STATISTICAL ANALYSIS PLAN

Study: EP0060

Product: Lacosamide

A MULTICENTER, OPEN-LABEL STUDY TO INVESTIGATE THE SAFETY AND TOLERABILITY OF INTRAVENOUS LACOSAMIDE IN CHILDREN (≥1 MONTH TO <17 YEARS OF AGE) WITH EPILEPSY

SAP/Amendment Number	Date
Final SAP	11 August 2017
SAP Amendment 1	02 July 2018
SAP Amendment 2	21 June 2019

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LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
AV	Atrioventricular
bid	twice daily
BP	Blood pressure
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	coefficient of variation
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EMU	epilepsy monitoring unit
ETV	Early Termination Visit
iv	Intravenous
ILAE	International League Against Epilepsy
IIL	Initiating intravenous lacosamide Group
LCM	lacosamide
LOQ	limit of quantification
MA	markedly abnormal
MedDRA	Medical Dictionary for Regulatory Activities
OLL	Open-label lacosamide Group
PDILI	potential drug-induced liver injury

PK	pharmacokinetic(s)
PK-PPS	Pharmacokinetic Per Protocol Set
PT	preferred term
RxL	Prescription lacosamide (eg, VIMPAT) Group
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
SOC	system organ class
SS	Safety Set
SS-iv	Safety Set iv
TEAE	treatment-emergent adverse event
TEMA	treatment-emergent marked abnormalities
ULN	upper limit of normal
VNS	vagus nerve stimulation
WHODD	World Health Organization Drug Dictionary

1 INTRODUCTION

This Statistical Analysis Plan (SAP) defines the scope of statistical analyses and provides a detailed description of statistical methodology for the statistical analyses to support the final clinical study report for EP0060. This SAP is based upon the following documents: (Final Protocol: 16Dec2014, Protocol Amendment 1: 21Jul2015, Protocol Amendment 2: 30Nov2016, Protocol Amendment 3: 30Apr2018).

2 PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objective

The primary objective of the study is to evaluate the safety and tolerability of intravenous (iv) Lacosamide (LCM) infusion(s) in pediatric study participants ≥1 month to <17 years with epilepsy.

2.1.2 Additional objective

An additional objective of the study is to evaluate the pharmacokinetics (PK) of iv LCM in pediatric study participants with epilepsy.

2.2 Study variables

2.2.1 Primary safety variables

Safety and tolerability will be assessed using the following primary variables:

- Adverse events (AEs) reported spontaneously by the study participant and/or caregiver (including parent/legal guardian) or observed by the investigator
- Study participant withdrawals due to AEs

2.2.2 Other safety variables

Other safety variables include the following:

- Changes in 12-lead electrocardiogram (ECGs)
- Changes in vital sign measurements (blood pressure [BP] and pulse rate)
- Changes in physical examinations
- Changes in neurological examinations

2.2.3 Other pharmacokinetic variables

The other PK variables will include plasma concentration of LCM and its main metabolite, SPM 12809.

2.3 Study design and conduct

EP0060 is a Phase 2/3, multicenter, open-label study to evaluate the safety and tolerability of iv LCM infusions in pediatric study participants ≥1 month to <17 years of age with epilepsy. Based on a local protocol amendment only patients between ≥ 1 month to <16 years of age will be enrolled in Ukraine. The study will include approximately 100 study participants.

The following patients will be eligible for enrollment in EP0060:

- Open-label LCM (OLL) patients: currently receiving oral LCM as adjunctive or monotherapy as participants in an open-label long-term study (SP848, EP0034, or other pediatric study).
- Prescribed-LCM (RxL) patients: currently receiving prescribed oral LCM from commercial supply (eg, VIMPAT) as adjunctive or monotherapy
- Initiating iv LCM (IIL) patients: not currently receiving LCM and will receive iv LCM as adjunctive treatment in EP0060. Initiation of LCM monotherapy is not permitted in IIL study participants.

Study participants can receive iv LCM as follows:

- Replacement for oral LCM treatment (OLL and RxL study participants):
  - Clinical need administration: study participants currently taking prescribed oral LCM (or any enteric LCM administration, eg, LCM administration by feeding tube) who need to undergo a procedure and are treated at an epilepsy monitoring unit (EMU) or health care facility, or other situations where iv administration is clinically appropriate and oral administration is not feasible (ie, surgery). In these study participants, the maximum number of iv doses of LCM is 10.
  - Elective administration: study participants currently taking oral LCM (or any enteric LCM administration, eg, LCM administration by feeding tube) who elect to receive iv LCM administration at an EMU or healthcare facility. In these study participants, the maximum number of iv doses of LCM is 2.
- Adjunctive iv LCM treatment initiation (IIL study participants):
  - Clinical need administration: study participants not currently taking LCM who need to undergo a procedure, be treated at an EMU or health care facility, or other situations where iv administration is clinically appropriate and oral administration is not feasible (ie, surgery). In these study participants, the maximum number of iv doses of LCM is 10.
  - Elective administration: study participants not currently taking LCM and elect to initiate adjunctive treatment using iv LCM in a healthcare facility. In these study participants, the maximum number of iv doses of LCM is 2.

EP0060 is composed of the following study periods:

- For all study participants:
  - Screening and/or Baseline Period (up to 7 days),
  - Treatment Period
    (1) Clinical need administration: up to 10 doses or up to 5 days (iv LCM will be administered bid at approximately 12-hour intervals, once in the morning and once in the evening, for up to 10 doses or up to 5 days).
    (2) Elective administration: up to 2 consecutive doses over approximately 24 hours
  - End-of-Study/Final Visit (1 day),

- End-of-Study/Telephone Contact 1 (1 to 3 days),

- Additional visits or contacts as follows:
  - RxL and IIL study participants who are eligible and choose to continue oral LCM for up to 2 years in SP848
    - Transition Visit, which can be concurrent with Final Visit or separate (up to 7 days after Final Visit)
  - RxL and IIL study participants who do not continue LCM treatment in SP848
    - End-of-Study/Telephone Contact 2 (30 days [±2 days] after last iv infusion of study LCM).

The maximum study durations are as follows:

- Approximately 16 days:
  - Study participants in the OLL group will resume participation in their respective study and either resume oral LCM treatment or follow taper regimen as described in the long-term, open-label study accordingly.
- Approximately 23 days:
  - Study participants in the RxL or IIL groups who, if determined clinically appropriate, are given the option to continue oral LCM treatment in SP848.
- Approximately 45 days:
  - Study participants in the RxL or IIL groups who will not continue oral LCM treatment in SP848.

EP0060 is planned to include up to 2 age-based cohorts and will begin with Cohort 1, including at least 40 study participants ≥8 to <17 years of age. Within Cohort 1, at least 20 study participants will be ≥12 to <17 years of age and at least 20 study participants will be ≥8 to <12 years of age. For the first 20 study participants in Cohort 1, iv LCM should be infused over a duration of 30 minutes but not longer than 60 minutes whenever possible.

The Data Monitoring Committee (DMC) will review the safety and tolerability data from the first 20 study participants completed in Cohort 1. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 30 additional study participants will be enrolled in Cohort 1 with target infusion duration of 15 minutes but no longer than 30 minutes only in study participants who would directly benefit from an increased infusion rate, in the opinion of the Investigator. Study participants who will not directly benefit from a 15 to 30 minute infusion duration, in the opinion of the Investigator, cannot receive the faster infusion. These study participants should receive an infusion of 30 minutes but not longer than 60 minutes,
- OR approximately 30 additional study participants will be enrolled in Cohort 1 with a target infusion duration of 30 minutes but not longer than 60 minutes,
- OR study should be stopped,

- AND whether Cohort 2 can be initiated.

For Cohort 2, approximately 44 study participants ≥1 month to <8 years of age will be enrolled to receive iv LCM. For the first 20 study participants in Cohort 2, iv LCM should be infused over a duration of 30 minutes but not longer than 60 minutes whenever possible.

After completion of the first 20 study participants in Cohort 2, the DMC will review the available safety and tolerability data from Cohort 1 and Cohort 2. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 30 additional study participants will be enrolled in Cohort 2 with a target infusion duration of 15 minutes but not longer than 30 minutes only in study participants who would directly benefit from an increased infusion rate, in the opinion of the Investigator. Study participants who will not directly benefit from a 15 to 30 minute infusion, in the opinion of the Investigator, cannot receive the faster infusion. These study participants should receive an infusion of 30 minutes but no longer than 60 minutes,
- OR approximately 30 additional study participants will be enrolled in Cohort 2 with a target infusion duration of 30 minutes but not longer than 60 minutes,
- OR Cohort 2 should be stopped.

The design will result in a total exposure of approximately 100 pediatric study participants to assess the safety and tolerability of iv LCM over a range of infusion durations. A completer for this study is defined as a study participant who completes at least 1 visit with iv LCM treatment and the associated assessments for that visit (eg, PK samples, vital signs, 12-lead ECG). The study participant should have 'Completed study participant' selected as a status at termination.

2.4 Determination of sample size

Approximately 100 study participants will be enrolled, which includes up to 2 cohorts of at least 40 study participants for Cohort 1 and approximately 44 study participants for Cohort 2. No formal sample size calculation has been performed. The sample size was deemed clinically appropriate for the evaluation of safety, tolerability, and PK of iv LCM administration in pediatric study participants with epilepsy.

The following cohorts are planned:

- Cohort 1: at least 40 study participants from ≥8 to <17 years of age, with at least 20 study participants from ≥12 to <17 years of age and at least 20 study participants from ≥8 to <12 years of age
- Cohort 2: approximately 44 study participants from ≥1 month to <8 years of age; every attempt will be made to enroll 20 study participants ≥4 to <8 years of age, 12 study participants ≥2 to <4 years of age, and 12 study participants ≥1 month to <2 years of age

The remaining study participants may be enrolled in either of the 2 age cohorts.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

Statistical analysis and generation of tables, figures, study participant data listings, and statistical outputs will be performed using SAS Version 9.1 or higher. All summaries will be descriptive;

no statistical hypothesis testing is planned. All tables and listings will use Courier New font size 9.

For categorical parameters, the number and percentage of study participants in each category will be presented. The denominator for percentages will be based on the number of study participants appropriate for the purpose of the analysis. Unless otherwise noted, all percentages will be displayed to 1 decimal place. No percentage will be displayed for zero counts, and no decimal will be presented when the percentage is 100%. For continuous parameters, descriptive statistics will include number of study participants (n), mean, standard deviation (SD), median, minimum, and maximum, unless otherwise stated. For PK parameters, the coefficient of variation (CV) and geometric mean may also be presented.

Decimal places for descriptive statistics will always apply the following rules:

- "n" will be an integer
- Mean, SD, and median will use 1 additional decimal place compared to the original data
- CV[%] will be presented with 1 decimal place
- Minimum and maximum will have the same number of decimal places as the original value

However, the maximum number of decimals displayed will not exceed 4.

