NONINTERVENTIONAL STUDY OBSERVATIONAL PLAN EP0045 AMENDMENT 1

A NONINTERVENTIONAL STUDY OF VIMPAT® (LACOSAMIDE) AS ADJUNCTIVE ANTIEPILEPTIC DRUG THERAPY IN PATIENTS WITH BRAIN TUMOR-RELATED EPILEPSY (VIBES)

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DECLARATION AND SIGNATURE OF TREATING PHYSICIAN

I confirm that I have carefully read and understood this noninterventional study observational plan and agree to conduct this study as outlined in this noninterventional study observational plan and local laws and requirements.

I will ensure that all physicians and other staff members read and understand all aspects of this noninterventional study observational plan.

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

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

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

Treating physician

<Insert name>

_____
Date/Signature

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LIST OF ABBREVIATIONS

ADR	adverse drug reaction
AE	adverse event
AED	antiepileptic drug
AESI	adverse event of special interest
BTRE	brain tumor-related epilepsy
CGIC	Clinical Global Impression of Change
CI	confidence interval
eDF	electronic Documentation form
EMA	European Medicines Agency
EQ-5D-5L	5-Level EuroQol-5 Dimension Quality of Life Assessment
ES	Enrolled Set
FAS	Full Analysis Set
HLT	High Level Term
LCM	lacosamide
MDASI-BT	M.D. Anderson Symptom Inventory - Brain Tumor
MedDRA®	Medical Dictionary for Regulatory Activities
NIS	noninterventional study
PGIC	Patient Global Impression of Change
PT	preferred term
QoL	quality of life
SOC	system organ class
SS	Safety Set
ULN	upper level of normal
VAS	visual analogue scale

1 RATIONALE FOR THE STUDY

Patients with brain tumor-related epilepsy (BTRE) present a complex therapeutic profile and require a unique and multidisciplinary approach. There are many factors to take into consideration, especially the management of epilepsy, which is often considered the most important risk factor for long-term disability (Maschio, 2012).

In patients with brain tumors, seizures are the onset symptom in 20-40% of patients, while a further 20-45% of patients will present with seizures during the course of the disease. Overall, the incidence of epilepsy in brain tumors, regardless of histological type and anatomical site of the lesion, varies from 35 to 70% (Rossetti and Stupp, 2010; Vecht and Wilms, 2010; Singh et al, 2007; Hildebrand et al, 2005; Wen and Marks, 2002; Glantz et al, 2000).

Lacosamide (LCM, VIMPAT®) is an antiepileptic drug (AED), which has been shown to provide a favorable benefit-risk profile and was approved by the European Medicine Agency (EMA) on 29 Aug 2008 (EU/1/08/470/01 to 013 and EU/1/08/470/016 to 023; EMA reference EMEA/H/C/000863) as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients with epilepsy aged 16 years and older (film-coated tablets of 50mg, 100mg, 150mg, and 200mg, syrup of 10mg/mL, and solution for infusion of 10mg/mL). In addition to the European Union, LCM is approved as adjunctive therapy in adults suffering from partial-onset seizures in at least 38 other countries to date. In the United States, LCM is approved as adjunctive therapy or monotherapy in patients age 17 years and older and suffering from partial-onset seizures.

The pharmacokinetic profile of LCM includes minimal cytochrome P450 interaction and low (<15%) protein binding, resulting in a low risk for drug-drug interaction (Lacosamide Summary of Product Characteristics, 2011). This is particularly important in the context of BTRE, since many chemotherapeutic agents are susceptible to metabolism via the P450 pathway, as are a number of AEDs which may be co-prescribed during the natural history of disease.

Lacosamide has been shown to be efficacious and generally well tolerated in real life clinical practice, from first adjunct to later treatment lines (Stephen et al, 2011; Villanueva et al, 2012).

The first noninterventional study (NIS) evaluating the use, effectiveness, and tolerability of LCM in routine clinical practice (VImpaT added to One Baseline AED, VITOBA, ClinicalTrials.gov NCT01098162) started in Germany in May 2009 in about 550 patients with less difficult-to-treat disease, excluding a complex therapeutic profile like patients with BTRE, and being treated with only a single Baseline AED. The Observation Period per patient in the VITOBA study was 6 months. The results of the second interim analysis based on >300 patients indicate improved seizure control with a favorable safety and tolerability profile when LCM is used as adjunctive treatment to AED monotherapy in routine clinical practice (Noack-Rink et al, 2012).

There are limited data available in patients with complex-to-treat diseases like BTRE, as well as limited established guidance. However, general consensus is that nonenzyme inducing AEDs, like LCM, should be preferred because chemotherapy and steroids are the main treatment in this population, and both are affected by enzyme inducers.

The most important published uses of LCM in this population are a retrospective analysis including 70 patients in 5 US centers (Saria et al, 2013) and prospective case series including

14 patients in Italy (Maschio et al, 2011), both of which show good tolerability and effectiveness of LCM in this subpopulation.

