STATISTICAL ANALYSIS PLAN

Study: EP0045

Product: Lacosamide

A NONINTERVENTIONAL STUDY OF <u>V</u>IMPAT® (LACOSAMIDE) AS ADJUNCTIVE ANTIEPILEPTIC DRUG THERAPY IN PATIENTS WITH <u>B</u>RAIN TUMOR RELATED <u>E</u>PILEP<u>S</u>Y (VIBES)

SAP/Amendment Number	Date
Final SAP	8 Jan 2015
SAP Amendment 1	7 Dec 2017

Confidentiality Statement

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LIST OF ABBREVIATIONS

aCRF	annotated Case Report Form
ADR	adverse drug reaction
AED	antiepileptic drug
AESI	adverse event of special interest
BTRE	brain tumor-related epilepsy
CGIC	Clinical Global Impression of Change
CI	confidence interval
CRF	Case Report Form
CSR	Clinical Study Report
D	The number of days in the time interval considered for the derivation of seizure frequency
DEM	Data Evaluation Meeting
EQ-5D-5L	5-Level EuroQol-5 Dimension Quality of Life Assessment
ES	Enrolled Set
FAS	Full Analysis Set
Gy	Gray
HLT	High Level Term
LCM	lacosamide
MDASI-BT	M.D. Anderson Symptom Inventory - Brain Tumor
MedDRA®	Medical Dictionary for Regulatory Activities
NIS	Non-interventional study
PGIC	Patient Global Impression of Change
PT	preferred term
QoL	quality of life
SAP	Statistical Analysis Plan
SEP	Submission excellence program
SOC	system organ class
SOP	Standard operating procedure
SD	standard deviation
SS	Safety Set
VAS	visual analogue scale

WHO   World Health Organization

WHO DD   World Health Organization Drug Dictionary

1   INTRODUCTION

This document outlines the planned analyses to support the EP0045 clinical study report (CSR). It includes all definitions and details for the evaluation of data recorded during the study. This SAP should be read in conjunction with the non-interventional study observation plan dated 1 June 2015 and the annotated case report forms (aCRF) dated 31 August 2017.

2   PROTOCOL SUMMARY

2.1   Study objectives

2.1.1   Primary objective

The primary objective of this study is to evaluate the effectiveness and patient global impression of lacosamide (LCM) added to 1 or 2 antiepileptic drugs (AEDs) in the treatment of patients with brain tumor-related epilepsy (BTRE) due to low-grade primary brain tumor.

2.1.2   Secondary objective

The secondary objective of this study is to evaluate the tolerability and quality of life (QoL) of patients with BTRE due to low-grade primary brain tumor who are treated with LCM added to 1 or 2 AEDs.

2.2   Study variables

2.2.1   Efficacy variables

2.2.1.1   Primary efficacy variables

The following primary variables will be measured:

- Response at the end of the 6-month Observation Period, where a responder is a patient experiencing a 50% or greater reduction in partial-onset seizure frequency from Visit 1 (Baseline) to Visit 3 (Month 6 or end of Observation Period)

- Patient Global Impression of Change (PGIC) rating at Visit 3 (Month 6 or end of Observation Period)

2.2.1.2   Secondary efficacy variables

The following secondary variables will be measured:

- Retention on LCM at the end of the 6-month Observation Period

- Time to discontinuation of LCM treatment from the date of first dose of LCM

- Change from Visit 1 (Baseline) to Visit 3 (Month 6 or end of Observation Period) in the 5-Level EuroQol-5 Dimension Quality of Life Assessment (EQ-5D-5L) visual analogue scale (VAS) score and change in utility as converted from the 5 dimensions

- Change from Visit 1 (Baseline) to Visit 3 (Month 6 or end of Observation Period) in the M.D. Anderson Symptom Inventory - Brain Tumor (MDASI-BT)

- Actual change from Visit 1 (Baseline) to Visit 3 (Month 6 or end of Observation Period) in seizure frequency (seizures per 28 days)

- Percentage change from Baseline in seizure frequency

- Seizure-free status (Yes/No) at the end of the 6-month Observational Period

- Discontinuation rate of LCM due to adverse drug reactions (ADRs)

- Discontinuation rate of LCM due to lack of effectiveness

- Clinical Global Impression of Change (CGIC) rating at Visit 3 (Month 6 or end of Observation Period)

2.2.2 Pharmacokinetic/Pharmacodynamic variables

Not applicable

2.2.3 Safety variables

The following safety variables will be collected:

- Occurrence of ADRs or adverse events of special interest (AESIs) spontaneously reported by the patient or observed by the treating physician

- Patient withdrawal due to ADRs

2.3 Study design and conduct

EP0045 is a multicenter, prospective, single-arm non-interventional study (NIS) conducted at specialized sites utilizing LCM added to existing treatment with 1 or 2 AEDs in patients ≥16 years of age with BTRE secondary to low-grade tumor.

There are expected to be approximately 100 patients enrolled in the study (see Section 2.4) with 93 evaluable patients expected. Approximately 20 specialized centers are planned for participation. The expected recruitment period is 12 months. The Observation Period per patient will be up to 6 months after initiation of LCM treatment.

The patients will be followed as per current clinical practice for their condition. No additional diagnostic or monitoring procedures will be applied. The choices of AED treatment are made independently by the treating physician in the regular course of practice and are, therefore, independent of participation in this NIS.

The clinical evaluation of patients with BTRE secondary to low-grade tumor will be performed by the treating physician following routine clinical practice. All visits and assessments will be scheduled and conducted per routine clinical practice. It is anticipated that visits will occur every 3 months based on standard of care; therefore, each patient will have approximately 3 visits during their participation in this study. These visits will consist of:

- Visit 1, Baseline

- Visit 2, approximately 3 months after Baseline according to routine practice

- Visit 3, approximately 6 months after Baseline according to routine practice or end of Observation Period

Patients who discontinue early should perform Visit 3 assessments as a Withdrawal Visit.

At the Baseline Visit patient demographics, seizure frequency, and Baseline epilepsy medication will be documented. Assessment of Baseline seizure frequency will be assessed by retrospectively collecting seizure incidence during a period of 8 weeks prior to first LCM intake.

During the study seizure counts will be collected at each visit. At the last visit the patient's impression of change using the PGIC score will be recorded. The management and reporting of ADRs and AESIs will be handled according to international drug safety regulations and UCB procedures.

2.4 Determination of sample size

A sample size of 100 enrolled patients to obtain 93 evaluable patients was chosen for this study based on an expected 6-month responder rate (where a responder is a patient experiencing a 50% or greater reduction in partial onset seizure frequency from Visit 1 [Baseline] to Visit 3 [Month 6 or end of Observation Period]) of 60% with an expected precision in the 95% confidence interval (CI) of approximately ±10% for this estimate of response.

When the sample size is 93, a 2-sided 95% CI for a single proportion using the large sample normal approximation will extend 0.10 from the observed proportion for an expected proportion of 0.60.

Recruitment will be stopped at 100 enrolled patients and withdrawals will not be replaced.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

All statistical analyses will be performed in an exploratory manner. Statistical analyses and generation of tables, figures, and listings will be performed using SAS version 9.1 or higher using validated program code according to relevant standard operating procedures. All tables and listings will use courier new font size 9.

A complete set of data listings containing both, documented data and all calculated data (eg, changes from Baseline) will be generated.

For continuous variables, summary statistics (number of available observations, mean, standard deviation (SD), minimum, lower quartile, median, upper quartile and maximum) will be tabulated. For categorical variables, frequency tables (number and percentages per category) will be presented. Unless otherwise specified the denominator for calculating percentages will be the number of patients in the respective population.

Unless otherwise noted, all percentages with the exception of 0 and 100 will be expressed to 1 decimal place, and 100% will be presented as integer. If a category has the frequency 0, the percentage value will be omitted. Mean and median changes from Baseline lower than the minimal displayable change will be displayed without sign (eg, -0.00 will be displayed as 0.00).