All summaries, unless otherwise stated, will be presented overall for all study participants and by age cohorts (≥ 1 month to <8 years and ≥8 to <17). Selected tables will be provided in addition by study participant groups (OLL and RxL, combined, and IIL) and target infusion duration (15-30 minutes, and 30-60 minutes).

A complete set of listings containing all documented data and relevant derived data (eg, change from Baseline) will be generated.

3.2 General study level definitions

3.2.1 Analysis time points

3.2.1.1 First and last dose of iv LCM

Unless otherwise noted, all references to the first dose of iv LCM in this SAP refer to the first dose of iv LCM during EP0060. Unless otherwise noted, all references to the last dose of iv LCM in this SAP refer to the last dose of iv LCM in this study.

3.2.1.2 Relative day and time

Relative Day is defined as the day relative to the first infusion of study drug.

If the current date occurred on or after the day of first dose of iv LCM and prior to or on the day of last iv LCM dose, the relative day will be calculated as the current date minus the date of first dose of iv LCM plus 1 (eg, the day of first dose will be Day 1).

If the current date occurred prior to the first dose of iv LCM, the relative day will be calculated as date of first dose of iv LCM minus the current date (eg, the day prior to first dose will be Day -1).

If the current date occurred after the last dose of iv LCM, the relative day will be calculated as the current date minus the date of last dose of iv LCM including a "+" to denote post-treatment days (eg, the day after the last dose will be Day +1).

Relative day will not be calculated for partial dates.

Time will also be collected to ascertain if the event/sample/collection was before or after the first iv LCM even if it happened on the same day.

In order to have a better insight into the times of AEs, concomitant antiepileptic drugs (AED), laboratory samples, ECG and vital signs collections relative to the administration of study medication, the relative time will be displayed in hours and minutes for relative times ≤24 hours before and after first iv LCM administration. For relative times >24 hours the relative times will be displayed in days as described above.

3.2.2 Analysis periods

This study consists of a Screening and/or Baseline Period, an iv Treatment Period and a Post-iv Treatment Period.

Screening and/or Baseline Period

This is defined as the period of time from Day -7 to Day 1 prior to the iv LCM first dose which means that the first visit can occur before or on the same day as the first iv LCM infusion.

iv Treatment Period

Treatment days are as follows:

(1) Clinical need administration: up to 10 doses or up to 5 days

(2) Elective administration: up to 2 consecutive doses over approximately 24 hours

The iv Treatment Period is defined as the period of time from the iv LCM first dose date and time to the iv LCM last dose date and time, inclusive.

Post-iv Treatment Period

This is defined as the period of time after the end date and time of the iv Treatment Period to the last contact with the study participant.

Listings will also include "Unscheduled Visit" as applicable.

3.2.3 Study visit labeling

Visits will be labeled in table summaries (according to the schedule outlined in Section 5.2 of the protocol) as follows:

- "Visit X (Descriptor)" for scheduled visits during the Screening/Baseline Period
- "Visit X" for scheduled visits during the iv Treatment Period
- "Final Visit"
- "Telephone Contact 1"
- "Telephone Contact 2"
- "Transition Visit"

3.2.4 Exposure duration

Exposure duration refers to the first and last dose of iv LCM. The date of first infusion of study medication is defined as the first study medication infusion date according to the standard case report form (CRF) page.

The date of last infusion of study medication is defined as the last infusion of study medication reported on the standard trial termination CRF.

The number of days of exposure is defined as the treatment stop date minus the treatment start date +1 day. Days with unknown or zero dosing which occur prior to the last infusion of study medication in the study should be included in the calculation.

3.2.5 Age and Age at first diagnosis

Age will be given in years and will be derived applying the rules for missing data imputation (see Section 4.2.1 and the SDTM derivation definition). The age at first diagnosis will be given in years and will be derived applying all rules for missing data imputation (see Section 4.2.1) with the following formulas:

Missing or partial epilepsy diagnosis date will be derived applying all rules for missing data imputation (see Section 4.2.1) and age at first diagnosis will use the following formulas, where applicable.

The following formula will be applied where birthdate is a complete date:

(Date of first diagnosis of epilepsy – Date of birth) / 365.25

The following formula will be applied where birthdate is a partial date:

(Enrollment age in years) – [(Informed consent date – Epilepsy diagnosis date) / 365.25], if the value is negative then age at diagnosis will be set to zero.

3.2.6 Time since first epileptic seizure and last status epilepticus

Time since first epileptic seizure and time since last status epilepticus will be given in years and will be derived applying all rules for missing date imputation (see Section 4.2.1) with the following formula (respectively):

(Date of informed consent - Date of first epileptic seizure) / 365.25

(Date of informed consent - Date of last status epilepticus) / 365.25

3.2.7 Body mass index (BMI)

BMI will be calculated using the formula:

$BMI = weight\ (kg) / (height\ (m))^2$

3.3 Definition of Baseline values

Baseline for laboratory variables (blood chemistry, hematology), vital signs, body weight, and quantitative electrocardiography (ECG) variables is defined as the last value prior to the first infusion of study drug (pre-iv LCM measurement). Individual laboratory variables should all come from the same timepoint. Same applies to the individual vital sign variables, except for weight. Both scheduled and unscheduled assessments from the central laboratory are considered.

3.4 Protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on the primary outcomes for an individual study participant. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and data evaluation. Important deviations will be identified and documented prior to database lock to confirm exclusion from analysis sets.

3.5 Analysis sets

3.5.1 Safety Set

The Safety Set (SS) will include study participants who received at least 1 dose of EP0060 study drug LCM (oral and/or iv). Selected safety summaries will be presented for the SS. If the SS and the SS-iv consist of the same number of study participants, tables will only be presented for the SS-iv.

3.5.2 Safety Set iv

The Safety Set iv (SS-iv) will include study participants in the SS who received at least 1 dose of EP0060 study drug iv LCM. The SS-iv will be the primary analysis set for the analysis of safety data.

3.5.3 Pharmacokinetic-Per Protocol Set

The Pharmacokinetic-Per Protocol Set (PK-PPS) will include all study participants in the SS-iv having provided at least 1 measurable post-dose plasma sample (with recorded sampling time) on at least 1 study day with documented iv LCM intake times and without important protocol deviations impacting the interpretability of the PK analysis.

3.6 Treatment assignment and treatment groups

This is an open-label study with a single treatment arm. Study participants are summarized based on the age-based cohorts defined as:

- ≥8 to <17 years (Age Cohort 1)
- ≥1 month to <8 years (Age Cohort 2)

3.7 Center pooling strategy

No pooling of centers is planned for this study.

3.8 Coding dictionaries

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.1. Medications will be coded using the World Health Organization Drug Reference List (WHODD SEP/2013). Medical procedures will not be coded.

3.9 Changes to protocol-defined analyses

There are no changes to analyses specified in the protocol.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

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

4.2 Handling of dropouts or missing data

No imputation of missing values for analysis parameters is planned unless otherwise noted. Imputations for missing or partial values for dates for AEs and concomitant medications will be applied to determine if an event is to be considered treatment-emergent or concomitant. Across safety and PK analysis, only reported data will be used.

4.2.1 General imputation rule for incomplete dates

Where necessary for the calculation of derived variables, partial dates will be completed using the earliest calendar date based on the partial date provided. This rule is valid for all partial dates with the exception of the following:

- Start and stop dates of concomitant medication
- Start and stop date of adverse events
- Start and stop dates of study medication
- Date of epilepsy diagnosis

Completely missing dates will not be replaced and the corresponding derived variables will be set to missing.

4.2.2 Handling of prior and concomitant medications with missing data

Any medications with incomplete start and end dates will be handled according to the following rules for classification as prior and concomitant and for the calculation of relative study days. Such imputations will only be performed for these classifications and calculations; in the listings all data will be shown as recorded on the electronic case report form (eCRF).

Imputation of Partial Start Dates

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

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

In the event of ambiguity or incomplete data which makes it impossible to determine whether a medication was concomitant or not, the medication will be considered as concomitant.

4.2.3 Handling of adverse events with missing data

Any AEs with incomplete onset and outcome (end) dates/times will be handled according to the following rules for classification as treatment-emergent. Such imputations will only be performed for these classifications; in the listings all data will be shown as recorded on the eCRF.

Imputation of Partial Onset Dates

- If only the month and year are specified and the month and year of first dose of iv LCM is not the same as the month and year of onset, then use the 1st of the month.
- If only the month and year are specified and the month and year of first dose of iv LCM is the same as the month and year of onset, then use the date/time of first dose of iv LCM.
- If only the year is specified, and the year of first dose of iv LCM is not the same as the year of onset, then use January 1 of the year of onset.
- If only the year is specified, and the year of first dose of iv LCM is the same as the year of onset, then use the date/time of first dose.
- If the AE onset date is completely unknown, then use the date of first dose of iv LCM.
- If the onset time of the event is unknown, impute it as 00:00 unless the known part of the onset date is the same as the date of first iv LCM dose; in this case impute the time of first dose of iv LCM dose.

Imputation of Partial End 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 31 of that year.
- If the AE resolved and the resolution date is completely unknown, then do not impute the resolution date.

With respect to AEs, events with missing intensity will be assumed to be severe. Events with missing relationship to iv LCM per the investigator will be assumed to be related.

Data handling for worsened AEs is provided below. The standard AE CRF has the outcome of "worsened" to be used when there is an increase in the intensity of an AE. The definition of "worsened" is when the AE is still present but at a heightened intensity. CRF instructions dictate to complete a new AE screen with the event term of the worsened event.

Note that the outcome of "worsened" is not allowed terminology within the CDISC standards. In the SDTM.AE, the data is mapped to the outcome "Not Recovered/Not Resolved". The outcome of "Worsened" will be kept in SDTM.SUPPAE. For study participant data listings, the convention will be to use the mapped SDTM terminology of "Not Recovered/Not Resolved".

4.2.4 Handling of study medication with missing data

No imputation should be performed for missing study medication start dates. This field on the CRF should not be partial or missing.

For partial or missing date of last dose of study medication, the following imputation rules will be applied for the purpose of calculating overall exposure:

- If the day is missing (but month and year available), impute the last dose date as the minimum of the last day of the month or the date of last contact reported on the trial termination CRF; if day and month are both missing (only year available), impute the last dose date as the minimum of the last day of the year or the date of last contact on the trial termination CRF.
- If a study participant died and has a partial or missing last administration date, the date is to set to the date of death. If there is a partial date of last dose and the month/year are prior to the month and year of the date of death, follow partial date imputation rules.
- If the last dose date is completely missing and no information could be obtained from data cleaning exercises, the last dose date should be imputed as the date of last contact according to the study termination CRF. A review of the data for study participants with completely missing last dose dates should be performed to ensure that the imputation does not result in an unrealistic value for duration of exposure.
- Imputed date of last dose dates should only be used for calculation of the duration of exposure. The date as recorded on the CRF should be presented in study participant data listings (no imputed dates should be included in study participant data listings).