To better evaluate the use of LCM in patients with BTRE in routine clinical practice, a new observational study is necessary. The present study (EP0045) will significantly add to the published experience, and hopefully lead to the possibility of informed design of comparative studies, which is currently not possible due to the paucity of data in this area.

EP0045 is a multicenter, prospective NIS conducted at specialized sites in approximately 6 European countries, with a 6-month Observation Period. Lacosamide will be added to any AED therapy (1 or 2 AEDs) in approximately 100 patients with BTRE.

The primary objective of this study is to evaluate in routine clinical practice the effectiveness of LCM added to 1 or 2 AEDs in the treatment of patients with BTRE due to low-grade glioma. 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.

This observational study is entirely noninterventional. Patients will receive their usual medical care, which may include but is not limited to diagnostic or therapeutic procedures and medical treatment. The decision for initiating LCM therapy will be independent of study participation.

The patient (or legal representative) will be required to provide written informed consent for the use of his/her medical data before enrolling in the study.

2 STUDY TYPE

EP0045 is a multicenter NIS conducted at specialized sites in approximately 6 European countries.

3 STUDY OBJECTIVES

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

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

4 STUDY VARIABLES

4.1 Primary 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)

4.2 Secondary 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)

4.3 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

5 STUDY DESIGN

EP0045 is a multicenter, prospective, single-arm NIS conducted at specialized sites utilizing LCM added to existing treatment with 1 or 2 Baseline 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 11.5).

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 observation of the first patient will start after a positive opinion to conduct the study has been received by the responsible ethics committee(s) (Section 12.4.2) and the regulatory authority(ies) if applicable (Section 12.4.3).

Eligible patients will be enrolled consecutively and all patients (and/or their parents or legal representatives) have to accept in writing that his/her medical data will be used for the evaluation of the study results by signing a study-specific Patient Data Consent form according to local requirements.

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.

All data to be collected at Visits 1, 2, and 3 are described in Section 15, Table 15–1 (to be collected as available). The management and reporting of ADRs and AESIs will be handled according to international drug safety regulations and UCB procedures.

Documentation of all study assessments is to be performed by the treating physician in the study-specific electronic Documentation form (eDF). Although the study is noninterventional in nature, every attempt must be made to assess all participating patients in the same way.

6 EXPECTED STUDY DURATION

The planned number of patients is 100 (see Section 11.5), with 93 evaluable patients expected. Approximately 25 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.

7 ANTICIPATED REGIONS AND COUNTRIES

The study will be conducted in approximately 6 European countries (France, Germany, Italy, Netherlands, Spain, United Kingdom) with possible extension to other countries.

8 SELECTION AND WITHDRAWAL OF PATIENTS

8.1 Selection criteria

Before any data are collected for any patient in this NIS, written data consent will be properly executed and documented.

The following selection criteria must be followed for patients entering the NIS:

1. Patient has never been treated with LCM prior to this NIS or treatment with LCM for the first time started no earlier than 7 days prior to enrollment in this NIS.
2. The decision by the treating physician to prescribe LCM falls within current standard clinical practice, and the treatment decision is clearly separated from the decision to consider inclusion of the patient in the NIS.
3. A Patient Data Consent form is signed and dated by the patient and/or by the parent(s) or legal representative.
4. Patient is a male or female ≥16 years of age.

5. Patient must have a diagnosis of BTRE secondary to low-grade glioma (World Health Organization Grade 1 to 2 at time of enrollment).
6. Patient has a retrospective Baseline seizure frequency of at least 1 partial-onset seizure in the 8 weeks prior to start of LCM treatment.
7. Patient does not have a previous diagnosis of epilepsy before tumor onset.
8. Patient does not have brain metastases.
9. Patient has a Karnofsky performance status scale index ≥60%.
10. Patient is currently taking only 1 or 2 Baseline AEDs for epilepsy other than LCM.
11. Patient has received a maximum of 4 different lifetime AEDs ever before entering the NIS.

8.2 Withdrawal criteria

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

Physicians are free to add or withdraw any medication or to withdraw the patient from the study at their own discretion.

If a patient needs to increase the dose of the Baseline AEDs (1 or 2) or needs to be treated with more than 2 AEDs other than LCM, these changes can be implemented, but the patient will be withdrawn from the study.

If the physician elects to stop LCM treatment, the patient will be withdrawn from the study.

The primary reason for withdrawal must be documented in the patient's eDF. When the primary reason for withdrawal is an ADR, the ADR must be reported as described in Section 10.1.7.

9 STUDY TREATMENT(S)

Patients will be treated with commercially available LCM and with commercially available AEDs, as prescribed by treating physicians, in accordance with current clinical practice.

9.1 Numbering of patients

Each patient will receive a unique 5-digit number assigned when entering the study that serves as the patient identifier throughout the study.

