SP0978, 2010-022534-84

CLINICAL STUDY REPORT SYNOPSIS

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This synopsis may include approved and non-approved uses, formulations or treatment regimens. The results from a single study may not reflect the overall results for the specific product. Prescribing decisions should be made by healthcare professionals based on the approved labeling information for the specific product in the respective country.

Personal information has been removed to protect the privacy of patients and the individuals named in the synopsis.

Sponsor:

UCB Pharma SA,
Allée de la Recherche 60,
1070 Brussels,
Belgium

Official study title:

A multicenter, open-label, single-arm study to evaluate hormone and lipid levels in male subjects with partial-onset seizures after a switch of treatment from carbamazepine as adjunctive treatment to levetiracetam to lacosamide as adjunctive treatment to levetiracetam

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Name of finished product: Vimpat®	**Volume:** Not applicable	
Name of active ingredient: Lacosamide	**Page:** Not applicable	

Title of study: A multicenter, open-label, single-arm study to evaluate hormone and lipid levels in male subjects with partial-onset seizures after a switch of treatment from carbamazepine as adjunctive treatment to levetiracetam to lacosamide as adjunctive treatment to levetiracetam

Investigator(s): This was a multicenter study in which 5 investigators enrolled subjects.

Study site(s): The study was conducted at 5 sites across [redacted].

Publication(s) (reference[s]): None.

Study period: Approximately 1 year and 7 months **First subject enrolled:** 14 Jul 2011 **Last subject completed:** 01 Mar 2013	**Phase of development:** Phase 3b

Objective(s): The objective of this study was to evaluate the change in hormonal parameters and lipid parameters in serum after switching from carbamazepine (CBZ) treatment to lacosamide (LCM) treatment as adjunctive therapy to levetiracetam (LEV).

Methodology: SP0978 was a Phase 3b, multicenter, open-label, single-arm study to evaluate the change in hormone and serum lipid levels in young (18 to 45 years of age) male subjects with partial-onset seizures when switched from CBZ treatment as adjunctive therapy to LEV to LCM treatment as adjunctive therapy to LEV. The maximum study duration per subject was approximately 17 weeks, which consisted of a 1-week Screening Period, a 12-week Treatment Period (comprised of a 4-week Titration Period and an 8-week Maintenance Period), and a Taper/Safety Follow-Up Period 3 to 4 weeks in duration. During the Screening and Treatment Periods, the dose of LEV remained stable and no antiepileptic drug (AED) other than LCM was added.

During the first week of the Titration Period, subjects were instructed to begin titration of LCM at a dose of 100mg/day (50mg bid). Lacosamide was titrated in 100mg/day/week increments, up to a dose of 400mg/day. Subjects began the down-titration of CBZ on Day 7, 1 week after the first dose of LCM. The total daily dose of CBZ was decreased approximately 25% each week, and intake of CBZ stopped at the end of the Titration Period (Visit 3).

During the first 4 weeks of the Maintenance Period (from Visit 3 to Visit 4), the LCM dose

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could have been changed, as clinically indicated, to further optimize efficacy and tolerability of the AED treatment. The change in LCM dose was in increments of 100mg/day/week, up to a maximum dose of 600mg/day or down to a minimum dose of 300mg/day.

Subjects who completed the study (Termination Visit) were to decide, together with the investigator, whether or not to continue receiving commercial LCM. Subjects who chose to continue receiving commercial LCM after completion were not required to taper off LCM or return for a Safety Follow-Up Visit. Subjects who completed the study and chose not to continue receiving commercial LCM were gradually tapered off LCM and returned for a Safety Follow-Up Visit approximately 2 weeks after the last dose of LCM.

On 03 Dec 2013, the sponsor had made the decision to end the study due to slow patient enrollment.

Number of subjects (planned and analyzed): For a 2-sided paired t-test of mean change equal to zero, assuming a μ_Δ of -6nmol/L and a σ_Δ of 9nmol/L and controlling the Type I error at 5%, a sample size of 22 subjects provided statistical test power of approximately 85%. To allow for the exclusion of 20% of the subjects due to important protocol deviations such as use of prohibited medication or premature discontinuation, the sample size was increased by 6 subjects. The final total number of subjects to be enrolled was 28.