4.2.5 Handling of epilepsy diagnosis with missing data

Imputation methods should be applied for missing or partial epilepsy diagnosis date.

- If the month and year are available, the diagnosis date is imputed as the later of the following dates: the first day of the month, the study participant's birthdate, or the date of the first seizure (if available).
- If only a year is available, the later of the following dates will be imputed: January 1st of the year, the study participant's birthdate, and the date of the first seizure.
- Completely missing dates will not be replaced and the corresponding derived variables will be set to missing.

4.3 Interim analyses and data monitoring

No formal interim analysis is planned for this study; however, data will be presented to and reviewed by a DMC after completion of the first 20 study participants in Cohort 1 and after completion of the first 20 study participants in Cohort 2.

No formal stopping rule will be applied. The DMC may give a recommendation to stop the study after reviewing the safety data as described below. A recommendation for stopping should be based on the collective experience of the DMC members. After meeting to review data from each cohort, the DMC will provide a recommendation in writing regarding whether to continue or to

stop the study. UCB will consider this recommendation and ensure the study investigators are informed of the sponsor's decision on how to continue as described below.

The DMC members will be defined in the DMC charter.

EP0060 will begin with Cohort 1, where at least 40 study participants ≥8 to <17 years of age will be enrolled to receive iv LCM. Within Cohort 1, at least 20 study participants will be ≥12 to <17 years of age and at least 20 study participants will be ≥8 to <12 years of age. For the first 20 study participants in Cohort 1, iv LCM should be infused over a duration of 30 minutes but not longer than 60 minutes whenever possible.

After completion of the first 20 study participants in Cohort 1, the DMC will review the safety and tolerability data from these study participants. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 30 additional study participants will be enrolled in Cohort 1 with target infusion durations as follows:
    - 15 minutes but not longer than 30 minutes only in study participants who would directly benefit from an increased infusion rate, in the opinion of the Investigator; OR,
    - 30 minutes but not longer than 60 minutes in study participants who would not directly benefit from an increased infusion rate, in the opinion of the Investigator
- OR approximately 30 additional study participants will be enrolled in Cohort 1 with a target infusion duration of 30 minutes but not longer than 60 minutes,
- OR study should be stopped,
- AND whether Cohort 2 can be initiated.

For Cohort 2, approximately 44 study participants ≥1 month to <8 years of age will be enrolled to receive iv LCM. For the first 20 study participants in Cohort 2, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 20 study participants in Cohort 2, the DMC will review the available safety and tolerability data from Cohort 1 and Cohort 2. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 30 additional study participants will be enrolled in Cohort 2 with target infusion durations as follows:
    - 15 minutes but not longer than 30 minutes only in study participants who would directly benefit from an increased infusion rate, in the opinion of the Investigator; OR,
    - 30 minutes but not longer than 60 minutes in study participants who would not directly benefit from an increased infusion rate, in the opinion of the Investigator
- OR approximately 30 additional study participants will be enrolled in Cohort 2 with target infusion duration of 30 minutes but not longer than 60 minutes,
- OR Cohort 2 should be stopped.

4.4 Multicenter studies

No multicenter analysis is planned therefore this section is not applicable for this study.

4.5 Multiple comparisons/multiplicity

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

4.6 Use of an efficacy subset of study participants

No efficacy data are collected; therefore, this section is not applicable for this study.

4.7 Active-control studies intended to show equivalence

This section is not applicable for this study.

4.8 Examination of subgroups

For analyses, the study participant groups and the target infusion duration groups will be combined to create a 4-level subgroup:

- OLL and RxL study participants/15 – 30 minutes
- OLL and RxL study participants/30 – 60 minutes
- IIL study participants/15 – 30 minutes
- IIL study participants/30 – 60 minutes

5 STUDY POPULATION CHARACTERISTICS

5.1 Study participant disposition

Study participants who were screen failures, broken down by primary reason for screening failure will be presented overall for all study participants screened.

A summary of disposition of study participants will be provided for all screened study participants. The date of first study participant in (date of first Screening visit), date of last study participant out (date of last visit (in clinic) for last study participant), number of study participants screened, and the number of study participants in each analysis set (SS-iv, SS and PK-PPS) will be summarized overall, by country and by investigator site. Study participants who transferred sites will be summarized according to their original site.

A summary of disposition of analysis sets will be provided for all study participants screened:

- The number and percentage of study participants in the SS-iv
- The number and percentage of study participants in the SS
- The number and percentage of study participants in the PK-PPS

A summary of disposition and discontinuation reasons will be presented for all study participants in the SS-iv and the SS. The summary will be presented by age cohort, all study participants and by subgroup. The following information is included:

- The number and percentage of study participants starting the study
- The number and percentage of study participants completing the study

- The overall number and percentage of study participants discontinuing and the number and percentage of study participants discontinuing by primary reason for discontinuation

A summary of discontinuations due to AEs for the SS-iv will present the number and percentage of study participants who discontinued this study due to AEs broken down by type of AE. The table will be presented by age cohort, all study participants and by subgroup and will be repeated for the SS.

The following listings will be provided: study participants who did not meet study eligibility criteria, study participant disposition, study discontinuation, study participant analysis sets, study participants excluded from at least one analysis set, visit dates, and study participant number.

5.2 Protocol deviations

Important protocol deviations defined in the protocol-specific document, and additionally identified at the data evaluation meetings, will be listed. In addition, the number and percentage of study participants with at least one important protocol deviation will be summarized overall and by category of important protocol deviation for the SS-iv and the SS. The number and percentage of study participants with no important protocol deviations will also be summarized.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics and other Baseline characteristics

Demographic variables will be presented for the SS-iv and the SS. The variables to be considered are:

- Age at entry into EP0060
- Categorized age:
    - EudraCT age categories: >=1 month to < 2 years, >=2 to <12 years and >=12 to <17 years
    - Age cohort categories: >=1 month to < 2 years, >=2 to <4 years, >=4 to <8 years, >=8 to <12 years and >=12 to <17 year
- Gender
- Study participant group (OLL, RxL, and IIL)
- Target infusion duration (15-30 minutes and 30-60 minutes)
- Subgroup: (OLL/15 – 30 minutes, OLL/30 – 60 minutes, RxL/15 – 30 minutes, RxL/30 – 60 minutes, IIL/15 – 30 minutes, IIL/30 – 60 minutes)
- Weight (kg)
    - Categorized weight: 0 to <30kg, 30 to <50kg, >=50kg
- Height (cm)
- BMI (kg/m^2) (as defined in Section 3.2.7)
- Racial group (American Indian/Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, and Other/Mixed)

- Ethnicity (Hispanic or Latino or Not Hispanic or Latino)
- Country
    - US
    - Germany
    - Hungary
    - Italy
    - Poland
    - Thailand
    - Ukraine
- Vagus nerve stimulation (VNS) use (Active VNS, No VNS, and VNS not active)

Listings of demographics, VNS at screening and childbearing potential will be provided.

6.2 Medical history

Medical history for RxL and IIL will be obtained from the Screening Visit Medical History eCRF module in EP0060. Medical History for OLL study participants will come from their medical history from their respective previous study.

The number and percentage of study participants with a medical history condition (except epilepsy), including both resolved and ongoing conditions, will be summarized by MedDRA primary system organ class (SOC) and preferred term (PT) for the SS-iv. Previous and ongoing medical history glossary and previous and ongoing medical history conditions listings (except epilepsy) will be provided.

6.3 Potential Drug-Induced Liver Injury (PDILI)

Where applicable, potential drug induced liver injury will be captured as described in Section 12.2.4 and DILI information will be listed (see Section 8.3).

6.4 History of epilepsy

6.4.1 History of seizure types

The number and percentage of study participants experiencing partial-onset seizures (type I), simple partial (type IA), complex partial (type IB), partial, secondary generalized (type IC), generalized (type II), absence (IIA), myoclonic (IIB), clonic (IIC), tonic (IID), tonic-clonic (IIE), and atonic (IIF) seizures during 4 weeks prior to the screening visit for EP0060 will be summarized for the SS-iv based on the International League Against Epilepsy (ILAE) Seizure Classification Historical Seizure Count eCRF module.

A study participant will be classified as having a history of partial-onset seizures (I) if the study participant has a history of simple partial (IA), complex partial (IB), or partial evolving to secondary generalized (IC) seizures. A study participant will be classified as having a history of generalized seizures (II) if the study participant has a history of primary generalized with an unknown subtype (II), absence (IIA), myoclonic (IIB), clonic (IIC), tonic (IID), tonic-clonic (IIE), or atonic (IIF) seizures. A study participant may also be classified as having a history of unclassified epileptic seizures (III).

6.4.2 History of seizure characteristics

History of withdrawal seizures, history of status epilepticus, age at first diagnosis (as defined in Section 3.2.5), time since first epileptic seizure (as defined in Section 3.2.6), and time since last status epilepticus (as defined in Section 3.2.6) will be summarized and listed where available. For direct enrollers, this information will be collected in the History of Epileptic Seizures eCRF for EP0060. For OLL study participants this information will come from their previous study.

6.4.3 Historical seizure counts

The Historical Seizure Count eCRF module records the number of seizures per pre-selected ILAE seizure code experienced by the study participant during the 4 weeks prior to the Screening Visit. These data will be provided in a study participant data listing. For OLL study participants this information will come from their previous study.

6.5 Prior and concomitant medications

Prior medications include any medications that started prior to the date of first dose of LCM study drug. Concomitant medications are medications taken at least one day in common with study drug LCM in EP0060. Medications may be both prior and concomitant.

For OLL study participants only concomitant medication which started during the EP0060 study will be recorded in the EP0060 study. Information of medication which started before EP0060 study start will come from the respective OLL study. Prior AEDs will be defined by a manual medical review of all unique combinations of ATC codes and indications reported in the database to identify prior medications taken to treat epilepsy.

Medications will be listed as follows: prior and concomitant non-AEDs, glossary of non-AEDs with verbatim term coded into ATC levels 1 and 2, prior and concomitant AEDs, and glossary of AEDs with verbatim term coded into ATC level 4.

Handling of prior and concomitant medications missing data is described in the Section 4.2.2.

6.5.1 Concomitant Non-AEDs

Non-AEDs taken at least one day in common with LCM study drug in EP0060 will be considered as concomitant medications. Medications will be summarized by ATC Code level 1 and 2 for the SS-iv. Study participants reporting multiple medications within an ATC class are counted once per medication and class.

6.5.2 Concomitant AEDs

Concomitant AEDs are defined as AEDs taken concomitantly for at least one day in common with LCM study drug in EP0060. AEDs are reported on the Concomitant Medications (AEDs only) eCRF page. Concomitant AEDs will be summarized by Level 4 ATC code and generic medication name. If a medication identified as an AED does not code to a level 4 ATC code, the highest level of coding will be displayed along with the generic medication name. Summaries of AEDs will be presented separately from other concomitant medications for the SS-iv population.