The patient identification list will be kept by the treating physician. Access to this list may be granted only to members of staff, authorized persons of UCB (or designees), and the competent authorities. The study monitor is also bound to confidentiality. After the end of the study, the identification list will remain with the physician.

10 ASSESSMENT OF SAFETY

For the assessment of safety of LCM, the causal relationship, seriousness, and outcome of ADRs and AESIs will be collected during the Observation Period. It is the task of the treating physician to make a judgment about a causal relationship with the LCM intake.

10.1 Adverse events and adverse drug reactions

10.1.1 Definitions of adverse events and adverse drug reactions

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

An ADR is a response to a medicinal product which is noxious and not intended. This includes adverse reactions which arise from:

- The use of a medicinal product within the terms of the marketing authorization;
- The use outside the terms of the marketing authorization, including overdose, off-label use, misuse, abuse, and medication errors; and
- Occupational exposure (this refers to the exposure to a medicinal product as a result of one's professional or nonprofessional occupation)

10.1.2 Reporting and description of adverse events

In order to ensure complete safety data collection, all ADRs and AESIs (Section 10.1.8) occurring during the study (ie, after signing the Patient Data Consent form or after first administration of the study drug, whatever comes first) must be reported. This includes all ADRs and AESIs not present prior to the initial visit and all ADRs and AESIs that recurred or worsened after the initial visit (eg, underlying or previous concomitant disease).

Signs or symptoms of the condition/disease for which the study treatment is being studied should be recorded as ADRs or AESIs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the treating physician from the patient's history or the Baseline Period.

When recording an ADR or AESI, the treating physician should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The Adverse Event Report form and source documents should be consistent.

Details for completion of the Adverse Event Report form are described in the AE reporting instructions.

10.1.3 Follow up on adverse events

An ADR or AESI should be followed until it has resolved, has a stable sequelae, the treating physician determines that it is no longer clinically significant, or the patient is lost to follow up.

If an ADR or AESI is still ongoing at the end of the study for a patient, follow up might be requested by local UCB's Drug Safety department, depending on the nature of the ADR/AESI. Follow up should be provided until resolution/stable level of sequelae, the treating physician no longer deems that it is clinically significant, or until the patient is lost to follow up (ie, cannot be contacted). If no follow up is provided, the treating physician must provide a justification.

10.1.4 Pregnancy

If a treating physician is notified that a patient has become pregnant after the first intake of LCM, the treating physician must notify UCB's local Drug Safety department immediately (a Pregnancy Report and Outcome form will be provided to the treating physician for completion). The treating physician shall inform the patient of the information currently known about potential risks and about available treatment alternatives.

The pregnancy and the outcome (birth, miscarriage, abortion) will be documented on the Pregnancy Report and Outcome form provided to the treating physician. The progression of the pregnancy and the eventual birth (if applicable) must be followed up using the Pregnancy Report and Outcome form in which the treating physician has to report on the health of the mother and of the child. Every reasonable attempt should be made to follow the development and health of the child for at least 30 days after birth for any significant medical issues or developmental delay.

If the patient is lost to follow up and/or refuses to give information, written documentation of attempts to contact the patient needs to be provided by the treating physician and filed at the site. UCB's local Drug Safety department is the primary contact for any questions related to the data collection for the pregnancy, birth, and follow up.

In cases where the partner of a male patient enrolled in a NIS becomes pregnant, the treating physician or designee is asked to contact the patient to request consent via the Partner Pregnancy Consent form. In case of questions about the consent process, the treating physician may contact UCB's local Drug Safety department. The treating physician will complete the Pregnancy Report and Outcome form and send it to UCB's local Drug Safety department only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form. UCB's local Drug Safety department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow up.

10.1.5 Overdose of lacosamide

Excessive dosing (beyond the maximal allowed dose according to marketing authorization) should be reported on the Adverse Event Report form, whether the overdose is associated with an ADR/AESI or not. Any ADR associated with excessive dosing must be followed as any other ADR would be followed.

10.1.6 Safety signal detection

Reported ADRs or AESIs from this study will be reviewed periodically together with other safety information received at UCB, to detect as early as possible any safety concern(s) related to the treatment so that treating physicians, clinical study patients, and regulatory authorities will be informed appropriately and as early as possible.

10.1.7 Procedures for reporting adverse events and adverse drug reactions

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

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

Following a causality assessment, the physician will document all spontaneously reported ADRs by the patient in the Adverse Event Report form. In addition, the treating physician should review any self-assessment procedures employed.

If an ADR or AESI is reported, UCB's local Drug Safety department must be informed within 1 working day of receipt of this information by the site (see contact details for safety reporting on the Study Contact Information page of this NIS observational plan). The treating physician must forward to UCB (or its representative) a duly completed Adverse Event Report form provided by UCB, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions. Information recorded on this form will be entered into the global safety database.

