STATISTICAL ANALYSIS PLAN

Study: SP1042

Product: Lacosamide

A MULTICENTER, OPEN-LABEL, FOLLOW-UP STUDY TO ASSESS THE LONG-TERM USE OF LACOSAMIDE (FLEXIBLE DOSE FROM 200 TO 600MG/DAY) USED AS MONOTHERAPY IN SUBJECTS WHO COMPLETED SP0994 AND RECEIVED LACOSAMIDE MONOTHERAPY TREATMENT

SAP/Amendment Number	Date
Final SAP	08 MAR 2016

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LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ATC	Anatomical Therapeutic Chemical
CBZ-CR	carbamazepine (controlled release)
CRF	case report form
CSR	Clinical Study Report
ES	Enrolled Set
IP	Investigational Product
IXR	interactive voice/web response system
LCM	lacosamide
MedDRA®	Medical Dictionary for Regulatory Activities
PT	Preferred Term
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System Organ Class
SS	Safety Set
TEAE	treatment-emergent adverse event
WHO-DRL	World Health Organization-Drug Reference

1 INTRODUCTION

This document outlines the planned analyses to support the SP1042 clinical study report (CSR).

2 PROTOCOL SUMMARY

2.1 Study objective(s)

The primary objective of the study is to assess the long-term safety and tolerability of lacosamide (LCM) dosed at 200mg/day to 600mg/day when used as monotherapy in subjects, with partial-onset seizures or generalized tonic-clonic seizures (without clear focal origin), who completed SP0994 and received LCM.

2.2 Study variable(s)

2.2.1 Safety variable(s)

The primary safety variables are as follows:

- Adverse events (AEs) reported spontaneously by the subject and/or caregiver or observed by the investigator
- Withdrawals due to AEs
- Serious adverse events (SAEs)

2.3 Study design and conduct

SP1042 is a long-term, open-label, follow-up study for subjects being treated with LCM monotherapy at the time of unblinding of SP0994. Subjects in SP0994 who were receiving LCM will have the opportunity to participate in SP1042 and will have access to open-label follow-up treatment with LCM. Subjects who were receiving carbamazepine (controlled realease) (CBZ-CR) or who were in LCM taper in SP0994 at the time of unblinding will not be allowed to participate in SP1042. Subjects who do not wish to continue LCM therapy after unblinding of SP0994 will be tapered off LCM and will not participate in SP1042.

Visit 1 for SP1042 will be the same as the Termination Visit of SP0994. Clinic visits are scheduled approximately every 26 weeks relative to the SP1042 Visit 1 date. Dose modifications required for optimization of seizure control or tolerability issues will be addressed in Unscheduled Visits or regularly scheduled visits. A visit window of ±7 days relative to Visit 1 is applicable for all regularly scheduled visits.

In SP0994, subjects will be receiving a dose of LCM 200mg/day, 300mg/day, 400mg/day, 500mg/day, or 600mg/day and will continue to receive the same dose in SP1042 until further dose adjustments are required.

During SP1042 visits, investigators will be allowed to increase or decrease the dose of LCM to optimize tolerability and seizure control for each subject. The investigator may maintain the subject's LCM dose, decrease the dose in decrements of 100mg/day per week to a minimum dose of LCM 200mg/day, or increase the dose in increments of 100mg/day per week up to a maximum dose of LCM 600mg/day. Lacosamide doses administered in this study must be from 200mg/day to 600mg/day, must comply with doses that can be administered with LCM 50mg tablets, and should be a dose that can be administered in equal divided doses twice daily. The

interactive voice/web response system (IXRS) should be called any time there is a dose increase or dose reduction.

If, in the investigator's opinion, a lower dose of LCM is medically more suitable for a subject, the decision to allow such patients to continue in the study on a lower dose of LCM will be made based on appropriate medical justification and after prior discussion with the study Medical Monitor.

In order to continue study participation, subjects must maintain treatment with LCM monotherapy.