6.6 VNS setting and ketogenic diet

Two separate listings for Vagus Nerve Stimulation Status at Screening and since last visit will be provided.

Ketogenic diets data reported on Special Diets eCRF will be presented in a study participant listing.

6.7 Medical procedures

Concomitant medical procedures per study participant will be listed.

In addition, a listing of procedure history for study participants who had any procedures or surgeries prior to study entry will be provided.

For RxL and IIL study participants, procedure history will be obtained from the Procedure History eCRF. For OLL study participants, procedures with stop dates prior to the date of first dose of iv LCM in EP0060, procedure history will be obtained from the respective OLL Concomitant Procedure eCRF.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Information reported on the eCRF Drug Accountability (iv formulation) will be listed. The data from the eCRF Drug Accountability (Oral solution) will also be listed. No summaries of these results are planned.

LCM dosing compliance will be evaluated through the review of important protocol deviations.

8 SAFETY ANALYSES

All analyses for extent of exposure and safety are performed for the SS-iv.

Inferential statistical tests are not planned for the safety variables.

8.1 Extent of exposure

The duration of iv LCM exposure, as defined in Section 3.2.4, will be summarized as a continuous parameter (in days). The number of LCM infusions received will be summarized categorically. The exposure table will be presented by age cohort, all study participants and by subgroup. Handling of study medication missing data is described in Section 4.2.4.

The following listings will be provided: LCM dosing history, oral LCM administration, study medication administration and exposure to study medication.

8.2 Adverse events

All adverse events occurring during EP0060 (ie, after signing of the ICF) must be reported. The treatment-emergent adverse events (TEAEs) are defined as those events that started on or after the date (and time) of first infusion of study medication and within 30 days following the date of last study medication, or adverse events whose intensity worsened on or after the date (and time) of first infusion of study medication and within 30 days following the last study medication infusion date. For OLL study participants where the adverse event started prior to EP0060 enrollment information will come from the respective OLL study.

Only RxL and IIL study participants who do not continue LCM treatment in SP848 will have a Telephone Contact 2 visit (Section 2.3) 30 days after the last dose follow-up.

Data handling rules for management of missing or partial start or stop dates for adverse events should follow those defined in the Section 4.2.3.

AE Summaries

The following summaries will be produced:

- Incidence of TEAEs – Overview
- Incidence of TEAEs
- Incidence of TEAEs – Study participant Numbers
- Incidence of serious TEAEs
- Incidence of non-serious TEAEs
- Incidence of serious TEAEs by relationship to LCM
- Incidence of non-serious TEAEs by relationship to LCM
- Incidence of other significant TEAEs (refer to Section 12.1 for a list of MedDRA preferred terms which define other significant TEAEs)
- Incidence of TEAEs related to Potentially Drug Induced Liver Injury (PDILI) (refer to Appendix 12.4 for a list of MedDRA preferred terms which define TEAEs related to PDILI)
- Incidence of TEAEs for iv Treatment Period and Post-iv Treatment Period
- Incidence of serious TEAEs for iv Treatment Period and Post-iv Treatment Period
- Incidence of drug-related TEAEs
- Incidence of TEAEs by Maximum Intensity
- Incidence of non-serious TEAEs occurring in at least 5% of study participants
- Incidence of non-serious TEAEs occurring in at least 5% of study participants by relationship to LCM
- Incidence of TEAEs leading to Study Discontinuation
- Incidence of fatal TEAEs by relationship to LCM
- Incidence of TEAEs leading to permanent discontinuation of LCM
- Incidence of TEAEs Leading to permanent discontinuation of LCM - Study participant Numbers

Overview of the incidence of AEs will include all study participants with at least one TEAE, serious TEAEs, non-serious TEAEs, study participant discontinuations due to TEAEs, permanent withdrawal of study medication due to TEAEs, drug-related TEAEs, drug-related serious TEAEs, severe TEAEs, all deaths (AEs leading to death), and TEAEs leading to death.

AEs will be summarized by MedDRA SOC and MedDRA PT. The tables will be presented by age cohort, all study participants and by subgroup. The number and percentage of study participants experiencing each event at least once will be summarized. All summaries will be sorted alphabetically by SOC and by frequency of events within PTs, starting with the most frequent event overall.

AE Listings

All AEs reported during the study will be provided in a study participant data listing.

The following AE listings will be provided:

- Glossary table for all TEAEs, where the terms included on the table should match those presented in other AE displays
- All AEs
- All serious AEs
- All AEs leading to study discontinuation
- Listing of all deaths
- Other significant TEAEs
- All AEs related to PDILI
- All AEs which worsened during the study
- All AEs which occurred under oral LCM

Should it occur, any uncoded AEs should be designated as "UNCODED" at all MedDRA levels, and such AEs should be included in summary tables and study participant data listings based on this classification (eg, SOC and PT set to UNCODED).

8.3 Clinical laboratory evaluations

Laboratory values are collected at screening and /or baseline visit (if baseline visit is a different day than screening visit) and at the Final Visit. Continuous laboratory variables (hematology and clinical chemistry) summary statistics of actual values and change from Baseline will be presented by age cohort, for all study participants overall and by subgroup at each study visit.

Shifts from baseline to end of treatment based on the normal range (ie, low, normal, high, and missing) for each hematology and clinical chemistry lab parameter will be presented.

The number and percentage of study participants with laboratory treatment-emergent marked abnormalities (TEMA) (hematology and clinical chemistry) as defined in Section 12.2 are to be summarized by laboratory parameter. Laboratory TEMA are those that are observed during the iv treatment period at scheduled or unscheduled visits and were not observed at any visit during the Baseline period. A study participant number table will be presented for study participants with laboratory assessments meeting the TEMA criteria.

The following listings will be provided: a separate study participant data listing for TEMA (all laboratory assessments for study participants with TEMA are to be included in the listing), all laboratory results of clinical chemistry and hematology and serum and urine pregnancy laboratory tests.

Study participants who meet one or more of the criteria for potential drug-induced liver injury (PDILI) at any timepoint (from both scheduled and unscheduled visits) will be listed (see Section 12.2.3). The listing will display only visits for which at least one of the criteria in Section 12.2.3 was fulfilled for a given study participant, and will display all results obtained at that visit for the specified variables. Potential Hy's law cases will be flagged. If applicable, a summary of study participants who met the criteria for PDILI will be presented separately from

all relevant data collected. Results from unscheduled visits and local laboratory should be included, if applicable.

All potential drug-induced liver injury (PDILI) events require immediate action, testing, and monitoring (see Section 12.2.4). The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are included but not limited to those listed in (laboratory measurements) and (Appendix 12.4) (additional information).

Additional PDILI information will also be listed. If specific PDILI information collected separately is matching to the entries in the standard eCRF pages collected for all study participants, the specific PDILI information will be added to the corresponding listing for the standard eCRF information. For information collected on top (eg, family history of PDILI, lifestyle) a new listing will be generated.

The number of study participants meeting the criteria for Hy's Law will be summarized. The criteria of Hy's Law are as follows:

• (ALT or AST ≥ 3×ULN) and total bilirubin ≥ 2×ULN

In order to meet the above criteria, a study participant must experience the elevation in total bilirubin and ALT or AST at the same visit. For example, a study participant who experiences a >=2 x ULN elevation of total 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. A study participant with ALT and AST values missing or a study participant with total bilirubin value missing has not fulfilled the Hy's Law criteria.

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

8.4.1 Vital signs

Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], and pulse rate) will be collected according to the protocol schedule of study assessments.

Observed values of SBP, DBP, and pulse rate will be summarized for each visit and time point. Change from Baseline for SBP, DBP, and pulse rate will be summarized for all post-Baseline visits and time points. Tables will be provided by age cohort and subgroup. Actual values and change from Baseline for SBP, DBP and pulse rate will be plotted for a line graph by visit, time point, and age cohort.

Markedly abnormal (MA) vital sign values are defined as those MA post-baseline values which occur on or after the first EP0060 iv LCM administration through to the end of the study.

The number and percentage of study participants with MA values at each post-Baseline visit will be presented. Percentages will be relative to the number of study participants with a value at each visit. Summary of MA vital signs study participant numbers will be provided. All post-baseline vital signs measurements (scheduled and unscheduled) will be assessed to determine MA criteria.

The abnormal vital sign criteria are defined as follows:

Table 8–1: Vital signs abnormality criteria

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
Temperature	>1m	>101 ^{0}F (38.3 ^{0}C)
Body Weight	1m - <17y	<3% or >97% of the normal body weight growth curve ranges based on gender and the age of study participant on date of weight assessment[a]

Table 8–1: Vital signs abnormality criteria

Parameter	Age Range	Abnormality Criteria
	≥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/

A study participant data listing of all vital signs values for all study participants will be presented. The listing will contain a column indicating the MA criteria if a study participant had abnormal vital sign value. A separate study participant data listing for MA values (all vital signs assessments for study participants with MA values are to be included in the listing) will be provided.

8.4.2 Electrocardiograms (ECGs)

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

Observed the values of the ECG will be summarized for each visit. Change from Baseline in ECG results will be summarized for all post-Baseline visits and time points. The table will be presented by age cohort and subgroup. Actual values and change from Baseline will be plotted by visit, time point, and age cohort.

The number and percentage of study participants with normal, abnormal not clinically significant and abnormal clinically significant findings, as assessed by the investigator, will be summarized for all visits. Percentages will be relative to the number of study participants with an ECG assessment at each visit. Study participants are counted at most once at each visit based on the worst observed outcome across all abnormalities reported at that visit.

Summaries of shifts from Baseline to post-Baseline visits will also be provided based on the categories normal, abnormal, not clinically significant, and abnormal, clinically significant.

The number and percentage of study participants with treatment-emergent ECG abnormalities will be presented for each post-Baseline visit. Abnormalities reported at an unscheduled visit will be summarized under the scheduled visit preceding the unscheduled visit (if the abnormality was not present already at the preceding scheduled visit). Treatment-emergent is defined as meeting the criteria at any post-Baseline visit during the iv Treatment Period (including unscheduled visits) and not meeting the same criteria during Baseline. Abnormality criteria to be used in the determination of ECG abnormalities are defined as follows, where increase and decrease are relative to Baseline values:

Table 8–2: ECG abnormality criteria

Parameter	Age	Abnormality Criteria
QT interval (ms)	1m-<12y	≥500

Table 8–2: ECG abnormality criteria

Parameter	Age	Abnormality Criteria
	≥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
	3y-<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.

A listing of ECG data will be provided for all study participants with other significant TEAEs in the Cardiac and ECG Related Terms category defined in Appendix 12.1. A study participant data listing of all ECG parameter values for all study participants will also be presented.