On 03 Dec 2013, the sponsor had made the decision to end the study due to slow patient enrollment and a total of 13 subjects had been screened and enrolled by this date.

Diagnosis and main criteria for inclusion: Subject had to be male and had to be between the age of ≥18 and ≤45 years. Subject must have had a diagnosis of epilepsy with partial-onset seizures according to the International Classification of Epileptic Seizures (1981) and was only taking LEV in combination with CBZ as adjunctive treatment for epilepsy. Subject must have been treated with CBZ for at least 12 months before study entry and both LEV and CBZ must have been at a stable dose during the 30 days before study entry. By Visit 1, subject must have been taking CBZ dose between ≥600mg/day to ≤1200mg/day and LEV dose must have been ≥1000mg/day. Subjects for whom a change from adjunctive treatment of CBZ and LEV to adjunctive treatment of LCM and LEV were expected to benefit according to the clinical judgment of the investigator (the benefits were related to: seizure control, tolerability of the treatment, endocrine/metabolic function, and/or drug-drug interactions).

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Test product, dose(s) and mode of administration, batch number(s): Commercial formulation of LCM tablets were used. Lacosamide tablets were supplied as oval, film-coated tablets debossed with "SP" on 1 side and the dose on the other. Lacosamide was provided in doses of 50mg (pinkish) and 100mg (yellow) tablets.

The LCM batch numbers were as follows:

LCM 50mg: [redacted]

LCM 100mg: [redacted]

Duration of treatment: The maximum study duration per subject was approximately 17 weeks, which consisted of a 1-week Screening Period, a 12-week Treatment Period (comprised of a 4-week Titration Period and an 8-week Maintenance Period), and a Taper/Safety Follow-Up Period 3 to 4 weeks in duration.

Reference therapy, dose(s) and mode of administration, batch number(s): None

Criteria for evaluation:

Safety:

The primary safety variable was change in serum sexual hormone binding globulin (SHBG) concentration from Baseline to the end of the Maintenance Period.

The secondary safety variables were the following:

- Change in the sexual hormone calculated free androgen index (=100xtestosterone/SHBG) levels from Baseline to the end of the Maintenance Period
- Change in the serum thyroid hormone free thyroxine (fT_4) level from Baseline to the end of the Maintenance Period
- Change in total cholesterol levels from Baseline to the end of the Maintenance Period

The other safety variables were:

- Change in the following serum sexual hormone levels from Baseline to the end of the Maintenance Period:
  - Testosterone
  - Dehydroepiandrosterone sulfate (DHEAS)
  - Luteinizing hormone (LH)

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  - Follicle stimulating hormone (FSH)
  - Prolactin
  - Progesterone
  - 17-beta-estradiol
- Change in the following serum thyroid hormone levels from Baseline to the end of the Maintenance Period
  - thyroid stimulating hormone (TSH)
  - thyroxine (T_4)
  - triiodothyronine (T_3)
- Change in the following serum lipid levels from Baseline to the end of the Maintenance Period
  - High density lipoprotein (HDL) cholesterol
  - Triglycerides
  - Non-HDL cholesterol fraction
  - Low density lipoprotein (LDL) cholesterol
  - Lipoprotein(a) (Lp[a])
- Change in serum C-reactive protein (CRP) levels from Baseline to the end of the Maintenance Period
- Incidence of overall adverse events (AEs) as reported spontaneously by the subject or observed by the investigator
- Overall serious adverse events (SAEs)
- AEs leading to study discontinuation
- Changes in hematology, clinical chemistry, and urinalysis parameters
- Changes in vital signs (including body weight)
- Physical and neurological examination findings

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- Changes in 12-lead electrocardiograms (ECGs)

Statistical methods: The primary safety variable was the change from Baseline to the end of the Maintenance Period (Termination Visit) in serum SHBG concentration. Due to premature termination of enrollment prior to achieving the planned sample size (a total of 28 subjects), this primary safety variable was assessed for descriptive purposes only. A matched-pair t-test was conducted and the corresponding 2-sided 95% confidence interval, and the p-value from the matched paired-t test were presented for the subjects in the Safety Set (SS) who completed the Maintenance Period.