If clarifications on the ADR or AESI are necessary, UCB shall request additional information from the treating physician.

The Adverse Event Report form and other requested information must be provided in English.

Additional information (eg, autopsy or laboratory reports) received by the treating physician must be provided within 24 hours. All documents in the local language must be accompanied by a translation in English, or the relevant information included in the same document must be summarized in the Adverse Event Report form.

The treating physician is specifically requested to collect and report to UCB (or its representative) any ADRs or AESIs (Section 10.1.8), and to also inform participating patients of the need to inform the treating physician of any AE during the study.

At the conclusion of the study, ADR or AESI data will be extracted from the global safety database and will be analyzed along with the clinical data to allow for the final summary of the safety variables (see Section 11.3.4). The current Summary of Product Characteristics for LCM should be considered for the evaluation of ADR expectedness.

10.1.8 Adverse events of special interest

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

The following are the LCM AESIs:

- The following arrhythmias: atrial fibrillation/flutter, ventricular tachycardia or fibrillation, atrioventricular block (second degree, Type I and II, and third degree), and marked bradycardia (<45 beats/min)
- Syncope or loss of consciousness (other than seizure related)
- Serious suspected multiorgan hypersensitivity reactions

  Serious suspected multiorgan hypersensitivity cases may be identified and reported to the sponsor by the treating physician using the following algorithm as agreed with the US Food and Drug Administration:

  – An AE or laboratory value (as defined in the following text) suggestive of internal organ involvement (including but not limited to hepatitis, nephritis, pneumonitis, carditis,

colitis, encephalitis, pancreatitis, myositis, arthritis, or hematologic system involvement) combined with at least 1 of the following: fever, rash, lymphadenopathy, or eosinophilia.

- Treatment-emergent abnormal laboratory value criteria suggestive of internal organ involvement or eosinophilia:
  - Eosinophils % ≥10%
  - Eosinophils absolute ≥0.5G/L
  - Neutrophils absolute <1.5G/L
  - Platelets ≤100G/L
  - Alanine aminotransferase ≥2x upper level of normal (ULN)
  - Aspartate aminotransferase ≥2xULN

11 STATISTICS

A description of statistical methods is presented below and will be described in more detail in the Statistical Analysis Plan.

11.1 Definition of analysis sets

For this NIS, the following definitions will apply:

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.

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.

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.

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.

11.2 General statistical considerations

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, median, 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% confidence intervals (CIs) will be presented.

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

11.3 Planned analyses

11.3.1 Analysis of the primary variable

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 for the FAS.

The number and percentage of patients with each PGIC value will be summarized at Visit 3 (Month 6 or end of the Observation Period) for the FAS. The number and percentage of patients who improved (scores 1 to 3), had no change (score 4), and worsened (scores 5 to 7) will also be provided.

11.3.2 Analysis of secondary variables

Secondary variables will be analyzed using descriptive statistics. The analysis set used for each variable will be defined in the SAP.

Retention rate will be summarized using descriptive statistics based on the number and percentage of patients remaining in the study and on LCM treatment for 6 months (6-month retention rate). A 2-sided 95% CI for the 6-month retention rate will be presented.

Time to discontinuation of LCM from the date of first dose of LCM will be analyzed using Kaplan-Meier methods. 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.

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 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).

Descriptive statistics for the observed value and change from Visit 1 (Baseline) to Visit 3 (Month 6 or end of Observation Period) in the MDASI-BT 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).

Descriptive statistics for percent change in seizure frequency per 28 days from Visit 1 (Baseline) to Visit 3 (Month 6 or end of Observation Period) will be presented. Median percentage of seizure change from Baseline to Visit 3 (Month 6 or end of Observation Period) will be presented.

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.

The number and percentage of patients who discontinue LCM due to an ADR and due to lack of effectiveness will be presented separately.

The number and percentage of patients with each CGIC value will be summarized at Visit 3 (Month 6 or end of the Observation Period). The number and percentage of patients who

improved (scores 1 to 3), had no change (score 4), and worsened (scores 5 to 7) will also be provided.

11.3.3 Subgroup analyses

Subgroup analyses of the more relevant variables will be performed. Details of these analyses will be described in the Statistical Analysis Plan.

11.3.4 Analysis of safety variables

Adverse drug reactions will be coded for analysis with the latest version of the Medical Dictionary for Regulatory Activities (MedDRA®).

Adverse drug reactions that occur during this study will be presented by MedDRA system organ class (SOC) and preferred term (PT) in a frequency table giving the number of events, the number of patients who experience the event, and the percentage of patients who experience the event. Patients with multiple ADRs will be counted only once within each PT and SOC for the number of patients and the percentage of patients who experience an event.

Serious ADRs that occur during the study will be presented by MedDRA SOC and PT in a frequency table giving the number of events, the number of patients who experience the event, and the percentage of patients who experience the event. Patients with multiple serious ADRs will be counted only once within each PT and SOC.