A study participant data listing will be provided that identifies study participants with a clinically significant finding after the first dose of iv LCM for each type of ECG abnormality. All ECG parameter values will be listed for study participants meeting any abnormality criteria.

8.4.3 Complete physical examination

A complete physical examination will be performed at Screening Visit and the Final Visit according to the protocol schedule of study assessments.

The complete physical examination will include cardiac and respiratory function via auscultation, and review of all body systems.

Clinically significant physical examination findings will be reported as AEs.

A listing of clinically significant physical examination abnormalities from the complete physical examination will be provided.

8.4.4 Complete neurological examination

A complete neurological examination will be performed at the Screening Visit according to the protocol schedule of study assessments. The complete neurological examination will include selected assessment of general neurological status (level of consciousness, mental status, speech), cranial nerves, reflexes, motor system (general motor status, muscle strength, muscle tone), coordination/cerebellar function, and sensation.

Clinically significant neurological findings will be reported as AEs.

A listing of neurological examination abnormalities from the complete neurological examination will be provided.

8.4.5 Assessment of suicidality

Suicidality will be assessed by trained study personnel using the Columbia Suicide Severity Rating Scale (C-SSRS). This will be completed according to the protocol schedule of study assessments.

For study participants ≥6 years of age, this scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. All study participants who are ≥6 years of age will complete the "Baseline/Screening" version of the C-SSRS at Visit 1 and will complete the "Since Last Visit" version at subsequent visits. If a study participant becomes 6 years of age during the study, the "Already Enrolled" version of the C-SSRS should be used at the first visit at which the study participant is 6 years of age and use the "Since Last Visit" version at subsequent visits.

The C-SSRS is not validated for study participants <6 years of age and will not be used for this population, but signs and symptoms of depression will be assessed at each visit.

Study participant data listings of the data for the C-SSRS will be provided. No summaries of these results are planned.

9 PHARMACOKINETICS AND PHARMACODYNAMICS

9.1 Pharmacokinetics

All study PK outcomes will be summarized for the PK-PPS.

Blood samples for the determination of LCM and SPM 12809 concentrations will be collected according to the protocol schedule of study assessments (on Visit 2 and if iv LCM treatment is continued after Day 1 also on Visit 3, pre-dose sample is taken between -59 min to -3 min in relation to iv LCM infusion and +1h to 4 hours after the end of the iv LCM infusion). Additional blood samples for the PK analysis can be taken at the discretion of the investigator, especially in the event of a relevant treatment-emergent AE. Blood samples with missing sampling time will be excluded from the analysis.

9.1.1 Pharmacokinetics Analysis

Descriptive summaries (n, geometric mean, geometric 95% confidence interval, geometric CV, mean, SD, median, minimum, and maximum) for the LCM and SPM 12809 plasma concentrations will be presented for pre-infusion and post-infusion time points on each infusion day where LCM and SPM 12809 plasma are collected. Summary statistics are only calculated if at least 2/3 of data are above the lower limit of quantification (LOQ). Values <LOQ will be set to LOQ/2 for the determination of all summary statistics. Data will be presented by age cohort and by weight group (0 to <30kg, 30 to <50kg, >=50kg).

A listing of plasma sample collection times and plasma concentrations of LCM and SPM 12809 will be provided.

9.2 Pharmacodynamics

This section is not applicable for this study.

10 EFFICACY ANALYSES

This section is not applicable for this study.

11 REFERENCES

This section is not applicable for this study.

12 APPENDICES

12.1 List of Other significant AEs of VIMPAT

MedDRA Preferred Term
CARDIAC AND ECG RELATED TERMS
Atrioventricular block third degree
Atrioventricular block second degree
Bradyarrhythmia*
Bradycardia*
Cardiac pacemaker insertion
Atrial fibrillation
Atrial flutter
Sinus bradycardia*
Ventricular tachycardia
Ventricular fibrillation
Heart Rate decreased*
Sick sinus syndrome
Atrial conduction time prolongation
Atrioventricular dissociation
Conduction disorder
Cardiac fibrillation
Cardiac flutter
Sinus arrest
Torsade de pointes
Ventricular asystole

MedDRA Preferred Term
Ventricular flutter
Ventricular tachyarrhythmia
Implantable defibrillator insertion
SUICIDALITY RELATED TERMS
Completed suicide
Depression suicidal
Suicidal behaviour
Suicidal ideation
Suicide attempt
Intentional self-injury
Self injurious behaviour
Self-injurious ideation
Intentional overdose
Multiple drug overdose intentional
Poisoning deliberate
ADDITIONAL TERMS
Loss of consciousness
Syncope
Appetite disorder
Decreased appetite
Diet refusal
Hypophagia
Food aversion

MedDRA Preferred Term
Abnormal behaviour

*All cases with reported reduced heart rate will be reviewed and only cases with marked bradycardia (marked reduction in heart rate) with HR <45 bpm will be listed as 'Other Significant AEs'.

12.2 Marked abnormality criteria for laboratory data

12.2.1 Hematology

PARAMETER	*AGE RANGE*	*UNIT (conventional)*	*ABNORMALITY CRITERIA (conventional)*	*UNIT* (standard)	*ABNORMALITY CRITERIA (standard)*
Hematocrit	<2y	%	≤27 >45	%	≤27 >45
	2y - <17y		≤29 >47		≤29 >47
	≥17y		≤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 - <17y		≤9.5 >16.0		≤95 >160
	≥17y		≤85% of LLN ≥115% of ULN		≤85% of LLN ≥115% of ULN
WBC/Leukocytes	All	10^9/L	≤3.0 ≥16.0	G/L	≤3.0 ≥16.0
Lymphocytes Absolute	<2y	10^9/L	<1.0 >9.8	G/L	<1.0 >9.8
	2y - <6y		<0.7 >6.9		<0.7 >6.9
	≥6y		<0.6 >5.0		<0.6 >5.0
Basophils	>1m	%	≥5.0	%	≥5.0
Basophils Absolute	>1m	10^9/L	≥0.4	G/L	≥0.4

PARAMETER	***AGE RANGE***	***UNIT (conventional)***	***ABNORMALITY CRITERIA (conventional)***	***UNIT*** (standard)	***ABNORMALITY CRITERIA (standard)***
Eosinophils	>1m	%	≥10	%	≥10
Eosinophils Absolute	>1m	10^9/L	≥1.0	G/L	≥1.0
Monocytes	>1m	%	≥20.0	%	≥20.0
Monocytes Absolute	>1m	10^9/L	≥2.0	G/L	≥2.0
Neutrophils Absolute	>1m	10^9/L	<1.5	G/L	<1.5
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: m =month, RBC=red blood cells, WBC=white blood cells, y = year. A month is defined as 30 days; a year is defined as 365.25 days.

12.2.2 Chemistry

PARAMETER	***AGE RANGE***	***UNIT (conventional)***	***ABNORMALITY CRITERIA (conventional)***	***UNIT*** (standard)	***ABNORMALITY CRITERIA (standard)***
AST (SGOT)	All	U/L	≥3.0 x ULN ≥5.0 x ULN ≥10.0 x ULN	U/L	≥3.0 x ULN ≥5.0 x ULN ≥10.0 x ULN
ALT (SGPT)	All	U/L	≥3.0 x ULN ≥5.0 x ULN ≥10.0 x ULN	U/L	≥3.0 x ULN ≥5.0 x ULN ≥10.0 x ULN

PARAMETER	***AGE RANGE***	***UNIT (conventional)***	***ABNORMALITY CRITERIA (conventional)***	***UNIT*** (standard)	***ABNORMALITY CRITERIA (standard)***
Alkaline Phosphatase	<4y	U/L	≥690	U/L	≥690
	4y - <10y		≥834		≥834
	10y - <17y		≥1761		≥1761
	≥17y		≥3.0 x ULN		≥3.0 x ULN
GGT	<6m	U/L	≥522	U/L	≥522
	6m - <1y		≥279		≥279
	1y - <13y		≥66		≥66
	13y - <17y		≥126		≥126
	≥17y		≥3.0 x ULN		≥3.0 x ULN
Total Bilirubin	>1m	mg/dL	≥2.0	umol/L	≥34.208
Total Protein	2m-<1y	g/dL	<3.0 >11.9	g/L	<30 >119
	1y - <17y		<4.3 >12.0		<43 >120
	≥17y		<4.3 >13.0		<43 >130
Albumin	<1y	g/dL	<1.6 >7.2	g/L	<16 >72
	≥1y - <17y		<2.4 >8.4		<24 >84

PARAMETER	***AGE RANGE***	***UNIT (conventional)***	***ABNORMALITY CRITERIA (conventional)***	***UNIT*** (standard)	***ABNORMALITY CRITERIA (standard)***
	≥17y		<2.6		<26
BUN	<1y	mg/dL	≥24	mmol/L	≥8.568
	1y - <17y		≥36		≥12.852
	≥17y		≥40		≥14.28
Urea	<1y	mg/dL	>42	mmol/L	>7.014
	≥1y		>60		>10.02
Creatinine	1y - <10y	mg/dL	>1.2	umol/L	>106.8
	10y - <16y		>1.8		>159.12
	≥16y		>2.0		≥176.8
Creatinine Clearance*	All	mL/min	<50	mL/s	<0.835
Bicarbonate	>1m - <17y	mEq/L	<15 >38	mmol/L	<15 >38
	≥17y		<18 >38		<18 >38
Calcium	<1y	mg/dL	<6.9 >12.2	mmol/L	<1.725 >3.05
	1y - <17y		<7.4 >11.7		<1.85 >2.925
	≥17y		≤7.6 ≥11.0		≤1.9 ≥2.75
Chloride	>1m	mEq/L	≤90	mmol/L	≤90

PARAMETER	***AGE RANGE***	***UNIT (conventional)***	***ABNORMALITY CRITERIA (conventional)***	***UNIT*** (standard)	***ABNORMALITY CRITERIA (standard)***
			≥112		≥112
Phosphorous	<1y	mg/dL	<1.8 >8.2	mmol/L	<0.5814 >2.6486
	1y - <17y		<1.8 >7.4		<0.5814 >2.3902
	≥17y		≤2.0 ≥6.0		≤0.646 ≥1.938
Potassium	<1y	mEq/L	≤3.0 ≥6.5	mmol/L	≤3.0 ≥6.5
	≥1y		≤3.0 ≥6.0		≤3.0 ≥6.0
Sodium	>1m	mEq/L	<127 >151	mmol/L	<127 >151
Glucose	>1m - <17y	mg/dL	<50 ≥180	mmol/L	<2.775 ≥9.99
	≥17y		<50 ≥200		<2.775 ≥11.1
Total Cholesterol	≥1y	mg/dL	>250	mmol/L	>6.475
LDL (calculated)	1y - <17y	mg/dL	>140	mmol/L	>3.626
	≥17y		>200		>5.18
HDL	≤2y	mg/dL	<10	mmol/L	<0.259
	>2y		<20		<0.518

PARAMETER	***AGE RANGE***	***UNIT (conventional)***	***ABNORMALITY CRITERIA (conventional)***	***UNIT*** (standard)	***ABNORMALITY CRITERIA (standard)***
Triglycerides	<1y	mg/dL	>750	mmol/L	>8.475
	≥1y		>300		>3.39
Uric Acid	<1y	mg/dL	>7.7	umol/L	>457.996
	1y - <13y		>6.5		>386.62
	13y - <17y		>8.6		>511.528
	≥17y		>9.5		>565.06
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 >4.5	g/L	<10 >45
	≥1y		<1.2 >5.3		<12 >53

Abbreviations: ALT= alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; dL = deciliter; GGT: gamma-glutamyltransferase; HDL = high density lipoprotein; LDL = low density lipoprotein; L = liter; 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 y): Cr Cl ml/min = [Height (cm) * 0.55] / serum creatinine; Cockroft equation (patients ≥12 y): 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.