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
- Minimum and maximum will have the same number of decimal places as the original value

3.2 General study level definitions

3.2.1 Analysis time points

The following visits are recommended documentation time points and will be considered for analysis. Due to the nature of a NIS, the time points given for each visit are approximated, expected time points only.

- Visit 1, Baseline

- Visit 2 (approximately 3 months after Baseline): Visits that occurred ≤ 135 days after Visit 1

- Visit 3 (approximately 6 months after Baseline or Withdrawal Visit for patients who discontinue early): All visits that occurred > 135 days after Visit 1

If there are 2 visits that meet the criteria for Visit 2, then the visit nearest to the scheduled assessment time for Visit 2 will be used (i.e. 90 days after Visit 1). If there are 2 visits that meet the criteria for Visit 3, then the visit nearest to the scheduled assessment time for Visit 3 will be used (i.e. 180 days after Visit 1). No different study periods will be considered for this NIS. However, the period for the analysis of safety variables is defined as follows:

- Observational Period: The Observational Period starts with the start date of LCM and ends at the day of study termination. In case the start date of LCM is missing, the date of Visit 1 will be used instead.

3.2.2 End date of the Observational Period

The end date of the Observational Period will be the date of Visit 3, which is approximately 6 months after Baseline for subjects completing the Treatment Period, or the Withdrawal Visit for subjects who discontinued during the Observational Period. If a subject does not have a Visit 3 for any reason including death, then either the date of early withdrawal or the date of last known dose of study drug during the Observational Period, whichever is later, will define the end date of the Observational Period.

3.3 Definition of Baseline values

Concomitant AEDs at Baseline are defined as AEDs given at the start date of LCM or the date of Visit 1 in case of a missing start date of LCM.

For all other variables, Baseline data are the values collected at Visit 1.

Baseline for the partial-onset seizure frequency per 28 days will be derived from the data of the Historical Seizure Count form as described in Section 3.10.4.

3.4 Protocol deviations

A Per-Protocol Set will not be used for the analyses. However, important protocol deviations will be identified prior to database lock and listed in the Clinical Study Report.

The definition of important protocol deviations is initiated by the Clinical Data Manager with the input from the PRA Project Manager and other stakeholders (please refer to applicable UCB submission excellence program [SEP] standard operating procedures [SOPs] for details). Search criteria for potential protocol deviations will be detailed in the important protocol deviations document, which is an addendum to the Data Cleaning Plan. Where possible, protocol deviations are to be identified programmatically.

Data cleaning meetings will be held where important protocol deviations identified programmatically or in other supplemental documents based on data not collected in the CRF are reviewed and discussed. Data Evaluation Meetings (DEMs) will also be held and during these meetings the protocol deviations will be discussed and any trends identified. Preparation and conduct of the Data Cleaning and Data Evaluation Meetings will be performed as per UCB's current SEP SOPs and Guidelines.

3.5 Analysis sets

For this study, 4 analysis sets are defined:

3.5.1 Enrolled Set

The Enrolled Set (ES) is defined as all patients included in the study and for whom at least Visit 1 is documented. The ES will be used for patient disposition and patient data listings only.

3.5.2 Safety Set

The Safety Set (SS) is defined as all patients included in this study receiving treatment with LCM at least once in the study. The SS will be used for the analysis of the retention and discontinuation rates, time to discontinuation, safety data, and Baseline characteristics of the patients.

3.5.3 Full Analysis Set

The Full Analysis Set (FAS) is defined as all patients in the SS who have at least 1 post-Baseline PGIC or seizure assessment. The FAS will be used for the analysis of the primary and most secondary variables including any subgroup analyses. In addition, demographic and baseline summaries will be based on the FAS.

3.5.4 Modified FAS

The modified FAS is defined as all patients in the FAS ≥16 years of age and treated with daily LCM doses ≤400mg, representing the on-label use of LCM. All efficacy analyses excluding subgroup analyses, demographic and baseline summaries and some safety summaries will be repeated in the modified FAS.

On-label use for this study is defined as receiving a LCM daily dose <= 400mg. Patients who receive at least one dose of LCM that is >400mg will be excluded from the modified FAS.

3.6 Treatment assignment and treatment groups

All patients treated received LCM with the dosage determined at the discretion of the physician. Data summaries will be presented based on the total number of patients and will not be differentiated by LCM dose with the exception of the frequency of seizures occurring at doses of LCM < 200 mg and ADRs presented by dose. Where appropriate, LCM dose will be presented on patient data listings.

3.7 Center pooling strategy

No data pooling strategies will be applied for analyses within this study. Unless otherwise stated, data from all centers will be combined and summarized collectively.

3.8　　　Coding dictionaries

Medical history and ADRs will be coded using version 16.1 of the Medical Dictionary for Regulatory Activities (MedDRA®). For coding of prior and concomitant medication, version Sep 2013 of World Health Organization Drug Dictionary (WHO DD) will be used.

3.9　　　Changes to protocol-defined analyses

Not applicable.

3.10　　　Definitions of study-specific derived variables

3.10.1　　　Relative Day

The relative day of a visit or an event with respect to the first application of LCM will be presented in patient data listings. Relative days will be calculated as follows:

1. If the start (stop) date occurred prior to the start of LCM, the relative day is calculated as start (stop) date minus date of first LCM intake. That means that in patient data listings, relative days based on this situation will be preceded by a '-'.

2. If the start (stop) date occurred on or after the start of LCM, the relative day is calculated as start (stop) date minus date of first LCM intake + 1.

If the visit or event occurred after the date of last dose of LCM, then the relative day is derived using the date of last dose of LCM rather than the date of first LCM intake. In this situation the relative days will be calculated as follows:

• The relative day is calculated as start (stop) date minus last dose date. In patient data listings, relative days based on this situation will be preceded by a '+' to differentiate this situation from item 2 above.

Relative days will not be presented for partial or missing dates.

3.10.2　　　Age

The age will be given in years and will be calculated as year of informed consent date – year of birth.

3.10.3　　　Time since first diagnosis

The time since first diagnosis will be given in years and will be derived applying all the rules for missing date imputation (see Section 4.2.3) with the following formula:

(Start date of LCM - date of diagnosis) / 365.25

Only completed years will be considered, ie, decimal places will be ignored. In cases where the start date of LCM is missing, the date of Visit 1 will be used instead.

3.10.4　　　Seizure Frequency

Partial-onset seizure frequency per 28 days will be derived from the number of days in the considered time interval (D) for which seizure information was provided:

(Number of seizures over the specified time interval) x (28/D)

The considered time interval is defined as 56 days for the historical seizure count at Baseline (8 weeks x 7 days) and as date of actual visit – date of previous visit for all other time points. Note

if any subjects have a diagnosis of epilepsy less than 8 weeks prior to study entry, then site will be instructed to give their best approximation of the 8-week seizure frequency and the reported historical seizure count will be assumed to be representative of the full 8 weeks. The seizure frequency per 28 days cannot be derived using the time from diagnosis of epilepsy to study start as the time period for reporting the historical seizure frequency for such subjects because only the month and year are collected for the date of diagnosis.

The absolute and percentage change in partial-onset seizure frequency from Baseline (Visit 1) will be derived for Visit 2 and Visit 3.

A responder is defined as a patient who experiences a 50% or greater reduction in partial-onset seizure frequency from Visit 1 (Baseline) to Visit 3 (Month 6 or end of Observation Period).

The seizure-free status (Yes/No) at the end of the 6-month Observation Period will be determined for each patient. A patient is seizure-free if the seizure count at Visit 3 (Month 6 or end of the Observation Period) is 0, otherwise the patient is not seizure-free at the end of the 6-month Observation Period.

