SP1007, 2010-019268-35

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.

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Sponsor:

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Official study title:

A Multicenter, Open-Label Study to Evaluate the Tolerability, Safety and Efficacy of Lacosamide (200mg - 400mg/day) as Add-On Therapy for Patients with Partial Onset Epilepsy Using a Flexible Dose-Escalation Schedule and Individualized Maintenance Doses

CLINICAL STUDY REPORT SYNOPSIS: SP1007

Name of company: UCB Pharma SA	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: VIMPAT®	**Volume:** Not applicable	
Name of active ingredient: Lacosamide	**Page:** Not applicable	

Title of study: A Multicenter, Open-Label Study to Evaluate the Tolerability, Safety and Efficacy of Lacosamide (200mg - 400mg/day) as Add-On Therapy for Patients with Partial Onset Epilepsy Using a Flexible Dose-Escalation Schedule and Individualized Maintenance Doses

Principal/coordinating investigator: Prof [redacted], MD, [redacted]

Study centers: This was a multicenter study. Thirty study centers in [redacted] participated in the study (ie, enrolled subjects in the study).

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

Studied period: Approximately 18 months **First subject enrolled:** 29 Jun 2010 **Last subject completed:** 19 Dec 2011	**Phase of development:** Phase 4

Objective: The objective of this study was to evaluate if a flexible dose escalation of VIMPAT, up to the maximum approved dose of 400mg/day, improved VIMPAT tolerability and effectiveness.

The 100mg dose-modification steps could occur over a period of a minimum of 1 week to a maximum of 3 weeks in this study, instead of the 1 week allowed in the pivotal studies and recommended in the Summary of Product Characteristics.

Methodology: This was a Phase 4, multicenter, open-label, study to evaluate the tolerability, safety, and efficacy of VIMPAT (200mg/day to 400mg/day) as adjunctive therapy for subjects with partial-onset seizures using a flexible dose-escalation schedule and individualized maintenance doses.

This was a 24-week study comprising a 12-week Titration Phase and a 12-week Maintenance Phase.

During the Titration Phase, subjects received VIMPAT 100mg/day (50mg bid) for a minimum of 1 week and a maximum of 3 weeks (duration decided by the investigator together with the subject) after which the dose was increased to 200mg/day (100mg bid), the lowest recommended therapeutic dose. After assessment of safety and tolerability at the Titration Phase visits, the dose could be further increased by 100mg/day to 300mg/day and

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later to a maximum possible dose of 400mg/day.

Subjects known to be very sensitive to starting new antiepileptic drugs (AEDs) could take transient intermediate doses such as 50mg/day, 150mg/day, 250mg/day, or 350mg/day at the beginning of each dose escalation step. These intermediate doses were transient and not to be taken for longer than 1 week each.

At the end of the Titration Phase, subjects should have reached their clinically effective dose, which they were to remain on throughout the subsequent Maintenance Phase. The clinically effective dose was defined as the dose that provided the best seizure control for the subject without intolerable adverse events (AEs). The lowest dose permitted for entry into the Maintenance Phase was 200mg/day. Subjects entering the Maintenance Phase received the dose to which they had been titrated (VIMPAT 200mg/day, 300mg/day, or 400mg/day) for a further 12 weeks. The subject's dose was only permitted to change once during the Maintenance Phase. The change could be either an increase or a decrease by 100mg/day but had to remain within the 200mg/day to 400mg/day dose range. If the subject has already had his or her dose decreased, no further modifications of VIMPAT dosage were permitted.

Subjects who discontinued from the study early had their VIMPAT dose gradually reduced, as instructed by the investigator, with a recommended taper rate of 200mg/week (Taper Phase). The Taper Phase began the day after Visit 4/Early Discontinuation Visit for those subjects not continuing on VIMPAT and ended on the date of the Follow-Up Safety Visit.

If the subject continued to tolerate and to benefit from VIMPAT, the subject could be issued, at the discretion of the investigator, an investigator prescription to receive commercially available VIMPAT.