12.2.3 Required Investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN[b]	NA	Hepatology consult.[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 10.6.2.3); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline values.[d]
≥5xULN	NA	NA				
≥3xULN	NA	Yes		Immediate, temporary or permanent, IMP discontinuation.		
≥3xULN (and ≥2x Baseline) and <5xULN	<2xULN	No	Discussion with Medical Monitor required if the criterion that allows for IMP continuation is met.	Further investigation – immediate IMP discontinuation not required (see Section 10.6.2.2).	Not required unless otherwise medically indicated (at discretion of investigator).	
≥5xULN (and ≥2x Baseline)	<2xULN	No	Discussion with Medical Monitor required.	Immediate, permanent IMP discontinuation.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 10.6.2.3).	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline values.[d]

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

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

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

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

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

12.2.4 PDILI laboratory measurements

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

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase; GGT=gamma-glutamyltransferase; HBcAb-IgM=hepatitis B core antibody-IgM; HBsAg=hepatitis B surface antigen; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PDILI=potential drug-induced liver injury; PK=pharmacokinetic; RBC=red blood cell; RNA=ribonucleic acid; ULN=upper limit of normal; WBC=white blood cell.
a Measured only for study participants with ALT >8xULN, elevations in total bilirubin, and symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

12.3 Additional PDILI information

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

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

12.4 List of MedDRA Preferred Term for PDILI

MedDRA Preferred Term for PDILI
Cholestasis
Cholestatic liver injury
Cholestatic pruritus
Drug-induced liver injury
Hepatitis cholestatic
Hyperbilirubinaemia
Icterus index increased
Jaundice
Jaundice cholestatic
Jaundice hepatocellular
Mixed liver injury
Ocular icterus
Acute hepatic failure
Asterixis
Cholestatic liver injury
Coma hepatic
Cryptogenic cirrhosis
Drug-induced liver injury
Hepatic cirrhosis
Hepatic encephalopathy
Hepatic failure
Hepatic infiltration eosinophilic

Hepatic necrosis
Hepatic steatosis
Hepatitis fulminant
Hepatobiliary disease
Hepatocellular foamy cell syndrome
Hepatocellular injury
Hepatotoxicity
Liver disorder
Liver injury
Mixed liver injury
Non-alcoholic steatohepatitis
Subacute hepatic failure
Allergic hepatitis
Chronic hepatitis
Hepatitis
Hepatitis acute
Hepatitis cholestatic
Hepatitis chronic active
Hepatitis chronic persistent
Hepatitis fulminant
Hepatitis toxic
Non-alcoholic steatohepatitis
Blood bilirubin abnormal
Blood bilirubin increased

Hyperbilirubinaemia

13 AMENDMENTS TO THE STATISTICAL ANALYSIS PLAN

13.1 AMENDMENT 1

Rationale for the amendment

The primary purpose of this SAP amendment is to include subjects with the age of <4 years to >=1 month in the second age cohort according to protocol amendment 3. In addition, non-content related issues which were detected during the DMC-SAP review were updated.

Modifications and changes

Global changes

The following changes have been made throughout the SAP:

Text has been modified to lower the age of subject enrollment to ≥1 month of age.

- Approximately 100 subjects will be included in EP0060.
- Age stratification has been included within Cohort 2. Every attempt will be made to enroll 20 subjects ≥4 to <8 years of age, 12 subjects ≥2 to <4 years of age, and 12 subjects ≥1 month to <2 years of age.
- Number of subjects in the DMC process in Cohort 2 has been revised.

  For Cohort 2, approximately 44 subjects ≥1 month to <8 years of age will be enrolled to receive iv LCM. For the first 20 subjects in Cohort 2, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

  After completion of the first 20 subjects in Cohort 2, the DMC will review the available safety and tolerability data from Cohort 1 and Cohort 2. Based on this review, the DMC will make recommendations as follows:

  - EITHER approximately 30 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 15 minutes but no longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the Investigator. Subjects who will not directly benefit from a 15 to 30 minute infusion, in the opinion of the Investigator, cannot receive the faster infusion. These subjects should receive an infusion of 30 minutes but no longer than 60 minutes.
  - OR approximately 30 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 30 minutes but no longer than 60 minutes.
  - OR Cohort 2 should be stopped.

- The following changes were made to PDILI laboratory measurements:

  Hematocrit, hemoglobin, platelet count, RBC count, WBC count, and WBC differential

count have replaced eosinophil count as hematology measurements.

- The SS-iv will be the primary analysis set for the analysis of safety data and PK-PPS will include all subjects in the SS-iv having provided at least 1 measurable postdose plasma sample (with recorded sampling time) on at least 1 study day with documented LCM intake times.
- Clarifications made to the definitions of prior and concomitant medication.
- Vital signs and ECG abnormality criteria added for age <4 years of age.
- General updates: “e.g.”/”i.e.” to “eg,”/”ie,”, dates without non-break space, spelling mistakes, wording and upper/lower case corrections.

Specific changes

Change #1

Title page

A MULTICENTER, OPEN-LABEL STUDY TO INVESTIGATE THE SAFETY AND TOLERABILITY OF INTRAVENOUS LACOSAMIDE IN CHILDREN (≥4 TO <17 YEARS OF AGE) WITH EPILEPSY

Has been changed to:

A MULTICENTER, OPEN-LABEL STUDY TO INVESTIGATE THE SAFETY AND TOLERABILITY OF INTRAVENOUS LACOSAMIDE IN CHILDREN **(≥1 MONTH** TO <17 YEARS OF AGE) WITH EPILEPSY

Change #2

Section 1 Introduction

This SAP is based upon the following documents: (Final Protocol: 16 Dec 2014, Protocol Amendment 1: 21Jul 2015, Protocol Amendment 2: 30 Nov 2016).

Has been changed to:

This SAP is based upon the following documents: (Final Protocol: 16Dec2014, Protocol Amendment 1: 21Jul2015, Protocol Amendment 2: 30Nov2016**, Protocol Amendment 3: 30Apr2018**).

Change #3

Section 2.1.1 Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of intravenous (iv) Lacosamide (LCM) infusion(s) in pediatric subjects ≥4 to <17 years with epilepsy.

Has been changed to:

Section 2.1.1 Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of intravenous (iv) Lacosamide (LCM) infusion(s) in pediatric subjects ≥**1 month** to <17 years with epilepsy.

Change #4

Section 2.2.3 Pharmacokinetic variables

The PK variables will include plasma concentration of LCM and its main metabolite, SPM 12809.

Has been changed to:

Section 2.2.3 **Other** pharmacokinetic variables

The **other** PK variables will include plasma concentration of LCM and its main metabolite, SPM 12809.

Change #5

Section 2.3 Study design and conduct

This is a Phase 2/3, multicenter, open-label study to evaluate the safety and tolerability of iv LCM infusions in pediatric subjects ≥4 to <17 years of age with epilepsy. The study will include approximately 75 subjects.

After completion of the first 20 subjects in Cohort 1, the Data Monitoring Committee (DMC) will review the safety and tolerability data from these subjects.

For Cohort 2, at least 20 subjects ≥4 to <8 years of age will be enrolled to receive iv LCM. For the first 10 subjects in Cohort 2, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first 10 subjects in Cohort 2, the DMC will review the available safety and tolerability data from Cohort 1 and Cohort 2. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 15 minutes but no longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the Investigator. Subjects who will not directly benefit from a 15 to 30 minute infusion, in the opinion of the Investigator, cannot receive the faster infusion. These subjects should receive an infusion of 30 minutes but no longer than 60 minutes.
- OR approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 30 minutes but no longer than 60 minutes,
- OR Cohort 2 should be stopped,

- AND whether to initiate a new iv LCM study in younger pediatric subjects (≥1 month to <4 years of age).

The design will result in a total exposure of approximately 75 pediatric subjects to assess the safety and tolerability of iv LCM over a range of infusion durations.

Has been changed to:

Section 2.3 Study design and conduct

EP0060 is a Phase 2/3, multicenter, open-label study to evaluate the safety and tolerability of iv LCM infusions in pediatric subjects **≥1 month** to <17 years of age with epilepsy. **Based on a local protocol amendment only patients between ≥ 1 month to <16 years of age will be enrolled in Ukraine.** The study will include approximately **100** subjects.

The Data Monitoring Committee (DMC) will review the safety and tolerability data from **the first 20** subjects **completed in Cohort 1**.

For Cohort 2, **approximately 44 subjects ≥1 month** to <8 years of age will be enrolled to receive iv LCM. For the first **20** subjects in Cohort 2, iv LCM should be infused over a duration of 30 minutes but not longer than 60 minutes whenever possible.

After completion of the first **20** subjects in Cohort 2, the DMC will review the available safety and tolerability data from Cohort 1 and Cohort 2. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately **30** additional subjects will be enrolled in Cohort 2 with a target infusion duration of 15 minutes but not longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the Investigator. Subjects who will not directly benefit from a 15 to 30 minute infusion, in the opinion of the Investigator, cannot receive the faster infusion. These subjects should receive an infusion of 30 minutes but no longer than 60 minutes,
- OR approximately **30** additional subjects will be enrolled in Cohort 2 with a target infusion duration of 30 minutes but not longer than 60 minutes,
- OR Cohort 2 should be stopped.

The design will result in a total exposure of approximately **100** pediatric subjects to assess the safety and tolerability of iv LCM over a range of infusion durations.

Change #6

Section 2.4 Determination of sample size

Approximately 75 subjects will be enrolled, which includes up to 2 cohorts of at least 40 subjects for Cohort 1and at least 20 subjects for Cohort 2. No formal sample size calculation has been performed. The sample size was deemed clinically appropriate for the evaluation of safety, tolerability, and PK of iv LCM administration in pediatric subjects with epilepsy.