The frequency of seizures with and without secondary generalization will also be calculated based upon the response to the question 'Number of partial-onset seizures with secondary generalization' in the CRF. If the number with secondary generalization is known, the number of seizures with secondary generalization will be taken from the CRF and the number of seizures without secondary generalization will be calculated as overall number of seizures – number of seizures with secondary generalization.

Partial-onset seizure frequency per 28 days at a dose of <200mg/day at Visit 2 and Visit 3 will be derived from the number of days in the considered time interval (D) for which seizure information was provided where the subject was on a dose of <200mg/day according the dosing log for LCM:

   (Number of seizures over the specified time interval) x (28/D).

The number of seizures is the number of partial onset seizures at a dose <200mg/day. The time interval for Visit 2 is the number of days between the Visit 1 and Visit 2 dates where the subject was on a dose <200mg/day for LCM. The time interval for Visit 3 is the number of days between the Visit 2 and Visit 3 dates where the subject was on a dose <200mg/day for LCM. The change from baseline will then be derived by subtracting the partial onset seizure frequency per 28 days reported at Baseline from the partial onset seizure frequency per 28 days on a dose <200mg/day at Visit 2 and Visit 3. If the number at less than 200 mg/day is not applicable, then the number of partial-onset seizures at less than 200 mg/day is treated as missing.

3.10.5   Patient Global Impression of Change

Patients will be categorized based on their PGIC value collected at Visit 3 into the following groups:

- Improved: scores 1 to 3

- No change: score 4

- Worsened: score 5 to 7

3.10.6   Retention rate

The 6-month retention rate is the percentage of patients remaining in the study and on LCM treatment for 6 months. This will be estimated using Kaplan-Meier methodology applied to the time to discontinuation of LCM. A cut of 180 days will be used for 6 months. The derivation of the time to discontinuation and the corresponding censoring flag are described in Section 3.10.7.

3.10.7   Time to discontinuation of LCM

Time to discontinuation of LCM will be defined as

The date of last administration of LCM while in the study - the date of first dose of LCM + 1

If the date of last administration of LCM while in the study is not available the study termination date will be used. If the start date of LCM is missing, then it is assumed that the patient did not receive treatment and they would be consequently excluded from the relevant analysis sets and therefore from this analysis.

A censor flag will be derived where patients who completed the study are censored and patients who have discontinued LCM prior to the end of the 6-month Observation Period (early withdrawals) are not censored.

3.10.8   EQ-5D-5L

The EQ-5D is comprised of 5 item health status measures and a visual analogue scale (VAS) scale. The EQ-5D VAS records the respondent's self-rated health state on a vertical 20 cm scale, 0 to 100 graduated (0=worst imaginable health state, 100=best imaginable health state).

Utility as converted from the 5 dimensions will be derived. Each patient's responses to the five 5-dimension questions are converted to a 'health state' which is summarized, for example, as 11111 (where the patient answered 1 to each of the 5 dimension questions). The health state is then mapped to a utility value from the most recent UK valuation set (http://www.euroqol.org/about-eq-5d/valuation-of-eq-5d/eq-5d-5l-value-sets.html).

Absolute scores and changes from Visit 1 (Baseline) to Visit 3 (Month 6 or end of Observational Period) for the VAS score and the utility will be derived for patients with an evaluable Baseline assessment.

3.10.9   M.D. Anderson Symptom Inventory Brain Tumor Module

The MDASI-BT includes 9 brain tumor specific symptom items in addition to the core MDASI 13 symptom items and the 6 interference items. The brain tumor specific symptom items include: weakness on one side of the body, difficulty understanding, difficulty speaking, seizures, difficulty concentrating, vision, change in appearance, change in bowel pattern (diarrhea or constipation), and irritability.

The mean core symptom severity is the mean of the 13 core symptom items. If at least 7 of the items have been scored, then the mean core symptom severity is the sum of the items answered divided by the number of items answered.

The mean module symptom severity is the mean of the 9 brain tumor specific symptom items. If at least 5 of the items have been scored, then the mean module symptom severity is the sum of the items answered divided by the number of items answered.

The mean total symptom severity is the mean of all 22 symptom items. If more than 50% of the items are answered, then the mean total symptom severity is the sum of the items answered divided by the number of items answered.

The mean interference is the mean of the 6 interference items. If more than 50% of the items are answered, then the mean interference is the sum of the items answered divided by the number of items answered.

Absolute scores and changes from Visit 1 (Baseline) to Visit 3 (Month 6 or end of Observational Period) for the individual items of the MDASI-BT, the mean core symptom severity scale, the mean module symptom severity, the mean total symptom severity and mean interference will be derived for patients with an evaluable Baseline assessment. Patients with an evaluable Baseline assessment for MDASI-BT are defined as patients who have not started LCM at the time of Visit 1.

3.10.10   Discontinuation of LCM due to an ADR

A patient who discontinued LCM due to an ADR is defined as a patient who prematurely terminated from the study and the primary reason for premature study termination = "ADVERSE DRUG REACTION".

3.10.11   Discontinuation of LCM due to lack of efficacy

A patient who discontinued LCM due to lack of efficacy is defined as a patient who prematurely terminated from the study and the primary reason for premature study termination = "LACK OF EFFICACY".

3.10.12   Discontinuation of LCM due to lack of effectiveness

A patient who discontinued LCM due to lack of effectiveness is defined as a patient who prematurely terminated from the study and the primary reason for premature study termination = "LACK OF EFFICACY" or "ADVERSE DRUG REACTION".

3.10.13   Clinical Global Impression of Change

Patients will be categorized based on their CGIC value collected at Visit 3 into the following groups:

- Improved: scores 1 to 3

- No change: score 4

- Worsened: score 5 to 7

3.10.14   Exposure

Actual dosing of LCM is documented on the Drug Dosing Log CRF. The duration of exposure to LCM in days is calculated as the end date of last administration of LCM minus the start date of first administration of LCM +1. If LCM is ongoing at the end of the study, the day of last administration of study drug recorded on the Study Termination CRF will be used as the end of administration. Gaps in LCM treatment or days on the Study Medication Administration form with unknown dosing will not be subtracted from the overall exposure days.

Subject-years of exposure will be calculated as the number of days of exposure (summed over all patients), divided by 365.25.

The maximum daily dose will be calculated as the highest total daily dose the patient received during the Observational Period.

The modal dose (mg/day) will be defined as the daily LCM dose the patient received for the longest duration during the Observational Period. The modal dose calculation is based on the number of days a patient was on a given daily dose. Gaps in LCM dosing will be excluded from the determination of modal dose (ie, no imputation for days with missing dosing information will be performed). If multiple doses have the same maximum number of days of occurrence, the maximum of these doses will be used as the modal dose.

3.10.15   Adverse Drug Reactions

Adverse drug reactions will be documented during the study only. Since an ADR is an adverse event related to the medication to be investigated (LCM), all reported ADRs are considered treatment-emergent and will be included in the analysis.

An ADR with action taken regarding UCB suspected drug reported as "Permanently discontinued" will be regarded as an ADR leading to discontinuation of LCM.

Adverse drug reactions that have the question "Seriousness indicators: Is the event/reaction serious?" answered "yes" are considered as serious.

Note AESIs are collected as ADRs and will be treated as ADRs in the analysis.

Other significant ADRs will be summarized.

4   STATISTICAL/ANALYTICAL ISSUES

No formal statistical analyses will be performed. All variables will be summarized using descriptive statistics; there will be no inferential analyses. For continuous variables, summary statistics (number of available observations, mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum) will be tabulated. Categorical variables will be summarized by the number of patients and the percent of patients in each category. For time to event variables, medians derived using Kaplan-Meier estimates and corresponding 95% CIs will be presented. Supporting Kaplan-Meier plots will be presented.

Data from patients who prematurely withdraw from the study will be analyzed up to the final visit attended.