Adverse drug reactions leading to withdrawal that occur during the study will be presented by MedDRA SOC and PT in a frequency table giving the number of events, the number of patients who experience the event, and the percentage of patients who experience the event. Patients with multiple ADRs leading to withdrawal will be counted only once within each PT and SOC.

A listing of all ADRs will be provided. An overall summary table of all ADRs will be presented 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.

All table summaries will be sorted alphabetically by SOC and by decreasing relative frequency of each PT within SOC.

11.4 Planned interim analysis 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.

11.5 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% 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.

12 STUDY MANAGEMENT AND ADMINISTRATION

12.1 Quality assurance

12.1.1 Monitoring

In order to safeguard and assure data quality, a site management plan will be developed that will include details on site monitoring visits, site management by telephone, and source data verification.

Training on study procedures (eg, the handling of the eDF and the reporting of ADRs or AESIs) will be provided during site initiation. Any medical and/or methodological questions arising during the study will be answered by UCB or designee.

12.1.2 Data handling

12.1.2.1 Case Report form completion

The study is performed using electronic data capture. The treating physician is responsible for prompt reporting of accurate, complete, and legible data in the eDFs and in all required reports. Any change or correction to the eDF after saving must be accompanied by a reason for the change. Corrections made after the treating physician's review and approval (by means of a password/electronic signature) will be reapproved by the treating physician. The treating physician should maintain a list of personnel authorized to enter data into the eDF. Detailed instructions will be provided in the eDF Completion Guidelines.

12.1.2.2 Database entry and reconciliation

Case Report forms/external electronic data will be entered/loaded into a validated electronic database using a clinical data management system. Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. The data are entered into the eDFs once and are subsequently verified. An electronic audit trail system will be maintained within the clinical data management system to track all data changes in the database once the data have been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

12.2 Termination of study

As soon as the planned number of 100 patients is included, no additional patients will be included in the study.

For the individual patient, this NIS will end with the documentation conducted during their final visit. Study participation can also be terminated by the patient at any time.

The sponsor reserves the right to terminate the study at an early stage and/or to close individual sites. Potential reasons for an early termination include:

- An insufficient number of patients enrolled in the study
- Upon the request of regulatory authorities
- The participating physician does not adhere to the applicable rules, provisions, laws, and guidelines

12.3 Data archiving

Immediately after approval of the final report, the documentation forms will be archived for a minimum period of 10 years, including the ADR/AESI documentation and ADR/AESI correspondence. The latter will be archived by the UCB Drug Safety department without any time constraints.

12.4 Legal provisions and ethics

12.4.1 Data protection and data privacy declaration

The legal provisions for data protection will be observed. Prior to inclusion, the patient will be given information in writing that describes the purpose and procedures of the study and explains the requirements of data protection. The patient has to agree in writing that his/her medical data will be used for the evaluation of the study results by signing a study-specific Patient Data Consent form.

Information relating to participating physicians will be declared, and the physicians will be informed, within the framework of their financial agreement, of their right to access, object to, and correct this information.

12.4.2 Report of the Ethics Committee

Prior to the implementation of this NIS, the treating physician will have written, signed, and dated full approval for the protocol from the appropriate national scientific and ethical bodies in accordance with any local regulations and laws.

12.4.3 Notification/submission to relevant Regulatory Authority(ies)

Prior to the implementation of this NIS, all regulatory aspects of the study will be fulfilled with regard to regulatory submissions/filings when required by local regulations for NIS.

12.4.4 Legally required reports

This NIS is not a clinical study because it only pursues the objective of documenting the standard practical procedures and/or the data associated with the treatment of patients suffering from epilepsy.

In accordance with the currently valid and applicable rules and provisions, the study will be entered into the official online registry of clinical studies that is maintained by the US National Institute of Health (http://www.clinicaltrials.gov) and is accessible to the public at large. In accordance with the applicable national and local regulations, the study will also be registered in national clinical study registries and/or results databases as necessary.

13 REMUNERATION

Any payments to physicians will be in accordance with any local regulations and laws and will compensate only the additional work load related to the conduct of the study. The remuneration shall be regulated in a separate agreement to be concluded between UCB BIOSCIENCES GmbH and the participating physician and/or his or her clinic administration.

14 FINAL REPORT AND PUBLICATION

A final report will be prepared describing the results of the study. The results of the study are to be submitted to the study physicians, Ethic Committees, and Regulatory Authorities according to local regulations and laws.