A subject who was not tolerating or benefiting from the treatment was, at the investigator's discretion, to discontinue treatment and receive further study-issued VIMPAT sufficient to taper VIMPAT treatment gradually as instructed by the investigator, with a recommended taper rate of 200mg/week (Taper Phase).

Number of subjects (planned and analyzed): It was planned that a total of 200 subjects would be enrolled in the study. The recruitment rate was slower than expected even after extending enrollment timelines for 5 months, which resulted in fewer subjects than planned being enrolled in the study. As no formal sample size calculation was performed, this was not considered to be a substantial change to the study. A total of 100 subjects were enrolled in the study. All 100 subjects (100%) were included in the Enrolled Set (ES; all subjects who signed the informed consent) and Safety Set (SS; all subjects in the ES who took at

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least 1 dose of VIMPAT). Of these, 93 subjects (93.0%) were included in the Full Analysis Set (FAS; all subjects in the SS who had a Baseline and at least 1 post-Baseline seizure assessment) and 74 subjects (74.0%) were included in the Completer Analysis Set (all subjects in the SS who had a Baseline and a post-Baseline seizure assessment during the Maintenance Phase and completed the study as stated on the End-of-Study electronic case report form [eCRF] page).

Diagnosis and main criteria for inclusion: Male or female subjects aged at least 18 years old who had epilepsy and were experiencing partial-onset epilepsy, whether or not secondarily generalized, classifiable according to the International Classification of Epileptic Seizures confirmed by appropriate diagnosis. Subjects were to have between 1 and 14 partial-onset seizures per month over a 3-month historical baseline seizure count and be treated with 1 or 3 concomitant marketed AEDs at study entry. Concomitant AEDs were to be taken at a stable dose regimen for at least 4 weeks before the entry visit. Subjects who met the following criteria were not eligible to enrol in the study: history of generalized epilepsy, partial-onset seizures that were not clearly identifiable (eg, seizures limited to psychic auras or subtle vegetative changes), history of status epilepticus within the 12-month period prior to inclusion in the study, and subjects with seizures that were uncountable due to clustering during the 12-week period prior to inclusion.

Test product, dose, and mode of administration, batch number: Commercial VIMPAT® film-coated tablets containing 50mg of lacosamide (batch number: [redacted]). VIMPAT was taken orally twice a day, once in the morning and once in the evening, at approximately the same time each day up to a possible maximum dose of 400mg/day (200mg bid).

Duration of treatment: The planned study duration for each subject was 24 weeks (+4 weeks). Eligible subjects entered a 12-week Titration Phase, during which their VIMPAT dose was periodically monitored and modified appropriately. After the Titration Phase, subjects started a 12-week Maintenance Phase, taking the VIMPAT dose to which they were titrated.

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

Criteria for evaluation:

Safety: Safety was assessed by AE monitoring, and physical and neurological examination results.

Efficacy: Daily record card data were used to assess the secondary efficacy variables of

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responder rate, percentage of seizure-free subjects, and the percent change in partial-onset seizure frequency per 28 days from historical Baseline to the end of the 12-week Maintenance Phase. The assessment of the efficacy variable of retention rate was evaluated using the last VIMPAT date on the End-of-Study eCRF page compared with the Visit 4 date.

Statistical methods: There were 2 primary safety variables, which included:

- Treatment-emergent AEs (TEAEs) reported spontaneously by the subject or observed by the investigator
- Subject withdrawal due to TEAEs

The following additional safety variables were evaluated:

- Serious AEs (SAEs) reported spontaneously by the subject or observed by the investigator
- Characteristics of dizziness
- Changes in physical and neurological examination findings

Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 14.1, and summarized by primary system organ class and preferred term. Safety data were summarized for the SS.