4.1   Adjustments for covariates

No formal statistical analyses will be performed and consequently there will be no adjustment for covariates.

4.2   Handling of dropouts or missing data

All available data will be used for analysis.

Missing data of the variables will not be substituted. However, imputations of missing values as described in this section will be done in order to use the available data as much as possible, eg, imputations for missing or partial values for dates will be applied to calculate derived variables or to determine prior and concomitant medication

With respect to ADRs, events with missing information about action taken regarding UCB suspected drug status are regarded as ADRs leading to premature discontinuation. Events with no

answer to the question "Seriousness indicators: Is the event/reaction serious?" will be regarded as serious.

4.2.1   Incomplete dates for medication and ADRs

In order to classify medication as prior or concomitant or to classify an ADR as treatment emergent, a complete date must be established. For the purposes of imputing missing components of partially-reported start and stop dates for medication use or ADRs, the algorithms listed below will be followed. Start and stop dates will be displayed as reported in the patient data listings (ie, no imputed values will be displayed in data listings).

- Missing start day but month and year present:

  If the start of LCM occurred in the same month and year as the start of the medication or ADR, the start day of the medication or ADR will be assigned to the day of first administration of LCM.

  Otherwise the start day will be set to the 1st day of the month.

- Missing start day and month but year present:

  If the start of LCM occurred in the same year as the start of the medication or ADR, the start day and month will be assigned to the date of first administration of medication.

  Otherwise the start day and month will be set to January 1st.

- Missing end day but month and year present:

  The end day will be set to the last day of the month.

- Missing end day and month but year present:

  The end day and month will be set to the date of study termination. However, if the study termination year is greater than the medication or ADR end year, the day and month are to be set to December 31st.

- Missing year but month or day and month present:

  The rules as described in Section 4.2.2 will be followed.

If the end date is completely missing, then the medication or ADR are assumed to be ongoing.

4.2.2   Definition of concomitant medication in case of missing dates

The following rules for classifying medication as prior or concomitant will be applied in the case of completely missing stop and/or start date information:

Table 4‒1: Rules for assignment of medication in case of missing start and/or stop dates

Start date	Stop date	Prior medication	Concomitant medication
Missing	Missing	Yes	Yes
Missing	Before start date of LCM	Yes	No
Missing	After start date of LCM	Yes	Yes

Table 4–1: Rules for assignment of medication in case of missing start and/or stop dates

Start date	Stop date	Prior medication	Concomitant medication
Before or on start date of LCM	Missing	Yes	Yes
After start date of LCM	Missing	No	Yes

In patient data listings, dates will be displayed as reported.

4.2.3 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:

- Year is missing
- Start and stop dates of ADRs
- Start and stop dates of medications (see Sections 4.2.1 and 4.2.2)
- Start and stop dates of LCM
- Date of final contact
- Date of premature discontinuation

Incomplete dates for final contact and premature discontinuation, respectively, will be completed using the latest calendar date based on the partial date provided.

Start and stop dates of ADRs and LCM will not be imputed.

Completely missing dates or dates with a missing year will not be replaced, and the corresponding derived variables will be set to missing.

4.3 Interim analyses and data monitoring

No interim analysis or data monitoring board is planned in this NIS. Selected interim data may be reviewed periodically to detect as early as possible any safety concern(s) related to LCM and appropriately inform the treating physicians, patients, regulatory authorities, and/or Investigational Review Boards/Independent Ethics Committees.

4.4 Multicenter studies

Descriptive summaries for individual centers will not be presented. Subject data listings will provide data grouped by center.

4.5 Multiple comparisons/multiplicity

No formal statistical analyses will be performed on the primary endpoints. Therefore no adjustment for multiplicity is required.

4.6 Use of an efficacy subset of subjects

The modified FAS will be used to represent the on-label use of LCM.

4.7   Active-control studies intended to show equivalence

This is a single arm study and consequently this section is not applicable.

4.8   Examination of subgroups

The primary endpoints will be summarized by the following subgroups, if at least 25 patients fall
into that subgroup:

- Starting dose of LCM (high starting dose - first dose >=200mg/day; titration – first dose
  <200mg/day)

- Prior tumor treatment (radiotherapy; chemotherapy; surgery; radiotherapy and chemotherapy;
  radiotherapy and surgery; chemotherapy and surgery; radiotherapy, chemotherapy and
  surgery)

- Concomitant tumor treatment (radiotherapy; chemotherapy; surgery; radiotherapy and
  chemotherapy; radiotherapy and surgery; chemotherapy and surgery; radiotherapy,
  chemotherapy and surgery)

- Number of different types of lifetime AEDs (1; 2; 3; 4)

- Core AED therapy (including but not limited to levitiracetam, valproate sodium, lamotrigine,
  oxcarbazepine, zonisamide, topiramate, pregabalin, gabapentin, phenytoin, carbamazepine,
  clonazepam clobazepam, phenobarbital, valproic acid, ergenyl chrono; combinations of these
  therapies)

  Note: Each subject can be only in 1 category for "Core AED therapy"

- Age (≥16 - ≤18; >18 - <65; ≥65)

- Sex (male; female)

- Historical seizure frequency (1; 2-5; 6+)

- Historical seizure type (Partial-onset seizures with secondary generalization; Partial-onset
  seizures without secondary generalization; Both)

- Time since tumor diagnosis (≤1 month; >1 - ≤3 months; >3 - ≤6 months; >6 months - ≤12
  months; >12 - ≤24 months; >24 months)

- Type of brain tumor (astrocytoma; oligodendroglioma; mixed [oligo-astro]; ependymoma;
  other)

- WHO grade (1; 2; 3; 4)

- Karnofsky performance status (<60%; 60%; 70%; 80%; 90%; 100%)

5   STUDY POPULATION CHARACTERISTICS

5.1   Subject disposition

The number and percentage of patients in each population (ES, SS, FAS and modified FAS) will
be presented. The number of patients in each population will also be provided by investigator in
addition to the dates of first patient in and the last patient out for each center.

Study eligibility criteria, patients who did not meet any of these criteria as well as patient disposition, patient analysis sets and visit dates will be provided in listings.

The number and percentage of patients who started treatment with LCM, completed, and discontinued from the study will be presented for the SS together with a summary of primary reason for prematurely terminating the study. Subjects who discontinued the study prematurely will be listed.

5.2   Protocol deviations

The number and percentage of patients with at least 1 important protocol deviation in each of the categories defined in the Important Protocol Deviations Template will be summarized for the SS and modified FAS. Percentages for single deviations are based on the number of patients with any deviation.

All important protocol deviations for patients in the ES will be listed by site, patient number, and protocol deviation category.

6   DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

If not stated otherwise, the following analyses will be performed for the SS, the FAS and the modified FAS. Corresponding listings will be based on the ES.

6.1   Demographics

The following demographics will be summarized and listed:

- Age (years) – continuous and categorized as ($\leq$18, >18-<65, $\geq$65 years)

- Gender (male, female)

6.2   Other Baseline characteristics

The following characteristics will be summarized at Baseline:

- Time since tumor diagnosis (years) – continuous

- Type of brain tumor (astrocytoma, oligodendroglioma, mixed [oligo-astro], ependymoma, other)

- Tumor (WHO) grade (1, 2, 3, 4)

- Karnofsky performance status

Details of concomitant procedures and procedure history will be listed. Karnofsky performance status and tumor characteristics will also be listed at Baseline and post-Baseline assessments.

6.3   Medical history and concomitant diseases

Medical history will be summarized for the SS by MedDRA system organ class (SOC) and preferred term (PT), displaying the number and percentage of patients with history present overall as well as for each SOC and each PT. Medical history and a glossary for medical history will be listed.

6.4   Prior and concomitant medications

The number and percentage of patients who used prior and concomitant medications (including chemotherapy and AEDs) will be summarized according to the anatomical therapeutic class main group, the therapeutic subgroup, and the generic drug name.