The following cohorts are planned:

- Cohort 1: at least 40 subjects from ≥8 to <17 years of age, with at least 20 subjects from ≥12 to <17 years of age and at least 20 subjects from ≥8 to <12 years of age
- Cohort 2: at least 20 subjects from ≥4 to <8 years of age

Has been changed to:

Approximately **100** subjects will be enrolled, which includes up to 2 cohorts of at least 40 subjects for Cohort 1 and **approximately 44** subjects for Cohort 2. No formal sample size calculation has been performed. The sample size was deemed clinically appropriate for the evaluation of safety, tolerability, and PK of iv LCM administration in pediatric subjects with epilepsy.

The following cohorts are planned:

- Cohort 1: at least 40 subjects from ≥8 to <17 years of age, with at least 20 subjects from ≥12 to <17 years of age and at least 20 subjects from ≥8 to <12 years of age
- Cohort 2: **approximately 44** subjects from **≥1 month** to <8 years of age; **every attempt will be made to enroll 20 subjects ≥4 to <8 years of age, 12 subjects ≥2 to <4 years of age, and 12 subjects ≥1 month to <2 years of age**

Change #7

Section 3.1 General presentation of summaries and analyses

All summaries, unless otherwise stated, will be presented overall for all subjects and by the age cohorts (≥4 to <8 years and ≥8 to <17). Selected tables will be provided in addition by the subject groups (OLL and RxL, and IIL) and target infusion duration (15-30 minutes, and 30-60 minutes).

Has been changed to:

All summaries, unless otherwise stated, will be presented overall for all subjects and by age cohorts (**≥ 1 month** to <8 years and ≥8 to <17). Selected tables will be provided in addition by subject groups (OLL and RxL, **combined**, and IIL) and target infusion duration (15-30 minutes, and 30-60 minutes).

Change #8

Section 3.2.2 Analysis periods

<u>iv Treatment Period</u>

Treatment days are as follows:

(1) Clinical need administration: up to 10 doses or up to 5 days

(2) Elective administration: up to 2 consecutive doses over approximately 24 hours

End-of-Study/Final Visit (1 day)

The iv Treatment Period is defined as the period of time from the iv LCM first dose date and time to the iv LCM last dose date and time, inclusive. The end date of the iv Treatment Period

will be either the last assessment date in Visit 3 for completers, or the date of the Early Termination Visit (ETV) for subjects who discontinued during the iv Treatment Period. If a subject does not have a Visit 3/ETV, then either the date of the last scheduled or unscheduled visit during the iv Treatment Period or the date of last known dose of iv LCM during the iv Treatment Period, whichever is later, will define the end date of the iv Treatment Period.

Post-iv Treatment Period

This is defined as the period of time after the end date of the iv Treatment Period to the last contact with the subject.

End-of-Study/Telephone Contact 1 (1 to 3 days).

Has been changed to:

iv Treatment Period

Treatment days are as follows:

(1) Clinical need administration: up to 10 doses or up to 5 days

(2) Elective administration: up to 2 consecutive doses over approximately 24 hours

The iv Treatment Period is defined as the period of time from the iv LCM first dose date and time to the iv LCM last dose date and time, inclusive.

Post-iv Treatment Period

This is defined as the period of time after the end date **and time** of the iv Treatment Period to the last contact with the subject.

Listings will also include "Unscheduled Visit" as applicable.

Change #9

Section 3.2.3 Study visit labeling

Visits will be labeled in table summaries (according to the schedule outlined in Section 5.2 of the protocol) as follows:

- "Visit X (Descriptor)" for scheduled visits during the Screening/Baseline Period
- "Visit X, Day X" for scheduled visits during the Treatment Period
- "Final Visit, Day X"
- "Telephone Contact, Day X"
- "Transition Visit, Day X"

Has been changed to:

Visits will be labeled in table summaries (according to the schedule outlined in Section 5.2 of the protocol) as follows:

- "Visit X (Descriptor)" for scheduled visits during the Screening/Baseline Period
- "**Visit X**" for scheduled visits during the **iv** Treatment Period

- "**Final Visit**"
- "Telephone Contact **1**"
- "**Telephone Contact 2**"
- "**Transition Visit**"

Change #10

Section 3.5 Analysis sets

3.5.1 Safety Set iv

The Safety Set iv (SS-iv) will include subjects who received at least 1 dose of iv LCM. The SS-iv will be the primary analysis set for the analysis of safety data.

3.5.2 Safety Set

The Safety Set (SS) will include subjects who received at least 1 dose of LCM (oral or iv). Selected safety summaries will be presented for the SS. If the SS and the SS-iv consist of the same number of subjects, tables will only be presented for the SS-iv.

3.5.3 Pharmacokinetic-Per Protocol Set

The Pharmacokinetic-Per Protocol Set (PK-PPS) will include all subjects in the SS having provided at least 1 measurable post-dose plasma sample (with recorded sampling time) on at least 1 study day with documented LCM intake times.

Has been changed to:

3.5.1 Safety Set

The Safety Set (SS) will include subjects who received at least 1 dose of **EP0060 study drug** LCM (oral **and/or** iv). Selected safety summaries will be presented for the SS. If the SS and the SS-iv consist of the same number of subjects, tables will only be presented for the SS-iv.

3.5.2 Safety Set iv

The Safety Set iv (SS-iv) will include subjects **in the SS** who received at least 1 dose of **EP0060 study drug** iv LCM. The SS-iv will be the primary analysis set for the analysis of safety data.

3.5.3 Pharmacokinetic-Per Protocol Set

The Pharmacokinetic-Per Protocol Set (PK-PPS) will include all subjects in the SS**-iv** having provided at least 1 measurable post-dose plasma sample (with recorded sampling time) on at least 1 study day with documented **iv** LCM intake times **and without important protocol deviations impacting the interpretability of the PK analysis.**

Change #11

Section 3.6 Treatment assignment and treatment groups

This is an open-label study with a single treatment arm. Subjects are summarized based on the age-based cohorts defined as:

- ≥8 to <17 years (Age Cohort 1)
- ≥4 to <8 years (Age Cohort 2)

Has been changed to:

This is an open-label study with a single treatment arm. Subjects are summarized based on the age-based cohorts defined as:

- ≥8 to <17 years (Age Cohort 1)
- **≥1 month** to <8 years (Age Cohort 2)

Change #12

Section 3.9 Changes to protocol-defined analyses

In the protocol the pharmacokinetic analyses were planned to be presented by age cohort and infusion duration, and the IIL and OLL and RxL groups. After careful consideration, it is more meaningful to have the analyses presented separately by age cohort and body weight group.

In the protocol, all safety analyses were planned to be presented by age cohort and infusion duration, cohorts overall, and all subjects overall and within cohort and infusion duration, by the Ill, OLL and RxL groups of subjects. After careful consideration, it is more meaningful to have all safety tables by age cohort and only specific safety tables presented by target infusion duration and subject group.

Has been changed to:

There are no changes to analyses specified in the protocol.

Change #13

Section 4.3 Interim analyses and data monitoring

No formal interim analysis is planned for this study; however, data will be presented to and reviewed by a DMC after completion of the first 20 subjects in Cohort 1 and after completion of the first 10 subjects in Cohort 2.

No formal stopping rule will be applied. The DMC may give a recommendation to stop the study after reviewing the safety data as described below. A recommendation for stopping should be based on the collective experience of the DMC members. After meeting to review data from each cohort, the DMC will provide a recommendation in writing regarding whether to continue or to stop the study. UCB will consider this recommendation when deciding the actions to take following each DMC meeting. UCB will and ensure the study investigators are informed of the sponsor's decision on how to continue as described below.

The DMC members will be defined in the DMC charter.

EP0060 will begin with Cohort 1, where at least 40 subjects ≥8 to <17 years of age will be enrolled to receive iv LCM. Within Cohort 1, at least 20 subjects will be ≥12 to <17 years of age and at least 20 subjects will be ≥8 to <12 years of age. For the first 20 subjects in Cohort 1, iv

LCM should be infused over a duration of 30 minutes but not longer than 60 minutes whenever possible.

After completion of the first 20 subjects in Cohort 1, the DMC will review the safety and tolerability data from these subjects. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 30 additional subjects will be enrolled in Cohort 1 with a target infusion duration as follows:

- 15 minutes but not longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the Investigator; OR,

- 30 minutes but not longer than 60 minutes in subjects who would not directly benefit from an increased infusion rate, in the opinion of the Investigator

- OR approximately 30 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 30 minutes but not longer than 60 minutes,

- OR the study should be stopped,

- AND whether Cohort 2 can be initiated.

For Cohort 2, at least 20 subjects ≥4 to <8 years of age will be enrolled to receive iv LCM. For the first 10 subjects in Cohort 2, iv LCM should be infused over a duration of 30 minutes but not longer than 60 minutes whenever possible.

After completion of the first 10 subjects in Cohort 2, the DMC will review the available safety and tolerability data from Cohort 1 and Cohort 2. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion duration as follows:

- 15 minutes but not longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the Investigator; OR,

- 30 minutes but not longer than 60 minutes in subjects who would not directly benefit from an increased infusion rate, in the opinion of the Investigator

- OR approximately 15 additional subjects will be enrolled in Cohort 2 with a target infusion duration of 30 minutes but no longer than 60 minutes,

- OR Cohort 2 should be stopped,.

- AND whether to initiate a new iv LCM study in younger pediatric subjects (≥1 month to <4 years of age).

Has been changed to:

No formal interim analysis is planned for this study; however, data will be presented to and reviewed by a DMC after completion of the first 20 subjects in Cohort 1 and after completion of the first **20** subjects in Cohort 2.

No formal stopping rule will be applied. The DMC may give a recommendation to stop the study after reviewing the safety data as described below. A recommendation for stopping should be

based on the collective experience of the DMC members. After meeting to review data from each cohort, the DMC will provide a recommendation in writing regarding whether to continue or to stop the study. UCB will consider this recommendation and ensure the study investigators are informed of the sponsor's decision on how to continue as described below.

The DMC members will be defined in the DMC charter.

EP0060 will begin with Cohort 1, where at least 40 subjects ≥8 to <17 years of age will be enrolled to receive iv LCM. Within Cohort 1, at least 20 subjects will be ≥12 to <17 years of age and at least 20 subjects will be ≥8 to <12 years of age. For the first 20 subjects in Cohort 1, iv LCM should be infused over a duration of 30 minutes but not longer than 60 minutes whenever possible.

After completion of the first 20 subjects in Cohort 1, the DMC will review the safety and tolerability data from these subjects. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately 30 additional subjects will be enrolled in Cohort 1 with target infusion durations as follows:
    - 15 minutes but not longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the Investigator; OR,
    - 30 minutes but not longer than 60 minutes in subjects who would not directly benefit from an increased infusion rate, in the opinion of the Investigator
- OR approximately 30 additional subjects will be enrolled in Cohort 1 with a target infusion duration of 30 minutes but not longer than 60 minutes,
- OR study should be stopped,
- AND whether Cohort 2 can be initiated.