Subjects who discontinue prematurely from SP1042 and who will not continue further treatment with LCM should gradually taper LCM following an Early Termination Visit. These subjects will perform an Early Termination Visit followed by the visits required for the End-of-Study Phase. Subjects should be tapered off LCM at recommended decreasing steps of 200mg/day/week. A slower taper (eg, 100mg/day/week) or faster taper is permitted, if medically necessary; however, the maximum duration of tapering should not exceed 6 weeks. Subjects will attend a Final Visit 2 weeks after the final dose of LCM. In the case of LCM withdrawal and taper, the investigator is allowed to add any other antiepileptic drug (AED) during the End-of-Study Phase, following the investigator's medical judgment.

Subjects who discontinue from the study as a result of requiring treatment with other AEDs will return for an Early Termination Visit, and may be prescribed LCM by their physician (ie, not supplied by UCB) as adjunctive therapy if LCM is well tolerated by the subject (dose should be adapted as per investigator's judgment). The Early Termination Visit will be the last study visit for these subjects.

A Termination Visit will be performed for subjects who are ongoing in the Treatment Phase at the time that the marketing application is approved and LCM is commercially available for monotherapy in the subject's country, or UCB has determined that the clinical development program for the monotherapy indication will be formally discontinued, or up to a maximum period of 3 years, whichever is earlier. Subjects may be immediately prescribed commercially available LCM. In this instance, the Termination Visit will be the last study visit completed by the subject. If subjects do not continue with LCM treatment, following the Termination Visit, subjects will be tapered off LCM. The Final Visit will be conducted 2 weeks after the final dose of LCM.

Subjects will be allowed to continue treatment in this study until marketing application is approved and LCM is commercially available for monotherapy in the subject's country, or UCB has determined that the clinical development program for the monotherapy indication will be formally discontinued, or up to a maximum period of 3 years, whichever is earlier. The maximum total duration of the study will be 164 weeks, including up to a 156-week Treatment Phase duration and up to an 8-week End-of-Study Phase.

The end of the study is defined as the date of the last visit of the last subject in the study.

2.4 Determination of sample size

No formal sample size calculations have been performed for this study as there are no statistical hypotheses being tested. The sample size will be determined by the number of subjects in SP0994 who have been treated with LCM that are eligible to enter this open-label follow-up

study. It is anticipated that approximately 150 subjects who receive LCM in SP0994 will participate in this follow-up study.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

Statistical analysis and generation of tables, figures, subject data listings, and statistical output will be performed using SAS® Version 9.3 or higher. All tables and listings will use Courier New font size 9.

For categorical parameters, the number and percentage of subjects in each category will be presented. The denominator for percentages will be based on the number of subjects appropriate for the purpose of analysis. Unless otherwise noted, all percentages will be displayed to one decimal place. No percentage will be displayed for zero counts, and no decimal will be presented when the percentage is 100%.

For continuous parameters, descriptive statistics will include n, mean, standard deviation (SD), median, minimum, and maximum.

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.

Unless otherwise specified, all analysis will be performed for the Safety Set (SS).

A complete set of data listings containing all documented data and all calculated data will be generated.

3.2 General study level definitions

3.2.1 Analysis time points

- Treatment Period: the start of the Treatment Period is the date of Visit 1. The end of the Treatment Period is the date of the Termination Visit or Early Termination Visit for subjects who are prematurely discontinued. For subjects who discontinued during the Treatment Period without an Early Termination Visit, the end of the Treatment Period is the date of last known visit date (including unscheduled visits), the date of last dose, the date of premature termination, or the date of final contact, whichever is the latest.
- End of Study Period: the day following the last day in the Treatment Period to the Final Visit, including tapering. Any additional data collected during the study but after the Final Visit will also be included in the End of Study Period.

3.2.2 Relative day

Relative day will be presented in subject data listings. Relative day will be calculated as follows:

- If the start (stop) date occurred prior to the first intake of LCM in SP1042, the relative day is calculated as start (stop) date minus first LCM dose date. In subject data listings, relative days based on this situation will be preceded by a '-'.

- If the start (stop) date occurred on or after the first intake of LCM but prior to the last dose of LCM in SP1042, the relative day is calculated as start (stop) date minus first LCM dose date + 1.
- If the start (stop) date occurred after the date of last dose of LCM in SP1042, the relative day is calculated as start (stop) date minus last dose date. In subject data listings, relative days based on this situation will be preceded by a '+'.

3.3 Definition of Baseline values

Baseline will be the Baseline values in SP0993. Only date of birth and gender will be collected for SP1042 when applicable.

