of Taper Visit or clinical data cutoff date if the subject is ongoing. If the end of taper period (V22) is missing, here it is the algorithm to impute it:

If EDV visit is missing then last date of evaluation period will be last contact date and taper and SFU period start/end dates will be missing.

Else if the last dose date is before EDV date, then we assume drug was not tapered and taper period start/end date will be set as missing and SFU start date will be EDV+1 and SFU end date will be final contact date.

Else if V22 is missing but SFU1 visit (V23) is not missing, then the end date of taper period be defined as max(last dose date, V23-7 days), but if this date is before the taper period start date, then taper period start/end dates will be set as missing.

Else if V23 is missing but SFU2 (V24) is not missing , the end date of taper period as min(last dose date, V24-30 days).

Else taper and SFU period start/end dates will be missing.

- SFU Period: The day after the End of Taper Visit to date of final contact or clinical data cutoff date if the subject is ongoing.

Change #2

13.2.1 Pharmacokinetic Per-Protocol Set

The Pharmacokinetic Per-Protocol Set (PK-PPS) will consist of subjects in the FAS who received at least 1 dose of UCB0942 in the EP0073 study and had at least 1 PK sample, and do not have a major protocol deviation impacting the PK.

Has been changed to:

13.2.1 Pharmacokinetic Per-Protocol Set

The Pharmacokinetic Per-Protocol Set (PK-PPS) will consist of subjects in the FAS who received at least 1 dose of UCB0942 in the EP0073 study and had at least 1 PK sample, and do not have a major protocol deviation impacting the PK for all the PK samples. PK-PPS exclusion should be based on the individual PK samples. Only if all PK samples are excluded, the subject will be excluded from the PK-PPS.

Change #3

9.1 Plasma concentrations

Plasma concentrations of UCB0942, [redacted], and [redacted] will be determined from blood samples obtained in the study during the first year (V3, V4, V5, V6, V7, V8, V9).

The individual concentrations of UCB0942, [redacted], and [redacted] will be listed for the FAS with blood sampling dates/times and elapsed time from last administration. Unless otherwise stated, measured values below the limit of quantification (BLQ) will be reported as LLOQ/2.

The concentrations of UCB0942 from samples taken 1-3 hours and 10-12 hours after the most recent UCB0942 administration will be summarized by visit using n, mean, median, SD, minimum, maximum, geometric mean, and geoCV and 95% CI of the geometric mean. This table will be repeated for UCB0942, [redacted], and [redacted]. PK samples taken at other timepoints will be included in the subject listing but not summarized.

Has been changed to:

9.1 Plasma concentrations

Plasma concentrations of UCB0942, [redacted], and [redacted] will be determined from blood samples obtained in the study during the first year (V3, V4, V5, V6, V7, V8, V9).

The individual concentrations of UCB0942, [redacted] and [redacted] will be listed for the FAS with blood sampling dates/times and elapsed time from last administration. Unless otherwise stated, measured values below the limit of quantification (BLQ) will be reported as LLOQ/2.

Change #4

The table in the section 12.1.2 was truncated and was updated to the correct one.

PARAMETER	*AGE RANGE*	*UNIT (conventional)*	*ABNORMALITY CRITERIA (conventional)*	*UNIT (standard)*	*ABNORMALITY CRITERIA (standard)*
AST (SGOT)	<14y	U/L	>180	U/L	>180
	≥14y		>144		>144
ALT (SGPT)	1y - <18y	U/L	>90	U/L	>90
	≥18y		>123		>123
Alkaline Phosphatase	<4y	U/L	>690	U/L	>690
	4y - <10y		>834		>834
	10y - <18y		>1174		>1174
	≥18y		>432 (F) >933 (M)		>432 (F) >933 (M)
GGT	<6m	U/L	>522	U/L	>522
	6m - <1y		>279		>279