For the primary safety analyses, careful attention was given to the distributional properties of the primary safety variable being evaluated in order to ensure that conditions necessary for the matched paired t-test technique were satisfied. If the normality condition was met, the mean change in SHBG levels, the corresponding 2-sided 95% confidence interval, and the p-value from the matched paired-t test were to be presented. If the normality condition was violated, it may have become necessary to use nonparametric methods. The Wilcoxon sign rank test was to be used as the nonparametric approach to assess the primary safety variable (endpoint) if the normality assumption was violated. If the Wilcoxon sign rank test was necessary, results from both the matched paired-t test and the Wilcoxon sign rank test were presented descriptively for the SS.

Summary and conclusions:

Subject disposition: A total of 13 subjects were screened and enrolled. A total of 2 subjects (15.4%) were reported as screen failures. The primary reasons for screen failure were lost to follow-up and consent withdrawn (1 subject each [7.7%]). A total 11 subjects received at least 1 dose of LCM, of which 10 subjects (90.9%) completed the study (ie, completed both the Titration and Maintenance Periods). None of the subjects who completed the study entered the Taper Period as they continued receiving LCM.

Safety results:

This study evaluated the change in hormonal (sexual and thyroid function) parameters and lipid parameters in serum after CBZ switching to LCM treatment as adjunctive therapy to a stable dose of LEV. For the primary safety analysis:

- The median SHBG concentration decreased during the study from Baseline levels at the upper end of the normal range (61.65nmol/L). By the end of the Maintenance Period at the Termination Visit, a decrease in the change from Baseline for the median was observed (-12.80nmol/L) and the median remained within the normal range

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(47.45nmol/L). The same direction of change from Baseline was observed for the mean. Both the matched-paired t-test and the Wilcoxon sign rank test demonstrated a decrease in SHBG from Baseline to the Termination Visit with p-values <0.05. For the matched-paired t-test, the p-value was 0.015 (95% confidence interval [CI]: -15.99, -2.19) and for the Wilcoxon sign rank test, it was 0.027.

For the secondary safety analyses:

The changes in hormone concentrations in the secondary safety analyses reflect the results observed in the primary safety analysis.

- The median of free androgen index increased during the study. At Baseline, the median was 25.433. By the end of the Maintenance Period at the Termination Visit, an increase from Baseline for the median was observed (9.493) and the median was 36.377. Both the matched-paired t-test and the Wilcoxon sign rank test demonstrated an increase in free androgen from Baseline to the Termination Visit with p-values <0.05. For the matched-paired t-test, the p-value was 0.001 (95% CI: 6.218, 18.286) and for the Wilcoxon sign rank test, it was 0.002.
- The median fT_4 concentration increased during the study from Baseline levels, which were at the lower end of the normal range (13.00pmol/L). By the end of the Maintenance Period at the Termination Visit, an increase from Baseline for the median was observed (2.70pmol/L) and the median remained within the normal range (14.85pmol/L). Both the matched-paired t-test and the Wilcoxon sign rank test demonstrated an increase in fT_4 from Baseline to the Termination Visit with p-values <0.05. For the matched-paired t-test, the p-value was <0.001 (95% CI: 2.19, 4.03) and for the Wilcoxon sign rank test, it was 0.002.
- The median total cholesterol concentration decreased during the study from Baseline levels, which were above the normal range (5.495mmol/L). By the end of the Maintenance Period at the Termination Visit, the median total cholesterol concentration decreased to within the normal range, with a change from Baseline for the median of -0.540mmol/L and the median returned within the normal range (4.870mmol/L). Both the matched-paired t-test and the Wilcoxon sign rank test demonstrated a decrease in total cholesterol from Baseline to the Termination Visit with p-values <0.05. For the matched-paired t-test, the p-value was 0.009 (95% CI: -0.852, -0.160) and for the Wilcoxon sign rank test, it was 0.012. Furthermore, 2 subjects in this study did not fast prior to providing their Baseline blood samples at Visit 2. Therefore, additional analyses were performed for serum lipid parameters in case of the distortion of results.