There were no primary efficacy variables for this study. All efficacy variables were secondary and were evaluated descriptively. There were 4 secondary efficacy variables:

- Percent change in partial-onset seizure frequency per 28 days from historical Baseline to the end of the 12-week Maintenance Phase.
- 50% response, where a responder was a subject experiencing a ≥50% reduction in partial-onset seizure frequency per 28 days from historical Baseline to the end of the 12-week Maintenance Phase.
- Subjects who achieved seizure-free status (yes/no) at the end of the 12-week Maintenance Phase.
- Retention rate, defined as the number of subjects continuing on VIMPAT up to and including Visit 4 (Week 24) expressed as a percentage relative to the number of subjects who were dosed

The number and percentage of subjects with ≥50% response at the end of the 12-week

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Maintenance Phase were summarized for all subjects in the FAS. Additionally, the number and percentage of subjects with ≥50% response were summarized by stable concomitant use of at least 1 traditional sodium channel-blocking AEDs (no or yes). Summary statistics for the partial-onset seizure frequency per 28 days at Baseline, at the end of the 12-week Maintenance Phase, and the percentage change from Baseline to the end of the Maintenance Phase are presented for the FAS.

The number and percentage of subjects achieving a seizure-free status during the Maintenance Phase are presented for subjects in the Completer Analysis Set.

The number and percentage of subjects maintained in the study and taking VIMPAT up to and including Visit 4 (ie, retention rate) are presented for the SS. The retention rate was also summarized by stable concomitant use of at least 1 traditional sodium channel-blocking AEDs (no or yes).

The VIMPAT exposure variables evaluated included:

- Duration of exposure during the Maintenance Phase and the Treatment Phase (defined as the period of time from the first dose of VIMPAT to the date of the final dose of VIMPAT)
- Mean daily dose, during the Titration Phase, the Maintenance Phase, and the Treatment Phase
- Dose at the start of the Maintenance Phase
- Minimum daily dose during the Maintenance Phase
- Maximum daily dose during the Maintenance Phase and the Treatment Phase
- Modal daily dose during the Maintenance Phase and the Treatment Phase
- Dose change (increase or decrease) during the Maintenance Phase
- Duration of titration to the start of the dose that was continued into the Maintenance Phase

The change in concomitant AEDs during the Titration and Maintenance Phases were described by the following 4 variables:

- The number of increases in the total daily dose of any concomitant AEDs
- The number of decreases in the total daily dose of any concomitant AEDs

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- The number of new concomitant AEDs
- The number of withdrawn concomitant AEDs

Summary and conclusions

Subject disposition: Of the 100 subjects who enrolled in the study and entered the Titration Phase, 75 subjects (75.0%) completed the Titration Phase and entered the Maintenance Phase. Overall, 74 subjects (74.0%) completed the study and 26 subjects (26.0%) discontinued the study. Of the 26 subjects who discontinued the study, 25 subjects discontinued during the Titration Phase and 1 subject discontinued during the Maintenance Phase.

Safety results: A total of 64 subjects (64.0%) experienced at least 1 TEAE. Treatment-emergent AEs were most frequently reported in the nervous system disorders system organ class (53 subjects [53.0%]). The 3 most frequently reported TEAEs were dizziness (42 subjects [42.0%]), headache (8 subjects [8.0%]), and asthenia (5 subjects [5.0%]). The majority of subjects reported TEAEs that were mild or moderate in severity. The incidence of TEAEs was higher in the Titration Phase (55 of 100 subjects [55.0%]) compared with the Maintenance (14 of 75 subjects [18.7%]) and Taper (2 of 98 subjects [2.0%]) Phases.

A total of 127 TEAEs reported for 61 subjects (61.0%) were considered related by the investigator. The most frequently reported TEAEs considered related by the investigator were dizziness (40 subjects [40.0%]), headache (6 subjects [6.0%]), and asthenia (5 subjects [5.0%]).

Episodes of dizziness were reported for 42 subjects (42.0%) with 37 subjects (37.0%) experiencing at least 1 dizziness episode with an occurrence of intermittent or an intensity pattern of fluctuating. Episodes were mainly intermittent only (32 subjects [32.0%]), fluctuating in intensity (32 subjects [32.0%]), and onset/reinforcement was within 4 hours after VIMPAT intake (30 subjects [81.1%]).