Prior medications are those medications started before the first dose of study drug. Medication taken after the first dose of study medication will be regarded as concomitant medication whether the start date is before, after or on the date of the first dose of study medication. Lifetime AEDs are AEDs with an end date before the first dose of study drug.

The core AED will be summarized separately using the "Core AED?" question on the CRF to select the relevant medications. The core AEDs are the AEDs that the patient is receiving at Baseline.

The number and percentage of patients according to Core AED therapies will be summarized according to preferred term combination.

The number and percentage of patients who had prior or concomitant radiotherapy will be summarized. The total dose in gray (Gy) and number of fractions will be summarized as continuous variables.

Rules for defining concomitant medications with missing dates are provided in 4.2.2.

All prior and concomitant medication and radiotherapy will be listed.

7   MEASUREMENTS OF TREATMENT COMPLIANCE

There are no assessments of compliance in this NIS.

8   EFFICACY ANALYSES

8.1   Statistical analysis of the primary efficacy variables

Summaries of the primary variables will be conducted in the FAS and the modified FAS. All efficacy data will be listed in the ES.

8.1.1   Derivations of primary efficacy variables

8.1.1.1   Seizure frequency response

A responder is defined as a patient who experiences a 50% or greater reduction in partial-onset seizure frequency from Visit 1 (Baseline) to Visit 3 (Month 6 or end of Observation Period).

8.1.1.2   Patient Global Impression of Change

Patients will be categorized based on their PGIC value collected at Visit 3 into the following groups:

- Improved: scores 1 to 3

- No change: score 4

- Worsened: score 5 to 7

8.1.2 Primary analysis of primary efficacy variables

8.1.2.1 Seizure frequency response

The number and percentage of responders, where a responder is a patient experiencing a 50% or greater reduction in partial onset seizure frequency from Visit 1 (Baseline) to Visit 3 (Month 6 or end of Observation Period), will be presented. The 95% CI for the percentage of responders will be calculated using the 2-sided Clopper-Pearson method.

Percentages are based on the number of patients with available data.

The seizure frequency response rate and corresponding 95% CI (2-sided Clopper-Pearson method) will be presented in each of the subgroups described in Section 4.8.

8.1.2.2 Patient's Global Impression of Change

The number and percentage of patients within each response category for PGIC (1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, and 7=very much worse) will be summarized.

Additionally, the number and percentage of patients who improved (impression of change <4), had no change (impression of change =4), and worsened (impression of change >4) will also be provided.

Percentages are based on the number of patients with available data.

Summaries of PGIC will be presented in each of the subgroups described in Section 4.8.

8.2 Statistical analysis of the secondary efficacy variables

Summaries of the secondary variables will be conducted in the FAS and modified FAS unless otherwise stated.

8.2.1 Retention rate

Retention rate is defined as the percentage of patients remaining in the study and on LCM treatment for 6 months (6-month retention rate). The number of patients remaining in the study and on LCM treatment for 6-months will be summarized with the retention rate in the SS, the FAS and the modified FAS. The retention rate will be derived using Kaplan-Meier methodology where patients who remain on treatment at the end of the 6-month Observation Period are censored at the date of last administration of LCM. A 2-sided 95% CI (based on Greenwood's formula) for the 6-month retention rate will be presented.

8.2.2 Time to discontinuation of LCM

Time to discontinuation of LCM from the date of first dose of LCM will be analyzed using Kaplan-Meier methods for the SS, the FAS and the modified FAS. The median time to discontinuation (days) of LCM including corresponding 2-sided 95% CIs for the median time to discontinuation will be calculated. Patients who complete the 6-month Observation Period will be censored on the date of the final LCM administration or the study termination date if the date of the final LCM administration is not available.

Supportive Kaplan-Meier plots of time to discontinuation of LCM from the date of first dose of LCM will be presented for the SS, the FAS and the modified FAS.

8.2.3   EQ-5D-5L

Descriptive statistics for the observed value and change from Visit 1 (Baseline) to Visit 3 (Month 6 or end of Observation Period) in the EQ-5D-5L VAS score and utility as converted from the 5 dimensions using the most recent value set will be presented. The EQ-5D-5L will be assessed only for patients with an evaluable Baseline assessment (eg, patients who have not started LCM at the time of the Visit 1 assessment).

8.2.4   M.D. Anderson Symptom Inventory Brain Tumor Module

Descriptive statistics for the observed value and change from Visit 1 (Baseline) to Visit 3 (Month 6 or end of Observation Period) in the individual items of the MDASI-BT, the mean core symptom severity scale, the mean module symptom severity, the mean total symptom severity and mean interference will be presented. The MDASI-BT will be assessed only for patients with an evaluable Baseline assessment (eg, patients who have not started LCM at the time of the Visit 1 assessment).

8.2.5   Seizure frequency

Descriptive statistics for absolute values and percent change from Baseline will be presented by visit for the following variables:

- Partial-onset seizure frequency per 28 days for focal seizures with and without secondary generalization

- Partial-onset seizure frequency per 28 days for focal seizures without secondary generalization.

- Partial-onset seizure frequency per 28 days for focal seizures with secondary generalization

- Partial-onset seizure frequency per 28 days that occurred at less than 200 mg/day

The Baseline for all subjects in the FAS and the Baseline for subjects who received at least one dose of <200mg/day LCM during the treatment period will be summarized for Visit 1 which only includes subjects who have a dose of <200mg/day at some point during the study and thus would have a seizure frequency at <200mg/day LCM reported. Percentages are based on the number of patients with available data.

8.2.6   Seizure-free status

The number and percentage of patients achieving a seizure-free status (Yes/No) at the end of the 6-month Observation Period will be presented. Percentages are based on the number of patients with available data. A 2-sided 95% CI (calculated using the 2-sided Clopper-Pearson method) for the percentage of patients achieving a seizure-free status (Yes/No) will be presented.

8.2.7   Discontinuation of LCM due to an ADR

The number and percentage of patients who discontinue LCM due to an ADR will be presented for the SS, the FAS and the modified FAS. A 2-sided 95% CI (calculated using the 2-sided Clopper-Pearson method) for the percentage of patients who discontinue LCM due to an ADR will be presented.

8.2.8 Discontinuation of LCM due to lack of efficacy

The number and percentage of patients who discontinue LCM due to lack of efficacy will be presented for the SS, the FAS and the modified FAS. A 2-sided 95% CI (calculated using the 2-sided Clopper-Pearson method) for the percentage of patients who discontinue LCM due to lack of efficacy will be presented.

8.2.9 Discontinuation of LCM due to lack of effectiveness

The number and percentage of patients who discontinue LCM due to lack of effectiveness will be presented for the SS, the FAS and the modified FAS. A 2-sided 95% CI (calculated using the 2-sided Clopper-Pearson method) for the percentage of patients who discontinue LCM due to lack of effectiveness will be presented.

8.2.10 Clinical Global Impression of Change

The number and percentage of patients within each response category for CGIC (1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse,6=much worse, and 7=very much worse) will be summarized for the FAS and modified FAS. Additionally, thenumber and percentage of patients who improved (impression of change <4), had no change (impression of change =4), and worsened (impression of change >4) will also be provided.

Percentages are based on the number of patients with available data.

9 PHARMACOKINETIC AND PHARMACODYNAMICS

Not applicable.

10 SAFETY ANALYSES

All statistical analyses for the safety variables will be performed for the SS and the modified FAS in an exploratory manner. Exposure data will be listed in the SS and adverse drug reactions will be listed in the ES.

10.1 Extent of exposure

The following information about intake of LCM during the study will be summarized:

- Duration of exposure (days) including patient years of exposure
- Maximum daily dose (mg/day)
- Modal daily dose (mg/day)
- LCM ongoing at the end of the study (yes, no)

10.2 Adverse events

Adverse drug reactions will be coded for analysis with version 16.1 of MedDRA. Note that AESIs will be collected as ADRs and consequently AESIs will be included in the summary tables and listings for ADRs.