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In general, the results were similar in the analyses conducted with the full Safety Set.

For other safety analyses:

There were median increases from Baseline in the following sexual hormones by the end of the Maintenance Period at the Termination Visit: testosterone, DHEAS, FSH, progesterone, and 17-beta-estradiol. Prolactin and LH concentrations decreased from Baseline to the Termination Visit. An opposite direction of change from Baseline was observed for the mean for LH.

Of the serum thyroid hormone levels, TSH decreased from Baseline, and T_4 and T_3 increased from Baseline by the end of the Maintenance Period at the Termination Visit.

The median serum lipid levels (triglycerides, non-HDL cholesterol, and LDL cholesterol) generally decreased from Baseline by the end of the Maintenance Period at the Termination Visit. The median Lp(a) increased from Baseline by the end of the Maintenance Period.

The median CRP levels decreased during the study. By the end of the Maintenance Period at the Termination Visit, a decrease from Baseline for the median was observed (-0.35mg/L). Although at the Termination Visit, the mean CRP was 7.55mg/L (±13.42), which was above the normal range (0 to 5mg/L), this was as a result of a single subject recording a CRP concentration of 43.9mg/L.

Overall, a total of 10 treatment-emergent adverse events (TEAEs) with onset during the Treatment Period were reported in 5 subjects (45.5%). The system organ classes (SOCs) with the highest incidence of events were nervous system disorders (5 events in 4 subjects [36.4%]) and infections and infestations (2 events in 2 subjects [18.2%]). There were no apparent trends with respect to the incidence of TEAEs with onset during the Treatment Period by LCM dose.

The majority of TEAEs with onset during the Treatment Period were of mild severity (7 events in 2 subjects). No severe TEAEs were reported. A total of 7 TEAEs with onset during the Treatment Period were considered to be related to study medication and were reported in 3 subjects (27.3%) and these 3 subjects (27.3%) had a total of 4 related TEAEs in the SOC of nervous system disorders. In all other SOCs or preferred terms, related TEAEs were reported in 1 subject.

No deaths or SAEs were reported in this study. One subject (9.1%) had a TEAE of partial seizures that led to the subject's discontinuation from the study. The TEAE was considered not to be related to the study medication.

No other significant TEAEs were reported in this study and no suicidal ideation or behavior was identified using the Columbia-Suicide Severity Rating Scale.

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There were no clinically meaningful hematology changes from Baseline or treatment-emergent markedly abnormal hematology or clinical chemistry laboratory data with the exception of treatment-emergent markedly abnormal laboratory data that were reported for total cholesterol, LDL cholesterol, and triglycerides (1 subject each).

There were no clinically meaningful changes from Baseline in mean vital signs values or abnormal treatment-emergent vital signs, except in 1 subject who had an abnormal treatment-emergent bradycardia at the Termination Visit and the Last Visit, as defined by a pulse rate of ≤50 bpm and a decrease from Baseline of ≥15 bpm. There were no clinically meaningful changes from Baseline in body weight, ECG, or other physical examinations.

Shifts from normal Baseline results to abnormal results at the end of the Treatment Period were observed in 2 parameters for 1 subject (motor system/general/muscle bulk/mass and motor system/muscle strength/trunk); however, this subject did not experience any TEAEs at the time of these abnormal neurological findings. All neurological examination results in the other subjects were normal.

Conclusions:

After switching from an enzyme inducing AED (CBZ) to a nonenzyme inducing AED (LCM) as an adjunctive therapy to LEV, significant changes in SHBG, free androgen index, lipid parameters, and thyroid function hormones were observed in male subjects with partial-onset seizures. Furthermore, LCM was generally well tolerated and there were no new safety findings observed in this study. Efficacy seemed to be maintained after replacing CBZ with LCM. Although favorable results were observed for this study, additional data are needed to confirm these results on the long-term basis and translate into clinical outcomes such as sexual function improvement and cardiovascular morbidity and mortality.

Report date: 06 Nov 2014