3.4 Protocol deviations

Important protocol deviations are deviations from the protocol that could potentially have a meaningful impact on study conduct or on the key safety outcomes for an individual subject. The criteria for identifying important protocol deviations and the classification of important protocol deviations will be defined within the appropriate protocol-specific document (eg, the Protocol Deviation Specification). To the extent feasible, rules for identifying protocol deviations will be defined without review of the data and without consideration of the frequency of occurrence of such deviations.

In general, the protocol deviations will be considered according to the following general categories:

- Informed Consent
- Inclusion/Exclusion criteria
- Withdrawal criteria
- Investigational Product (IP) / Study treatment
- Disallowed medications
- AE / SAE
- Visit schedule
- Procedure / Test
- Other

Important protocol deviations will be reviewed as part of the ongoing data cleaning process prior to database lock.

3.5 Analysis sets

3.5.1 Enrolled Set

The Enrolled Set (ES) will consist of all subjects who have given informed consent in SP1042.

3.5.2 Safety Set

The SS will consist of all subjects in the ES who have received at least 1 dose of study medication in SP1042.

3.6 Treatment assignment and treatment groups

This is a follow-up study to assess the long-term use of LCM used as monotherapy in subjects who completed SP0994. Subjects treated with LCM monotherapy in SP0994 will continue to be treated with LCM.

Analysis will be performed overall as only subjects treated by LCM will be enrolled.

3.7 Center pooling strategy

Centers will be pooled by country and region for the purpose of disposition analysis. Countries will be pooled as follows:

Europe: Bulgaria, Finland, France, Germany, Latvia, Poland, Russia, Sweden, Switzerland, Ukraine;

North America: Mexico;

Asian Pacific: Japan, Philippines, South Korea.

3.8 Coding dictionaries

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

3.9 Changes to protocol-defined analyses

Not applicable.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

No adjustments of covariates will be applied.

4.2 Handling of dropouts or missing data

No imputation of missing values associated with an individual date or visit is planned, with the exception of incomplete and missing dates specified in the following section. With respect to AEs, events with missing severity will be assumed to be severe. Events with a missing relationship to study medication per the investigator will be assumed to be related.

For evaluation of safety variables, subjects who prematurely discontinue the study will be evaluated based on the data collected at each visit attended.

4.2.1 Incomplete dates for adverse events and concomitant medications

In order to correctly identify an AE or medication as occurring during an analysis period, a complete date must be established. The algorithm listed below will be followed to impute incomplete or missing start dates for AEs and concomitant medications. In subject data listings, start dates of AEs or medications will be displayed as reported (ie, no imputed dates will be displayed).

- Missing start day, but month and year present

If the start date of study medication in SP1042 occurred in the same month and year as the occurrence of the AE or medication, the start date of the AE or medication will be assigned to the day of first dose of study medication in SP1042.

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

- Missing start day and month, but year present

If the start date of study medication in SP1042 occurred in the same year as the occurrence of the AE or medication, the start date of the AE or medication will be assigned to the day of first dose of study medication in SP1042.

Otherwise the start date will be set to January 1st.

- Complete missing start date

If the start date is completely missing and the stop date is unknown or not prior to the first dose of study medication in SP1042, the start date will be assigned to the date of first dose of study medication in SP1042.

4.2.2 Incomplete dates for the last administration of study medication

The complete date of last administration of study medication must be established in order to calculate the duration of exposure. The algorithm listed below will be followed to impute incomplete or missing date of the last administration of study medication.

- Missing day of the last administration, but month and year present

The date of last administration will be set to the last day of the month or the date of the final contact, whichever is earlier in the month.

- Missing day and month of the last administration but year present

The date of last administration will be set to December 31st of the year or the date of the final contact, whichever is earlier in the year.

- Completely missing the date of the last administration

The date of last administration will be set to the date of final contact.

If the imputed date of last administration according to the rules above is after the date of a death, the date of last administration will be set to the date of death.

4.3 Interim analyses and data monitoring

No formal interim analysis or data monitoring is planned in the study. However, interim data may be reported prior to the completion of this study to support annual reports, regulatory submissions, and publications.

4.4 Multicenter studies

No analysis per center is foreseen due to the small number of subjects recruited per center.