15 RECOMMENDED SCHEDULE OF STUDY ASSESSMENTS

Table 15–1: Recommended schedule of study assessments

Assessments	Visit 1[a] (Baseline)	Visit 2 Approximately 3 months after Baseline according to routine practice[b]	Visit 3 (End of Observation Period or Withdrawal Visit[c]) Approximately 6 months after Baseline according to routine practice[b]
Signed data consent	X		
Demographic data	X		
Medical history	X[d]		
Seizure history	X[d]		
Tumor diagnosis and grade (including review of most recent brain imaging results [CT or MRI])	X		X
Prior and concomitant tumor management (surgical procedures, chemotherapies, radiotherapy)	X[d]		X
Prior and concomitant AEDs	X	X	X
Other prior and concomitant epilepsy treatment	X	X	X
Other prior and concomitant relevant medications	X[d]	X	X
Verification of selection criteria	X		
Documentation of LCM administration	X	X	X
Documentation of seizure information (including seizure frequency and type)[e]		X	X
Karnofsky performance status	X	X	X
EQ-5D-5L	X		X

Table 15–1: Recommended schedule of study assessments

Assessments	Visit 1[a] (Baseline)	Visit 2 Approximately 3 months after Baseline according to routine practice[b]	Visit 3 (End of Observation Period or Withdrawal Visit[c]) Approximately 6 months after Baseline according to routine practice[b]
MDASI-BT	X		X
PGIC			X
CGIC			X
Recording of ADRs and AESIs	X	X	X
Withdrawal criteria		X	X

ADR=adverse drug reactions; AED=antiepileptic drug; AESI=adverse event of special interest; CGIC=Clinical Global Impression of Change; CT=computerized tomography; EQ-5D-5L=5-Level EuroQol-5 Dimension Quality of Life Assessment; LCM=lacosamide; MRI=magnetic resonance imaging; MDASI-BT=M.D. Anderson Symptom Inventory - Brain Tumor; PGIC=Patient Global Impression of Change

[a] Visit 1 will be performed after the decision is taken to start adjunctive LCM therapy. Treatment with LCM should be initiated according to routine clinical practice. If the first dose of LCM is given on the same day as Visit 1, it should be administered after Baseline assessments are complete. Previous treatment with LCM is allowed for up to 7 days prior to enrollment.

[b] The frequency of visits after Visit 1 will be based on local clinical practice and the patients' requirements. The clinical procedures performed at each visit will also follow local clinical practice. It is estimated that patients will be followed at least every 3 months.

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

[d] During the previous 8 weeks and relevant information in the past according to the physician's decision.

[e] The treating physician will evaluate at each visit, as part of standard practice with the patient, the frequency and type of seizures experienced by the patient since the previous study visit.

16 REFERENCES

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17 APPENDICES

17.1 NIS Observational Plan Amendment 1

Rationale for the amendment

The main purpose of this substantial amendment is to amend the selection criteria in order to facilitate patient recruitment by the sites. Feedback from the study sites has confirmed that the current selection criteria are too restrictive and are consequently impeding access to suitable patients who could be eligible for study entry whilst undergoing routine care. This noninterventional study will add valuable data concerning the effectiveness of LCM within routine clinical practice when added to an existing treatment regime of 1 or 2 Baseline AEDs in patients with BTRE.

Modifications and changes

Global changes

The following changes were made throughout the NIS observational plan:

- The study title was amended as patients can receive more than 1 (either 1 or 2) Baseline AEDs.
- Section 1 Rationale for the study, Section 3 Study objectives, Section 5 Study design, Section 8.1 Selection criteria and Section 8.2 Withdrawal criteria were amended so patients can receive either 1 or 2 Baseline AEDs.
- The number of specialized centers was increased to approximately 25 centers.
- Selection Criterion 1 was amended to include patients who had never previously received LCM and those who had received LCM within 7 days prior to enrollment in the study.
- Selection Criteria 2 and 6 were amended as patients can be on LCM prior to enrollment in the study.
- Selection Criterion 5 was amended as the number of Baseline AEDs taken for epilepsy was increased from 1 to either 1 or 2.
- Selection Criterion 10 was amended to increase the number of Baseline AEDs taken for epilepsy from 1 to either 1 or 2.
- Selection Criterion 11 was amended to allow a lifetime maximum of 4 different AEDs.
- Selection Criterion 12 was removed as this criterion was covered by Selection Criterion 2.
- Administrative changes: minor changes were made to study contact information; the section Declarations and signatures of persons responsible for the study was updated for electronic signature; minor edits were made to the Pregnancy section.

Specific changes

This section displays the modifications in this amendment compared with the final noninterventional observational plan dated 23 Jun 2014. The changes are displayed in the order of appearance.