The mean (SD) duration of VIMPAT treatment at the time of the first onset of dizziness was 46.3 (43.09) days. The most frequently taken concomitant medications (including AEDs) for subjects with any TEAE of dizziness were lamotrigine (13 subjects [31.0%]), and levetiracetam and oxcarbazepine (11 subjects [26.2%] each). Subjects could have been taking more than 1 AED.

No subjects died during the study. Overall, 3 subjects (3.0%) experienced 7 SAEs (including 1 SAE of dizziness). No individual SAE was reported for more than 1 subject.

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Overall, 14 subjects (14.0%) experienced 21 TEAEs leading to treatment discontinuation. The most frequently reported TEAEs leading to treatment discontinuation were dizziness (6 subjects [6.0%]), and vomiting and tremor (2 subjects [2.0%] each).

Overall, 14 subjects (14.0%) experienced 23 TEAEs leading to a dose reduction. Thirteen subjects had a dose reduction in the Titration Phase and 1 subject had a dose reduction in the Taper Phase. The most frequently reported TEAEs leading to a dose reduction were dizziness (9 subjects [9.0%]) and gait disturbance (3 subjects [3.0%]).

No other significant TEAEs were reported.

For TEAEs of relevance to the partial-onset seizure population, the most frequently reported seizure-related TEAEs were convulsion and complex partial seizures (3 subjects [3.0%] each). A TEAE of simple partial seizure was reported for 1 subject (1.0%). Status epilepticus was reported as an SAE for 1 subject (1.0%). No subjects discontinued treatment due to TEAEs of complex partial seizure, simple partial seizure, or status epilepticus. No TEAEs of grand mal convulsion, epilepsy, aura, epileptic aura, or myoclonus were reported.

Memory impairment was reported as a TEAE for 1 subject (1.0%) and resulted in treatment discontinuation. No TEAEs of amnesia or TEAEs related to psychotic disorders were reported.

The TEAE of weight increased was reported in 3 subjects (3.0%).

Assessment of results from physical and neurological examinations did not reveal any clinically relevant findings.

Efficacy results: The median percentage reduction in the partial-onset seizure frequency per 28 days from Baseline to the end of the Maintenance Phase was 69.66%.

At the end of the Maintenance Phase, 52 of 75 subjects (69.3%) had a ≥50% response (defined as subjects who experienced a ≥50% reduction in partial-onset seizure frequency per 28 days from historical Baseline to the end of the 12-week Maintenance Phase). A higher proportion of subjects who used at least 1 traditional sodium channel-blocking AEDs had a ≥50% response (42 of 58 subjects [72.4%]) compared with subjects who did not use traditional sodium channel-blocking AEDs (10 of 17 subjects [58.8%]).

In total, 21 of the 74 subjects (28.4%) who completed the Maintenance Phase achieved a seizure-free status during the Maintenance Phase (defined as subjects who completed the study and reported no seizures of any type during the Maintenance Phase).

Overall, 73 subjects (73.0%) in the SS were maintained in the study and took VIMPAT up to and including Visit 4 (Week 24) (ie, the retention rate). There was 1 additional subject

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who was retained in the study through Visit 4 but started commercial VIMPAT treatment outside of the clinical study before Visit 4. This subject is not included in the retention rate analysis but was considered to have completed the study.

In the SS, the retention rate was higher for subjects who were using traditional sodium channel-blocking AEDs (80.0% [56 of 70 subjects]) compared with subjects who were not using traditional sodium channel-blocking AEDs (56.7% [17 of 30 subjects]).

Conclusions: Tolerability and safety data in this open-label study suggest that flexible dose escalation of VIMPAT resulted in overall VIMPAT tolerability that was generally consistent with that observed in other studies with VIMPAT using the forced-titration dosing schedule and may improve tolerability in patients taking traditional sodium channel-blocking AEDs. Treatment with VIMPAT in this open-label flexible dose escalation study demonstrated a seizure reduction during the 12-week Maintenance Phase; however, interpretation of the comparisons between SP1007 and the double-blind, placebo-controlled studies that used forced titration is limited due to differences in study design, study duration, and the subject population.

Report date: 26 Oct 2012