4.5 Multiple comparisons/multiplicity

Not applicable for this study.

4.6 Use of an efficacy subset of subjects

Not applicable for this study.

4.7 Active-control studies intended to show equivalence

Not applicable for this study.

4.8 Examination of subgroups

No subgroup analysis is planned.

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

The number of subjects in the ES and SS will be presented overall, by region (Europe, North America, and Asian Pacific), by country and by investigator. The date of first subject in and date of last subject out will also be included for each investigator.

The number and percentage of subjects who completed and discontinued from the study with associated reasons for discontinuation will be summarized for the SS.

In addition, the number and percentage of subjects who discontinued due to AE will be summarized to address the EudraCT requirement.

5.2 Protocol deviations

Number and percentage of subjects with important protocol deviations will be summarized by the categories defined in Section 3.4 for the SS. Subjects will not be excluded from the SS because of important protocol deviations. All important protocol deviations will be listed in the subject data listing.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics

Demographics will be summarized for the SS:

- Age (years) at SP1042 entry – continuous and categorized (18 to < 65 years; 65 to <85 years; ≥85 years and ≤18 years; ≥19 to <65 years ; ≥ 65 years)
- Gender (male, female)

6.2 Other Baseline characteristics

No other Baseline characteristics will be collected and analyzed.

6.3 Medical history and concomitant diseases

No analysis will be performed in SP1042.

6.4 Concomitant medications

Medications will be summarized using the Anatomical Therapeutic Chemical (ATC) codes from the WHO-DRL dictionary. All tabulations will be sorted by frequency of the higher level ATC code and by frequency of the lower level ATC code within the higher level ATC code.

Concomitant medications are medications reported on the Concomitant Medications case report form (CRF) page or on the Concomitant Medications ongoing from study SP0994 CRF page taken on or after the first dose of study medication and the start date is not after the date of last dose in SP1042. If the date of last dose is unknown, any medications taken on or after the first dose of study medication will be considered as concomitant medications. Medications with a missing start date whose stop date is either unknown or after the date of the first dose of study medication will be considered as concomitant.

Antiepileptic drugs (AEDs) are medications reported on the Concomitant Medications CRF page or on the Concomitant Medications ongoing from study SP0994 CRF page, with indications related to epilepsy or seizure. Antiepileptic drugs will be summarized separately from the other medications (non-AEDs).

Concomitant AEDs during the study will be presented by 4-level ATC (4-digit) terms and preferred medication name. Concomitant non-AED medications will be summarized separately by 1-level and 2-level ATC (3 digit) terms.

A glossary of ATC codes and associated investigator's terms for all medications will also be listed.

6.5 Concomitant medical procedures

Concomitant medical procedures will be listed by subject.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Subjects identified to have non-protocol LCM dosing will be summarized in tabular format under the protocol deviations category of LCM Dosing Regimen (See Section 3.4). Information reported on the CRF regarding tablets dispensed and returned will be reported in subject data listings. LCM dosing compliance will be evaluated through the review of important protocol deviations classified under LCM Dosing Regimen (See Section 3.4).

8 EFFICACY ANALYSES

Not applicable for this study.

9 PHARMACOKINETICS AND PHARMACODYNAMICS

9.1 Pharmacokinetics

Not applicable for this study.

9.2 Pharmacodynamics

Not applicable for this study.

10 SAFETY ANALYSES

Safety analyses will be performed in the SS.

10.1 Extent of exposure

Overall exposure to LCM in days during the Treatment Period is calculated as the date of last administration of LCM minus the date of first administration in SP1042 plus 1.

Subject-years of exposure will be calculated as the number of days of exposure, divided by 365.25.

Gaps in LCM treatment or days on the LCM dosing log CRF with unknown dosing will not be subtracted from the overall exposure days and subject-years of exposure.

LCM modal dose (mg/day) will be defined as the daily LCM dose the subject received for the longest duration during the Treatment Period. The modal dose calculation is based on the number of days a subject 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 log information will be performed).

The maximum daily dose will be calculated as the highest total daily dose the subject received during the treatment period.