Adverse drug reactions that occur during this study will be presented by MedDRA SOC and PT in a frequency table giving the number and percentage of patients experiencing each event at least once as well as the number of events. For the number and percentage of patients, patients

with multiple ADRs will be counted only once within each PT and SOC. All table summaries will be sorted alphabetically by SOC and by decreasing relative frequency of each PT within SOC.

The following tabular summaries will be presented.

- Adverse drug reactions

- Serious ADRs

- Non-serious ADRs

- Non-serious ADRs above reporting threshold of 5% (as per the requirements for the EU agency)

- Adverse drug reactions leading to discontinuation

- Deaths

- ADRs by dose at onset (dose categories will be agreed during the DEM to obtain a sensible distribution)

- Other significant ADRs

An overall summary table of all ADRs will be presented summarizing the ADR categories given above (except non-serious ADRs above reporting threshold).

A listing of all ADRs will be provided as follows:

- Individual patients (identified by patient numbers) experiencing a given ADR grouped by SOC, High Level Term (HLT), PT, and severity.

- A glossary of all physician-reported terms, grouped by coded SOC, HLT, and PT. This table will serve as a glossary of PTs, showing which reported terms are summarized under each PT.

11   OTHER ANALYSES

Not applicable.

12   REFERENCES

Not applicable.

13 APPENDICES

13.1 Other Significant ADRs

The following preferred terms will be used to define other significant ADRs:

Table 13–1: Preferred terms of other significant ADRs

MedDRA Preferred Term
Hepatotoxicity related terms
Hepatitis toxic
Hepatotoxicity
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
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

*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'.

14 AMENDMENT(S) TO THE STATISTICAL ANALYSIS PLAN (SAP)

14.1 AMENDMENT 1

Rationale for the amendment

The observational study plan was amended on 1 June 2015. These changes were incorporated into the SAP. In additional, during the course of the study clarification was added to the SAP where required. The clarifications are also reflected in this SAP amendment. Other significant ADRs were also added along with clarification of seizure frequency and safety analyses for patients who take at least 1 dose of LCM that is <200mg/day. In addition, the modified FAS definition was updated to reflect the changes in the label where patients are allowed to received LCM as a monotherapy.

Modifications and changes

Change 1 - Study title

A NONINTERVENTIONAL STUDY OF VIMPAT® (LACOSAMIDE) ADDED TO ONE BASELINE ANTIEPILEPTIC DRUG THERAPY IN PATIENTS WITH BRAIN TUMOR RELATED EPILEPSY (VIBES)

Has been changed to:

A NONINTERVENTIONAL STUDY OF <u>V</u>IMPAT® (LACOSAMIDE) **AS ADJUNCTIVE** ANTIEPILEPTIC DRUG THERAPY IN PATIENTS WITH <u>B</u>RAIN TUMOR RELATED <u>E</u>PILEP<u>S</u>Y (VIBES)

Change 2 - Abbreviations

LOCF   Last observation carried forward

Has been removed.

Change 3 – 1 Introduction

This document outlines the planned analyses to support the EP0045 clinical study report (CSR). It includes all definitions and details for the evaluation of data recorded during the study. This SAP should be read in conjunction with the non-interventional study observation plan dated 23 June 2014 and the annotated case report forms (aCRF) dated 23 September 2014.

Has been changed to:

This document outlines the planned analyses to support the EP0045 clinical study report (CSR). It includes all definitions and details for the evaluation of data recorded during the study. This SAP should be read in conjunction with the non-interventional study observation plan dated **1 June 2015** and the annotated case report forms (aCRF) dated **31 August 2017**.

Change 4 – 2.1.1 Primary objective

The primary objective of this study is to evaluate the effectiveness and patient global impression of lacosamide (LCM) added to a single antiepileptic drug (AED) in the treatment of patients with brain tumor-related epilepsy (BTRE) due to low-grade primary brain tumor.

Has been changed to:

The primary objective of this study is to evaluate the effectiveness and patient global impression of lacosamide (LCM) added **to 1 or 2** antiepileptic drug**s** (AED**s**) in the treatment of patients with brain tumor-related epilepsy (BTRE) due to low-grade primary brain tumor.

Change 5 – 2.1.2 Secondary objective

The secondary objective of this study is to evaluate the tolerability and quality of life (QoL) of patients with BTRE due to low-grade primary brain tumor who are treated with LCM added to a single AED.

Has been changed to:

The secondary objective of this study is to evaluate the tolerability and quality of life (QoL) of patients with BTRE due to low-grade primary brain tumor who are treated with LCM added to **1 or 2** AED**s**.

Change 6 – 2.3 Study design and conduct

EP0045 is a multicenter, prospective, single-arm non-interventional study (NIS) conducted at specialized sites utilizing LCM added to AED monotherapy in patients ≥16 years of age with BTRE secondary to low-grade tumor.

Has been changed to:

EP0045 is a multicenter, prospective, single-arm non-interventional study (NIS) conducted at specialized sites utilizing LCM added to **existing treatment with 1 or 2 AEDs** in patients ≥16 years of age with BTRE secondary to low-grade tumor.

Change 7 – 2.3 Study design and conduct

These visits will consist of:

- Visit 1, Baseline (to be performed before the first dose of LCM)

- Visit 2, approximately 3 months after Baseline according to routine practice

- Visit 3, approximately 6 months after Baseline according to routine practice or end of Observation Period

Has been changed to:

These visits will consist of:

- Visit 1, Baseline

- Visit 2, approximately 3 months after Baseline according to routine practice

- Visit 3, approximately 6 months after Baseline according to routine practice or end of Observation Period

Change 8 – 3.2.1 Analysis time points

- Visit 1, Baseline (prior to first dose of LCM)

- Visit 2 (approximately 3 months after Baseline)

- Visit 3 (approximately 6 months after Baseline or Withdrawal Visit for patients who discontinue early)

Has been changed to:

- Visit 1, Baseline

- Visit 2 (approximately 3 months after Baseline): **Visits that occurred ≤ 135 days after Visit 1**

- Visit 3 (approximately 6 months after Baseline or Withdrawal Visit for patients who discontinue early): **All visits that occurred > 135 days after Visit 1**

If there are 2 visits that meet the criteria for Visit 2, then the visit nearest to the scheduled assessment time for Visit 2 will be used (i.e. 90 days after Visit 1). If there are 2 visits that meet the criteria for Visit 3, then the visit nearest to the scheduled assessment time for Visit 3 will be used (i.e. 180 days after Visit 1).

Change 9 – 3.5.3 Full Analysis Set

The Full Analysis Set (FAS) is defined as all patients in the SS who have at least 1 post-Baseline PGIC or seizure assessment. The FAS will be used for the analysis of the primary and most secondary variables.

Has been changed to:

The Full Analysis Set (FAS) is defined as all patients in the SS who have at least 1 post-Baseline PGIC or seizure assessment. The FAS will be used for the analysis of the primary and most secondary variables **including any subgroup analyses. In addition, demographic and baseline summaries will be based on the FAS**.

Change 10 – 3.5.4 Modified FAS

The modified FAS is defined as all patients in the FAS ≥16 years of age and treated with daily LCM doses ≤400mg, representing the on-label use of LCM. All efficacy analyses, demographic and baseline summaries and some safety summaries will be repeated in the modified FAS.

On-label use for this study is defined as not receiving a LCM dose of >400mg and continuing to receive one core AED. Patients who receive at least one dose of LCM that is >400mg or whose dosage of the core AED changes to 0mg (i.e. patient starts to receive LCM as monotherapy) will be excluded from the modified FAS.