Change #1

Title page, 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 VIMPAT® (LACOSAMIDE) AS ADJUNCTIVE ANTIEPILEPTIC DRUG THERAPY IN PATIENTS WITH BRAIN TUMOR-RELATED EPILEPSY (VIBES)

Change #2

STUDY CONTACT INFORMATION

Study Physician

Name:	[redacted], MD
Address:	UCB Pharma S.A. Allée de la Recherche 60 1070 Brussels BELGIUM
Phone:	[redacted]
Fax:	
Email:	

Has been changed to:

Study Physician

Name:	[redacted], MD
Address:	UCB Pharma S.A. Allée de la Recherche 60 1070 Brussels BELGIUM
Phone:	[redacted]
Fax:	
Email:	

Clinical Trial Biostatistician

Name:	[redacted]
Address:	UCB BIOSCIENCES GmbH Alfred-Nobel-Strasse 10 40789 Monheim GERMANY
Phone:	[redacted]
Fax:	
Email:	

Has been changed to:

Clinical Trial Biostatistician

Name:	[redacted]
Address:	UCB BIOSCIENCES GmbH Alfred-Nobel-Strasse 10 40789 Monheim GERMANY
Phone:	[redacted]
Fax:	
Email:	

Clinical Monitoring Contract Research Organization

Name:	PRA
Address:	Gottlieb-Daimler-Strasse 10 68165 Mannheim GERMANY
Phone:	+49 621 8782 872
Fax:	+49 621 8782 184

Has been changed to:

Clinical Monitoring Contract Research Organization

Name:	PRA GmbH
Address:	Gottlieb-Daimler-Strasse 10 68165 Mannheim GERMANY
Phone:	+49 621 8782 0
Fax:	+49 621 8782 184

Change #3

Declarations and signatures of persons responsible for the study

I confirm that I have carefully read and understand this noninterventional study observational plan and agree to conduct this noninterventional study as outlined.

Clinical Project Manager

[redacted]

Date/Signature

Clinical Trial Biostatistician

[redacted]

Date/Signature

Study Physician

[redacted], MD

Date/Signature

Lead Clinical Development Representative

[redacted]

Date/Signature

Medical Affairs Medical Director

[redacted]

Date/Signature

Has been revised and moved to Section 18:

Declarations and signatures of persons responsible for the study

I confirm that I have carefully read and understand this noninterventional study observational plan and agree to conduct this noninterventional study as outlined.

Change #4

Section 1 RATIONALE FOR THE STUDY, paragraphs 3, 10, and 11

Lacosamide (LCM, VIMPAT®) is an antiepileptic drug (AED), which has been shown to provide a favorable benefit-risk profile and was approved by the European Medicine Agency (EMA) on 29 Aug 2008 (EU/1/08/470/01 to 013 and EU/1/08/470/016 to 023; EMA reference EMEA/H/C/000863) as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients with epilepsy aged 16 years and older (film-coated tablets of 50mg, 100mg, 150mg, and 200mg, syrup of 10mg/mL, and solution for infusion of 10mg/mL). In addition, LCM is approved as adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy in the United States and in other regions.

EP0045 is a multicenter, prospective NIS conducted at specialized sites in approximately 6 European countries, with a 6-month Observation Period. Lacosamide will be added to any AED monotherapy in approximately 100 patients with BTRE.

The primary objective of this study is to evaluate in routine clinical practice the effectiveness of LCM added to a single AED in the treatment of patients with BTRE due to low-grade glioma. 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.

Have been changed to:

Lacosamide (LCM, VIMPAT®) is an antiepileptic drug (AED), which has been shown to provide a favorable benefit-risk profile and was approved by the European Medicine Agency (EMA) on 29 Aug 2008 (EU/1/08/470/01 to 013 and EU/1/08/470/016 to 023; EMA reference EMEA/H/C/000863) as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients with epilepsy aged 16 years and older (film-coated tablets of 50mg, 100mg, 150mg, and 200mg, syrup of 10mg/mL, and solution for infusion of 10mg/mL). In addition to the European Union, LCM is approved as adjunctive therapy in adults suffering from partial-onset seizures in at least 38 other countries to date. In the United States, LCM is approved as adjunctive therapy or monotherapy in patients age 17 years and older and suffering from partial-onset seizures.

EP0045 is a multicenter, prospective NIS conducted at specialized sites in approximately 6 European countries, with a 6-month Observation Period. Lacosamide will be added to any AED therapy (1 or 2 AEDs) in approximately 100 patients with BTRE.

The primary objective of this study is to evaluate in routine clinical practice the effectiveness of LCM added to 1 or 2 AEDs in the treatment of patients with BTRE due to low-grade glioma.

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.

Change #5

Section 3 STUDY OBJECTIVES

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

The secondary objective of this study is to evaluate the tolerability and 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 primary objective of this study is to evaluate the effectiveness and patient global impression of LCM added to 1 or 2 AEDs in the treatment of patients with BTRE due to low-grade primary brain tumor.

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

Change #6

Section 5 STUDY DESIGN, paragraph 1

EP0045 is a multicenter, prospective, single-arm NIS conducted at specialized sites utilizing LCM added to AED monotherapy 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 11.5).

Has been changed to:

EP0045 is a multicenter, prospective, single-arm NIS conducted at specialized sites utilizing LCM added to existing treatment with 1 or 2 Baseline 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 11.5).