For Cohort 2, **approximately 44** subjects ≥**1 month** to <8 years of age will be enrolled to receive iv LCM. For the first **20** subjects in Cohort 2, iv LCM should be infused over a duration of 30 minutes but no longer than 60 minutes whenever possible.

After completion of the first **20** subjects in Cohort 2, the DMC will review the available safety and tolerability data from Cohort 1 and Cohort 2. Based on this review, the DMC will make recommendations as follows:

- EITHER approximately **30** additional subjects will be enrolled in Cohort 2 with target infusion durations as follows:
    - 15 minutes but not longer than 30 minutes only in subjects who would directly benefit from an increased infusion rate, in the opinion of the Investigator; OR,
    - 30 minutes but not longer than 60 minutes in subjects who would not directly benefit from an increased infusion rate, in the opinion of the Investigator
- OR approximately **30** additional subjects will be enrolled in Cohort 2 with target infusion duration of 30 minutes but not longer than 60 minutes,
- OR Cohort 2 should be stopped.

Change #14

Section 5.1 Subject disposition

A summary of disposition of analysis sets will be provided for all subjects screened and the SS-iv:

The following listings will be provided: study eligibility criteria text, subjects who did not meet study eligibility criteria, subject disposition, study discontinuation, subject analysis sets, subjects excluded from at least one analysis set, and visit dates.

Has been changed to:

A summary of disposition of analysis sets will be provided for all subjects screened:

The following listings will be provided: subjects who did not meet study eligibility criteria, subject disposition, study discontinuation, subject analysis sets, subjects excluded from at least one analysis set, visit dates, **and subject number**.

Change #15

Section 6.1 Demographics and other Baseline characteristics

Demographic variables will be presented for the SS-iv and the SS. The variables to be considered are:

- Age at entry into EP0060 (as defined in Section 3.1.6) – continuous and categorized as
- For EudraCT age categories are >=4 to <12 years and >=12 to <=17 years and the age cohort categories are >=4 to <8 years, >=8 to <12 years and >=12 to <17 years.

Has been changed to:

Section 6.1 Demographics and other Baseline characteristics

Demographic variables will be presented for the SS-iv and the SS. The variables to be considered are:

- Age at entry into EP0060
- Categorized age:
  - EudraCT age categories: **>=1 month to < 2 years, >=2** to <12 years and >=12 to <17 years
  - Age cohort categories: **>=1 month to < 2 years, >=2 to <4 years,** >=4 to <8 years, >=8 to <12 years and >=12 to <17 year

Change #16

Section 6.2 Medical history

Medical history for RxL and IIL will be obtained from the Screening Visit Medical History eCRF module in EP0060. Medical History for OLL subjects is the sum of their medical history from their respective previous study and if applicable data from the subject's Medical History update form in EP0060.

Has been changed to:

Medical history for RxL and IIL will be obtained from the Screening Visit Medical History eCRF module in EP0060. Medical History for OLL subjects **will come from** their medical history from their respective previous.

Change #17

Section 6.4.2 History of seizure characteristics

History of epileptic seizures, history of status epilepticus, age at diagnosis (as defined in Section 3.2.5), time since first epileptic seizure (as defined in Section 3.2.6), and time since last status epilepticus (as defined in Section 3.2.6) will be summarized and listed where available. For direct enrollers, this information will be collected in the History of Epileptic Seizures eCRF for EP0060. For OLL subjects this information will come from their previous study.

Has been changed to:

History of **withdrawal** seizures, history of status epilepticus, age at **first** diagnosis (as defined in Section 3.2.5), time since first epileptic seizure (as defined in Section 3.2.6), and time since last status epilepticus (as defined in Section 3.2.6) will be summarized and listed where available. For direct enrollers, this information will be collected in the History of Epileptic Seizures eCRF for EP0060. For OLL subjects this information will come from their previous study.

Change #18

Section 6.5 Prior and concomitant medications

Added:

Prior medications include any medications that started prior to the date of first dose of LCM study drug. Concomitant medications are medications taken at least one day in common with study drug LCM in EP0060. Medications may be both prior and concomitant.

Change #19

Section 6.5.1 Concomitant Non-AEDs

Non-AEDs taken at any time during the Treatment Period will be considered as concomitant medications. Medications will be summarized by ATC Code level 1 and 2 for the SS-iv. Subjects reporting multiple medications within an ATC class are counted once per medication and class.

Section 6.5.2 Concomitant AEDs

AEDs are reported on the Concomitant Medications (AEDs only) eCRF as concomitant medications. Concomitant AEDs will be summarized by Level 4 ATC code and generic

medication name. If a medication identified as an AED does not code to a level 4 ATC code, the highest level of coding will be displayed along with the generic medication name. Summaries of AEDs will be presented separately from other concomitant medications for the SS-iv population.

Has been changed to:

Section 6.5.1 Concomitant Non-AEDs

Non-AEDs taken at **least one day in common with LCM study drug in EP0060** will be considered as concomitant medications. Medications will be summarized by ATC Code level 1 and 2 for the SS-iv. Subjects reporting multiple medications within an ATC class are counted once per medication and class.

Section 6.5.2 Concomitant AEDs

Concomitant AEDs are defined as AEDs taken concomitantly for at least one day in common with LCM study drug in EP0060. AEDs are reported on the Concomitant Medications (AEDs only) eCRF **page**. Concomitant AEDs will be summarized by Level 4 ATC code and generic medication name. If a medication identified as an AED does not code to a level 4 ATC code, the highest level of coding will be displayed along with the generic medication name. Summaries of AEDs will be presented separately from other concomitant medications for the SS-iv population.

Change #20

Section 8.2 Adverse events

AE Summaries

- Incidence of AEs – Overview

Has been changed to:

- Incidence of **TE**AEs – Overview

Added:

- Incidence of TEAEs related to Potentially Drug Induced Liver Injury (PDILI) (refer to Appendix 12.4 for a list of MedDRA preferred terms which define TEAEs related to PDILI)

AE Listings

Added:

- All AEs related to PDILI

Change #21

Section 8.3 Clinical laboratory evaluations

Added:

The number of subjects meeting the criteria for Hy's Law should also be summarized. The criteria of Hy's Law are as follows:

• (ALT or AST ≥ 3×ULN) and total bilirubin ≥ 2×ULN

In order to meet the above criteria, a subject must experience the elevation in total bilirubin and ALT or AST at the same visit. For example, a subject who experiences a >=2 x ULN elevation of total 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. A subject with ALT and AST values missing or a subject with total bilirubin value missing has not fulfilled the Hy's Law criteria.

Change #22

Section 8.4.5 Assessment of suicidality

Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2008). This will be completed according to the protocol schedule of study assessments.

For subjects ≥6 years of age, this scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. All subjects who are ≥6 years of age will complete the "Baseline/Screening" version of the C-SSRS at Visit 1 and will complete the "Since Last Visit" version at subsequent visits. If a subject becomes 6 years of age during the study, the "Already Enrolled" version of the C-SSRS should be used at the first visit at which the subject is 6 years of age and use the "Since Last Visit" version at subsequent visits.

The C SSRS is not validated and will not be used for subjects <6 years of age. For those subjects, signs and symptoms of depression will be assessed at each visit.

Subject data listings of the data for the C-SSRS will be provided. No summaries of these results are planned.

Has been changed to:

Suicidality will be assessed by trained study personnel using the Columbia **Suicide Severity Rating Scale (C-SSRS)**. This will be completed according to the protocol schedule of study assessments.

For subjects ≥6 years of age, this scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. All subjects who are ≥6 years of age will complete the "Baseline/Screening" version of the C-SSRS at Visit 1 and will complete the "Since Last Visit" version at subsequent visits. If a subject becomes 6 years of age during the study, the "Already Enrolled" version of the C-SSRS should be used at the first visit at which the subject is 6 years of age and use the "Since Last Visit" version at subsequent visits.

The C-SSRS is not validated **for subjects <6 years of age** and will not be used for **this population, but** signs and symptoms of depression will be assessed at each visit.

Subject data listings of the data for the C-SSRS will be provided. No summaries of these results are planned.

Change #23

Section 9.1 Pharmacokinetics

Blood samples for the determination of LCM and SPM 12809 concentrations will be collected according to the protocol schedule of study assessments (on Visit 2 and 3, pre-dose between -59min to -3min in relation to iv LCM infusion and +1h to 4 hours after the end of the iv LCM infusion). Additional blood samples for PK analysis can be taken at the discretion of the investigator, especially in the event of a relevant treatment-emergent AE.

Has been changed to:

Blood samples for the determination of LCM and SPM 12809 concentrations will be collected according to the protocol schedule of study assessments (on Visit 2 and **if iv LCM treatment is continued after Day 1 also on Visit** 3, pre-dose **sample is taken** between -59 min to -3 min in relation to iv LCM infusion and +1h to 4 hours after the end of the iv LCM infusion). Additional blood samples for the PK analysis can be taken at the discretion of the investigator, especially in the event of a relevant treatment-emergent AE. **Blood samples with missing sampling time will be excluded from the analysis**.

Change #24

Table 8–1: Vital signs abnormality criteria

Criteria for age <4 years of age were added.

Table 8–2: ECG abnormality criteria

Criteria for age <4 years of age were added.

Appendices 12.1 List of Other significant AEs of VIMPAT

List of Other significant AEs of VIMPAT has been updated

Appendices 12.2.4 PDILI laboratory measurements

List of hematology PDILI laboratory measurements has been updated.

List of chemistry PDILI laboratory measurements has been updated.

Appendices 12.4 List of MedDRA Preferred Term for PDILI

List of MedDRA Preferred Term for PDILI was added.

13.2 AMENDMENT 2

Change #1

Section 3.2.5 Age and Age at first diagnosis

Age will be given in years and will be derived applying the rules for missing data imputation (see Section 4.2.1 and the SDTM derivation definition). The age at first diagnosis will be given in years and will be derived applying all rules for missing data imputation (see Section 4.2.1) with the following formula:

(Date of first diagnosis of epilepsy – Date of birth) / 365.25

Has been changed to:

Age will be given in years and will be derived applying the rules for missing data imputation (see Section 4.2.1 and the SDTM derivation definition). The age at first diagnosis will be given in years and will be derived applying all rules for missing data imputation (see Section 4.2.1) with the following formula**s**:

Missing or partial epilepsy diagnosis date will be derived applying all rules for missing data imputation (see Section 4.2.1) and age at first diagnosis will use the following formulas, where applicable.

The following formula will be applied where birthdate is a complete date:

(Date of first diagnosis of epilepsy – Date of birth) / 365.25

The following formula will be applied where birthdate is a partial date:

(Enrollment age in years) – [(Informed consent date – Epilepsy diagnosis date) / 365.25], if the value is negative then age at diagnosis will be set to zero.

Change #2

Change the word “subject” to “study participant” throughout the document.

Change the word “subject” to “patient” in part of section 2.3, study design and conduct.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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