Has been changed to:

The modified FAS is defined as all patients in the FAS ≥16 years of age and treated with daily LCM doses ≤400mg, representing the on-label use of LCM. All efficacy analyses **excluding subgroup analyses**, demographic and baseline summaries and some safety summaries will be repeated in the modified FAS.

On-label use for this study is defined as receiving a LCM daily dose <= 400mg. Patients who receive at least one dose of LCM that is >400mg will be excluded from the modified FAS.

Change 11 – 3.6 Treatment assignment and treatment groups

All patients treated received LCM with the dosage determined at the discretion of the physician. Data summaries will be presented based on the total number of patients and will not be differentiated by LCM dose with the exception of the frequency of seizures occurring at doses of LCM < 200 mg. Where appropriate, LCM dose will be presented on patient data listings.

Has been changed to:

All patients treated received LCM with the dosage determined at the discretion of the physician. Data summaries will be presented based on the total number of patients and will not be differentiated by LCM dose with the exception of the frequency of seizures occurring at doses of LCM < 200 mg **and ADRs presented by dose**. Where appropriate, LCM dose will be presented on patient data listings.

Change 12 – 3.10.4 Seizure Frequency

The considered time interval is defined as 56 days for the historical seizure count at Baseline (8 weeks x 7 days) and as date of actual visit – date of previous visit for all other time points.

Has been changed to:

The considered time interval is defined as 56 days for the historical seizure count at Baseline (8 weeks x 7 days) and as date of actual visit – date of previous visit for all other time points. **Note if any subjects have a diagnosis of epilepsy less than 8 weeks prior to study entry, then site will be instructed to give their best approximation of the 8-week seizure frequency and the reported historical seizure count will be assumed to be representative of the full 8 weeks. The seizure frequency per 28 days cannot be derived using the time from diagnosis of epilepsy to study start as the time period for reporting the historical seizure frequency for such subjects because only the month and year are collected for the date of diagnosis.**

Change 13 – 3.10.4 Seizure Frequency

Similarly, the frequency of partial-onset seizures observed at a dose less than 200 mg/day will also be calculated based upon the response to the question 'Number of partial-onset seizures that occurred at a lacosamide dose less than 200 mg/day' in the CRF.If the number at less than 200 mg/day is not applicable, then the number of partial-onset seizures at less than 200 mg/day is 0 otherwise it will be taken from the CRF.

Has been changed to:

Partial-onset seizure frequency per 28 days at a dose of <200mg/day at Visit 2 and Visit 3 will be derived from the number of days in the considered time interval (D) for which seizure information was provided where the subject was on a dose of <200mg/day according the dosing log for LCM:

    (Number of seizures over the specified time interval) x (28/D).

The number of seizures is the number of partial onset seizures at a dose <200mg/day. The time interval for Visit 2 is the number of days between the Visit 1 and Visit 2 dates where the subject was on a dose <200mg/day for LCM. The time interval for Visit 3 is the number of days between the Visit 2 and Visit 3 dates where the subject was on a dose <200mg/day for LCM. The change from baseline will then be derived by subtracting the partial onset seizure frequency per 28 days reported at Baseline from the partial onset seizure frequency per 28 days on a dose <200mg/day at Visit 2 and Visit 3. If the number at less than 200

mg/day is not applicable, then the number of partial-onset seizures at less than 200 mg/day is **treated as missing**.

Change 14 – 3.10.6 Retention rate

The 6-month retention rate is the percentage of patients remaining in the study and on LCM treatment for 6 months. This will be estimated using Kaplan-Meier methodology applied to the time to discontinuation of LCM. The derivation of the time to discontinuation and the corresponding censoring flag are described in Section 3.10.7.

Has been changed to:

The 6-month retention rate is the percentage of patients remaining in the study and on LCM treatment for 6 months. This will be estimated using Kaplan-Meier methodology applied to the time to discontinuation of LCM. **A cut of 180 days will be used for 6 months.** The derivation of the time to discontinuation and the corresponding censoring flag are described in Section 3.10.7.

Change 15 – 3.10.7 Time to discontinuation of LCM

Time to discontinuation of LCM will be defined as

   The date of last administration of LCM while in the study - the date of first dose of LCM + 1

If the date of last administration of LCM while in the study is not available the study termination date will be used. If the start date of LCM is missing, then it is assumed that the patient did not receive treatment and they would be consequently excluded from the relevant analysis sets and therefore from this analysis.

A censor flag will be derived where patients who remain on treatment at the end of the 6-month Observation Period are censored and patients who have discontinued LCM prior to the end of the 6-month Observation Period are not censored.

Has been changed to:

Time to discontinuation of LCM will be defined as

   The date of last administration of LCM while in the study - the date of first dose of LCM + 1

If the date of last administration of LCM while in the study is not available the study termination date will be used. If the start date of LCM is missing, then it is assumed that the patient did not receive treatment and they would be consequently excluded from the relevant analysis sets and therefore from this analysis.

A censor flag will be derived where patients who **completed** the **study** are censored and patients who have discontinued LCM prior to the end of the 6-month Observation Period **(early withdrawals)** are not censored.

Change 16 – 3.10.9 M.D. Anderson Symptom Inventory Brain Tumor Module

The symptom severity scale is the mean of the 13 symptom items. If at least 7 of the items have been scored, then the symptom severity scale is the sum of the items answered multiplied by 13 and divided by the number of items answered.

The overall symptom distress is the mean of the 6 interference items. If more than 50% of the items are answered, then the overall symptom distress is the sum of the items answered multiplied by 6 and divided by the number of items answered.

Absolute scores and changes from Visit 1 (Baseline) to Visit 3 (Month 6 or end of Observational Period) for the individual items of the MDASI-BT, the symptom severity scale and the overall symptom distress will be derived for patients with an evaluable Baseline assessment. Patients with an evaluable Baseline assessment for MDASI-BT are defined as patients who have not started LCM at the time of Visit 1.

Has been changed to:

The **mean core** symptom severity is the mean of the 13 **core** symptom items. If at least 7 of the items have been scored, then the **mean core symptom severity** is the sum of the items answered divided by the number of items answered.

The mean module symptom severity is the mean of the 9 brain tumor specific symptom items. If at least 5 of the items have been scored, then the mean module symptom severity is the sum of the items answered divided by the number of items answered.

The mean total symptom severity is the mean of all 22 symptom items. If more than 50% of the items are answered, then the mean total symptom severity is the sum of the items answered divided by the number of items answered.

The **mean interference** is the mean of the 6 interference items. If more than 50% of the items are answered, then the **mean interference** is the sum of the items answered divided by the number of items answered.

Absolute scores and changes from Visit 1 (Baseline) to Visit 3 (Month 6 or end of Observational Period) for the individual items of the MDASI-BT, **the mean core symptom severity scale, the mean module symptom severity, the mean total symptom severity and mean interference** will be derived for patients with an evaluable Baseline assessment. Patients with an evaluable Baseline assessment for MDASI-BT are defined as patients who have not started LCM at the time of Visit 1.

Change 17 – 3.10.11 Discontinuation of LCM due to lack of efficacy

The following text has been added:

3.10.11 Discontinuation of LCM due to lack of efficacy

A patient who discontinued LCM due to lack of efficacy is defined as a patient who prematurely terminated from the study and the primary reason for premature study termination = "LACK OF EFFICACY".

Change 18 – 3.10.12 Discontinuation of LCM due to lack of effectiveness

A patient who discontinued LCM due to lack of effectiveness is defined as a patient who prematurely terminated from the study and the primary reason for premature study termination = "LACK OF EFFICACY".

Has been changed to:

A patient who discontinued LCM due to lack of effectiveness is defined as a patient who prematurely terminated from the study and the primary reason for premature study termination = "LACK OF EFFICACY" **or "ADVERSE DRUG REACTION"**.

Change 19 – 3.10.15 Adverse Drug Reactions

The following text has been added:

Other significant ADRs will be summarized.