Change #7

Section 5 STUDY DESIGN, paragraph 5

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 (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:

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

Change #8

Section 6 EXPECTED STUDY DURATION

The planned number of patients is 100 (see Section 11.5), with 93 evaluable patients expected. Approximately 20 specialized centers are planned for participation. The expected recruitment period is 12 months.

Has been changed to:

The planned number of patients is 100 (see Section 11.5), with 93 evaluable patients expected. Approximately 25 specialized centers are planned for participation. The expected recruitment period is 12 months.

Change #9

Section 8.1 Selection criteria

Selection Criterion 1

1. Patient has never been treated with LCM prior to this NIS.

Has been changed to:

1. Patient has never been treated with LCM prior to this NIS or treatment with LCM for the first time started no earlier than 7 days prior to enrollment in this NIS.

Selection Criterion 2

2. The decision by the treating physician to prescribe LCM for the first time falls within current standard clinical practice, and the treatment decision is clearly separated from the decision to consider inclusion of the patient in the NIS.

Has been changed to:

2. The decision by the treating physician to prescribe LCM falls within current standard clinical practice, and the treatment decision is clearly separated from the decision to consider inclusion of the patient in the NIS.

Selection Criterion 5

5. Patient must have a diagnosis of BTRE secondary to low-grade glioma (World Health Organization Grade 1 to 2 at time of enrollment), not sufficiently controlled by 1 Baseline AED.

Has been changed to:

5. Patient must have a diagnosis of BTRE secondary to low-grade glioma (World Health Organization Grade 1 to 2 at time of enrollment).

Selection Criterion 6

6. Patient has a retrospective Baseline seizure frequency of at least 1 partial-onset seizure in the 8 weeks prior to Visit 1 (enrollment/Baseline visit).

Has been changed to:

6. Patient has a retrospective Baseline seizure frequency of at least 1 partial-onset seizure in the 8 weeks prior to start of LCM treatment.

Selection Criterion 10

10. Patient is currently taking only 1 Baseline AED for epilepsy.

Has been changed to:

10. Patient is currently taking only 1 or 2 Baseline AEDs for epilepsy other than LCM.

Selection Criterion 11

11. Patient has received a maximum of 3 different lifetime AEDs ever before entering the NIS.

Has been changed to:

11. Patient has received a maximum of 4 different lifetime AEDs ever before entering the NIS.

Selection Criterion 12

The following selection criterion has been deleted:

12. Patient does not have contraindications according to the Summary of Product Characteristics for LCM.

Change #10

Section 8.2 Withdrawal criteria, paragraph 3

If a patient needs to increase the dose of the Baseline AED or needs to be treated with further AEDs, these changes can be implemented, but the patient will be withdrawn from the study.

Has been changed to:

If a patient needs to increase the dose of the Baseline AEDs (1 or 2) or needs to be treated with more than 2 AEDs other than LCM, these changes can be implemented, but the patient will be withdrawn from the study.

Change #11

Section 10.1.4 Pregnancy, final paragraph

In cases where the partner of a male patient enrolled in a NIS becomes pregnant, the treating physician or designee is asked to contact the patient to request consent via the Partner Pregnancy Consent form that should be available in the treating physician's site file. In case of questions about the consent process, the treating physician may contact UCB's local Drug Safety department. The treating physician will complete the Pregnancy Report and Outcome form and send it to UCB's local Drug Safety department only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form. UCB's local Drug Safety department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow up.

Has been changed to:

In cases where the partner of a male patient enrolled in a NIS becomes pregnant, the treating physician or designee is asked to contact the patient to request consent via the Partner Pregnancy Consent form. In case of questions about the consent process, the treating physician may contact UCB's local Drug Safety department. The treating physician will complete the Pregnancy Report and Outcome form and send it to UCB's local Drug Safety department only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form. UCB's local Drug Safety department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow up.

Change #12

Table 15–1: RECOMMENDED SCHEDULE OF STUDY ASSESSMENTS
Footnote a

[a] Visit 1 will be performed before the first dose of LCM and after decision is taken to start adjunctive LCM therapy. Lacosamide can be administered on the same day of Visit 1 after Baseline assessments are complete.

Has been changed to:

[a] Visit 1 will be performed after the decision is taken to start adjunctive LCM therapy. Treatment with LCM should be initiated according to routine clinical practice. If the first dose of LCM is given on the same day as Visit 1, it should be administered after Baseline assessments are complete. Previous treatment with LCM is allowed for up to 7 days prior to enrollment.

18 DECLARATIONS AND SIGNATURES

Declarations and signatures of persons responsible for the study

I confirm that I have carefully read and understand this noninterventional study observational plan and agree to conduct this noninterventional study as outlined.

EP0045 Protocol Amendment 1

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
[redacted]	Clinical Approval	01-Jun-2015 11:08 GMT+02