PARAMETER	*AGE RANGE*	*UNIT (conventional)*	*ABNORMALITY CRITERIA (conventional)*	*UNIT (standard)*	*ABNORMALITY CRITERIA (standard)*
	1y - <13y		>66		>66
	13y - <18y		>126		>126
	≥18y		>255		>255
Total Bilirubin	>1m	mg/dL	≥1.5	umol/L	≥25.656
Total Protein	2m-<1y	g/dL	<3.0 >10.0	g/L	<30 >100
	≥1y		<4.3 >10.0		<43 >100
Albumin	<1y	g/dL	<1.6 >6.0	g/L	<16 >60
	≥1y		<2.4 >7.0		<24 >70
BUN	<1y	mg/dL	>21	mmol/L	>7.497
	≥1y		>30		>10.71
Urea	<1y	mg/dL	>42	mmol/L	>7.014

PARAMETER	*AGE RANGE*	*UNIT (conventional)*	*ABNORMALITY CRITERIA (conventional)*	*UNIT (standard)*	*ABNORMALITY CRITERIA (standard)*
	≥1y		>60		>10.02
Creatinine	1y - <10y	mg/dL	>0.9	umol/L	>79.56
	10y - <16y		>1.4		>123.76
	≥16y		>1.6		>141.44
Creatinine Clearance*	All	mL/min	<70	mL/s	<1.169
Calcium	<1y	mg/dL	<6.9 >12.2	mmol/L	<1.725 >3.05
	1y - <18y		<7.4 >11.7		<1.85 >2.925
	≥18y		<7.9 >11.1		≤1.975 ≥2.775
Phosphorous	<1y	mg/dL	<1.8 >8.2	mmol/L	<0.5814 >2.6486
	≥1y		<1.8 >7.4		<0.5814 >2.3902

PARAMETER	*AGE RANGE*	*UNIT (conventional)*	*ABNORMALITY CRITERIA (conventional)*	*UNIT (standard)*	*ABNORMALITY CRITERIA (standard)*
Potassium	<1y	mEq/L	<3.0 >6.5	mmol/L	<3.0 >6.5
	≥1y		<3.0 >5.8		<3.0 >5.8
Sodium	>1m	mEq/L	≤130 ≥150	mmol/L	≤130 ≥150
Glucose	>1m	mg/dL	<50 >180	mmol/L	<2.775 >9.99
Total Cholesterol	1y - <18y	mg/dL	>250	mmol/L	>6.475
	≥18y		>300		>7.77
LDL (calculated)	1y - <18y	mg/dL	>140	mmol/L	>3.626
	≥18y		>200		>5.18
HDL	≤2y	mg/dL	<10	mmol/L	<0.259
	>2y		<20		<0.518
Triglycerides	<1y	mg/dL	>750	mmol/L	>8.475

PARAMETER	*AGE RANGE*	*UNIT (conventional)*	*ABNORMALITY CRITERIA (conventional)*	*UNIT (standard)*	*ABNORMALITY CRITERIA (standard)*
	≥1y		>250		>2.825
Uric Acid	<1y	mg/dL	>7.7	umol/L	>457.996
	1y - <13y		>6.5		>386.62
	13y - <18y		>8.6		>511.528
	≥18y		>6.8 (F) >9.6 (M)		>404.464 (F) >571.008 (M)
Thyroxine (T4)	<1y	ug/dL	≤4.3 ≥18.4	nmol/L	≤55.3453 ≥236.8264
	≥1y		≤3.8 ≥13.5		≤48.9098 ≥173.7585
Globulin	<1y	g/dL	<1.0 >3.8	g/L	<10 >38
	≥1y		<1.2 >4.4		<12 >44

Abbreviations: ALT= alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; dL = deciliter; F=female; GGT: gamma-glutamyltransferase; HDL = high density lipoprotein; LDL = low density lipoprotein; L = liter; M=male; m = month (a month is defined as 30 days) mg = milligram; mmol = millimoles; µg = microgram; U = unit; ULN = upper limit of normal; y = years (a year is defined as 365.25 days).

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.

Approval Signatures

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