Change 20 – 4.8 Examination of subgroups

The primary endpoints will be summarized by the following subgroups, if at least 25 patients fall into that subgroup:

- Starting dose of LCM (loading dose; titration – identified based on increases in the LCM dose recorded for patients who were titrated)

- Prior tumor treatment (radiotherapy; chemotherapy; surgery)

- Concomitant tumor treatment (radiotherapy; chemotherapy; surgery)

- Number of different types of lifetime AEDs (1; 2; 3)

- Core AED (levitiracetam; sodium valproate; lamotrigine; oxcarbazepine; zonisamide; topiramate; pregabalin; gabapentin; phenytoin; carbamazepine)

- Age ($\geq$16 - $\leq$18; >18 - <65; $\geq$65)

- Sex (male; female)

- Historical seizure frequency (1; $\geq$1-<5; $\geq$5)

- Historical seizure type (Partial-onset seizures with secondary generalization; Partial-onset seizures without secondary generalization)

- Time since tumor diagnosis ($\leq$1 month; >1 - $\leq$3 months; >3 - $\leq$6 months; >6 months - $\leq$12 months; >12 - $\leq$24 months; >24 months)

- Type of brain tumor (astrocytoma; oligodendroglioma; mixed [oligo-astro]; ependymoma; other)

- WHO grade (1; 2; 3; 4)

- Karnofsky performance status (<60%; 60%; 70%; 80%; 90%; 100%)

Has been changed to:

The primary endpoints will be summarized by the following subgroups, if at least 25 patients fall into that subgroup:

- Starting dose of LCM (**high starting dose - first dose >=200mg/day; titration – first dose <200mg/day**)

- Prior tumor treatment (radiotherapy; chemotherapy; surgery; **radiotherapy and chemotherapy; radiotherapy and surgery; chemotherapy and surgery; radiotherapy, chemotherapy and surgery**)

- Concomitant tumor treatment (radiotherapy; chemotherapy; surgery; **radiotherapy and chemotherapy; radiotherapy and surgery; chemotherapy and surgery; radiotherapy, chemotherapy and surgery**)

- Number of different types of lifetime AEDs (1; 2; 3; **4**)

- Core AED **therapy** (**including but not limited to** levitiracetam, **valproate sodium,** lamotrigine, oxcarbazepine, zonisamide, topiramate, pregabalin, gabapentin, phenytoin, carbamazepine, **clonazepam clobazepam, phenobarbital, valproic acid, ergenyl chrono; combinations of these therapies**)

- **Note: Each subject can be only in 1 category for "Core AED therapy"**

- Age (≥16 - ≤18; >18 - <65; ≥65)

- Sex (male; female)

- Historical seizure frequency (1; **2-5; 6+)**

- Historical seizure type (Partial-onset seizures with secondary generalization; Partial-onset seizures without secondary generalization**; Both**)

- Time since tumor diagnosis (≤1 month; >1 - ≤3 months; >3 - ≤6 months; >6 months - ≤12 months; >12 - ≤24 months; >24 months)

- Type of brain tumor (astrocytoma; oligodendroglioma; mixed [oligo-astro]; ependymoma; other)

- WHO grade (1; 2; 3; 4)

- Karnofsky performance status (<60%; 60%; 70%; 80%; 90%; 100%)

Change 21 – 5.2 Protocol Deviations

The number and percentage of patients with at least 1 important protocol deviation in each of the categories defined in the Important Protocol Deviations Template will be summarized for the SS. Percentages for single deviations are based on the number of patients with any deviation.

Has been changed to:

The number and percentage of patients with at least 1 important protocol deviation in each of the categories defined in the Important Protocol Deviations Template will be summarized for the SS **and modified FAS**. Percentages for single deviations are based on the number of patients with any deviation.

Change 22 – 6.4 Prior and concomitant medications

The number and percentage of patients who used prior and concomitant medications (including chemotherapy and AEDs) will be summarized according to the anatomical therapeutic class main group, the therapeutic subgroup, and the generic drug name.

The core AEDs will be summarized separately using the "Core AED?" question on the CRF to select the relevant medications. The core AED is the AED that the patient is receiving at Baseline.

Has been changed to:

The number and percentage of patients who used prior and concomitant medications (including chemotherapy and AEDs) will be summarized according to the anatomical therapeutic class main group, the therapeutic subgroup, and the generic drug name.

Prior medications are those medications started before the first dose of study drug. Medication taken after the first dose of study medication will be regarded as concomitant medication whether the start date is before, after or on the date of the first dose of study medication. Lifetime AEDs are AEDs with an end date before the first dose of study drug.

The core AEDs will be summarized separately using the "Core AED?" question on the CRF to select the relevant medications. The core AED**s are** the AED**s** that the patient is receiving at Baseline.

The number and percentage of patients according to Core AED therapies will be summarized according to preferred term combination.

Change 23 – 8.2.4 M.D. Anderson Symptom Inventory Brain Tumor Module

Descriptive statistics for the observed value and change from Visit 1 (Baseline) to Visit 3 (Month 6 or end of Observation Period) in the individual items of the MDASI-BT, the symptom severity scale and the overall symptom distress will be presented. The MDASI-BT will be assessed only for patients with an evaluable Baseline assessment (eg, patients who have not started LCM at the time of the Visit 1 assessment).

Has been changed to:

Descriptive statistics for the observed value and change from Visit 1 (Baseline) to Visit 3 (Month 6 or end of Observation Period) in the individual items of the MDASI-BT, the mean core symptom severity, **the mean module symptom severity, the mean total symptom severity and mean interference** will be presented. The MDASI-BT will be assessed only for patients with an evaluable Baseline assessment (eg, patients who have not started LCM at the time of the Visit 1 assessment).

Change 24 – 8.2.5 Seizure frequency

The following text has been added:

The Baseline for all subjects in the FAS and the Baseline for subjects who received at least one dose of <200mg/day LCM during the treatment period will be summarized for Visit 1 which only includes subjects who have a dose of <200mg/day at some point during the study and thus would have a seizure frequency at <200mg/day LCM reported.

Change 25 – 8.2.8 Discontinuation of LCM due to lack of efficacy

The following text has been added:

8.2.8 Discontinuation of LCM due to lack of efficacy

The number and percentage of patients who discontinue LCM due to lack of efficacy will be presented for the SS, the FAS and the modified FAS. A 2-sided 95% CI (calculated using the 2-sided Clopper-Pearson method) for the percentage of patients who discontinue LCM due to lack of efficacy will be presented.

Change 26 – 8.2.10 Clinical Global Impression of Change

The number and percentage of patients within each response category for CGIC (1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse,6=much worse, and 7=very much worse) will be summarized for the SS. Additionally, thenumber and

percentage of patients who improved (impression of change <4), had no change (impression of change =4), and worsened (impression of change >4) will also be provided.

Has been changed to:

The number and percentage of patients within each response category for CGIC (1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse,6=much worse, and 7=very much worse) will be summarized for the **FAS and modified FAS**. Additionally, thenumber and percentage of patients who improved (impression of change <4), had no change (impression of change =4), and worsened (impression of change >4) will also be provided.

Change 27 – 10 Safety Analyses

All statistical analyses for the safety variables will be performed for the SS and the modified FAS in an exploratory manner. Exposure data will be listed in the SS and adverse drug reactions will be listed in the ES.

Has been changed to:

All statistical analyses for the safety variables will be performed for the SS and the modified FAS in an exploratory manner. All safety data will be listed in the SS.

Change 28 – 10.2 Adverse Events

The following text has been added:

•   Other significant ADRs

Change 29 – 13.1 Other Significant ADRs

The following text has been added:

The following preferred terms will be used to define other significant ADRs:

Table 13-1: Preferred terms of other significant ADRs

MedDRA Preferred Term
Hepatotoxicity related terms
Hepatitis toxic
Hepatotoxicity
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
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

*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'.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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