The following exposure summaries and a listing will be produced:

- Number of subjects and subject-years of exposure by cumulative time intervals (months) (ie, >0, >=6, >=12, >=18, >=24, >=30, >=36, where one month is defined as 28 days). The categories of intervals may be adjusted according to the actual data
- Summary statistics for modal dose, maximum daily dose and duration of exposure
- Summary statistics for duration of exposure and subject-years of exposure by modal dose and by maximum daily dose cohorts
- Number and percentage of subjects within each LCM treatment duration category by modal dose and by maximum daily dose cohorts. LCM treatment duration categories (days) are as follows: 1 to 84, 85 to 168, 169 to 336, 337 to 504, 505 to 672, 673 to 840, 841 to 1008, >1008, and any duration. The categories may be adjusted according to the actual data.

10.2 Adverse events

The primary safety variables are as follows:

- AEs reported spontaneously by the subject and/or caregiver or observed by the investigator
- Withdrawals due to AEs
- SAEs

Treatment-emergent adverse events (TEAEs) are defined as AEs that started on or after the date of first dose of study medication in SP1042 and within 30 days following the date of last study medication administration, or AEs whose intensity worsened on or after the date of first dose of study medication and within 30 days following the date of last dose. If the date of the last dose of study medication is unknown, any AEs occurring on or after the first dose of study medication will be considered treatment-emergent.

TEAEs will be assigned to an analysis period based on the AE onset dates. AEs will be tabulated by MedDRA system organ class (SOC) and MedDRA preferred term (PT). The number and percentage of subjects experiencing each event at least once will be summarized. Numbers of individual AE occurrences will be also presented in selected tables. All summaries will be sorted alphabetically by SOC and by decreasing frequency of events within SOC.

The following summaries will be presented for the AEs:

- Ongoing AEs at SP1042 study entry.
- Adverse events during the Treatment Period:
  - An overview summary of TEAEs during the Treatment Period will be presented. It will include the numbers and percentages of subjects with at least one TEAE, at least one Serious TEAE, at least one TEAE leading to discontinuation, at least one drug-related TEAE, at least one severe TEAE, and death.
  - Incidence of TEAE during the Treatment Period.
  - Incidence of TEAEs by maximum intensity during the Treatment Period. If the intensity of an AE is missing, it will be assumed to be severe.
  - Incidence of TEAEs during the Treatment Period by maximum relationship per investigator. If the relationship is missing, the AE will be assumed to be related to study medication.
  - Subject number listing for TEAEs during the Treatment Period
  - Incidence of Serious TEAEs during the Treatment Period
  - Subject number listing for Serious TEAEs during the Treatment Period
  - Incidence of TEAEs leading to discontinuation during the Treatment Period
  - Subject number listing for TEAEs leading to discontinuation during the Treatment Period
  - Incidence of other significant TEAEs during the Treatment Period. Other significant TEAEs are defined by the MedDRA terms in Appendix 12.1.
  - Subject number listing for other significant TEAEs during the treatment period
  - Incidence of TEAEs during the Treatment Period per 100 Subject-months.
- Adverse events during the study (including the Treatment and End of Study Periods)
  - Overview of TEAEs during the study
- Adverse events by relationship during the study
  - Incidence of TEAEs during the study by relationship to study drug per investigator
  - Incidence of serious TEAEs during the study by relationship to study drug per investigator
  - Incidence of non-serious TEAEs during the study by relationship to study drug per investigator
  - Incidence of non-serious TEAEs occurring in >5% of subjects during the study by relationship to study drug per investigator
  - Incidence of fatal TEAEs during the study by relationship to study drug per investigator
- Subject number listing for all deaths

Individual subject data listings will be presented for all AEs in the SP1042 clinical database, serious AEs, AEs leading to death, TEAEs leading to discontinuation, and other significant AEs.

A glossary of MedDRA terms and associated investigator's terms for TEAEs will also be presented.

11 REFERENCES

No reference.

12 APPENDICES

12.1 Other significant TEAEs

Table 12–1: List of other significant TEAEs

MedDRA Preferred Term
HEPATOTOXICITY RELATED TERMS
Hepatitis toxic
Hepatotoxicity
CARDIAC AND ECG RELATED TERMS
Atrioventricular block complete
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
Poisoning deliberate
ADDITIONAL TERMS

Table 12–1: List of other significant TEAEs

MedDRA Preferred Term
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.

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.