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Assessment of the effects of lacosamide on sleep parameters in healthy subjects

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ABSTRACT

Purpose: Seizures and antiepileptic drugs (AED) may disrupt sleep patterns in patients with epilepsy, thus evaluation of lacosamide effects on objective and subjective sleep measures is warranted.
Methods: A multicenter, interventional, open-label study (NCT01530386) was conducted in healthy subjects without confounding effects of concomitant AED use, co-morbidities, or disease state to determine whether lacosamide impacts sleep parameters after 22 days of lacosamide exposure. After overnight polysomnography (PSG) to assess baseline parameters, lacosamide was initiated at 100 mg/day (50 mg twice daily) and increased by 100 mg/day weekly to 300 mg/day (the mid-range maintenance dose for adjunctive therapy). The primary variable was change from baseline to post-treatment in wake after sleep onset (WASO). Secondary variables included additional objective sleep measures, subject-reported measures of sleep quality, daytime sleepiness, and tolerability. Change from baseline in WASO was analyzed using the Wilcoxon rank-sum test.
Results: A total of 27 subjects received ≥1 dose of lacosamide and 25 subjects completed the study. For WASO, median change from baseline was a 6-min reduction (95% confidence interval: −38, 77.5; $p = 0.1074$) after lacosamide treatment; this was considered not clinically relevant. No clinically relevant changes were observed in any secondary variables. Thirteen subjects (48%) reported a treatment-emergent adverse event, none of which was severe or led to study discontinuation.
Conclusion: Lacosamide 300 mg/day had no effect on objective or subjective sleep parameters in healthy subjects and was generally well tolerated.

1. Introduction

A complex relationship exists between epilepsy and sleep. Seizure activity is often associated with specific phases of the sleep/wake cycle, and sleep deprivation can precipitate seizure activity.[1,2] Inadequate or fragmented sleep, excessive daytime sleepiness, and decreased quality of life are often reported by patients with epilepsy and may be due to the presence or occurrence of seizures. Many antiepileptic drugs (AED) influence sleep parameters [2–9] and sleep architecture.[10] Negative effects on sleep associated with some AEDs include an increased percentage of light sleep, and reduced rapid eye movement (REM) and/or slow wave sleep (Stage 3).[7,11–13] AEDs may also cause daytime somnolence, fatigue, or drug-induced insomnia.[2,7,11–14] Since sleep disturbances significantly impair quality of life in patients with epilepsy,[15,16] formal assessment of the effects of AEDs on sleep parameters in individuals with and without epilepsy helps to identify any drug-induced impact on sleep and distinguish drug effects from a variety of medication and disease-related confounding factors. In addition, a better understanding of the effects of AEDs on sleep parameters may provide clinicians further information necessary for optimal AED selection.[1] Hence, a formal evaluation of the effects of lacosamide on sleep parameters was conducted in this study with healthy individuals.

Lacosamide is approved for monotherapy and adjunctive therapy of partial-onset seizures in patients 17 years of age and

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older in the US and as adjunctive therapy in adult and adolescent (16–18 years of age) patients in the European Union.[17,18] The recommended maintenance dose is 200–400 mg/day for adjunctive therapy and the World Health Organization daily defined dose is 300 mg/day.[19] Lacosamide acts via a novel mechanism of action, through selective enhancement of slow inactivation of voltage-gated sodium channels.[20,21] Efficacy and tolerability of lacosamide as adjunctive AED treatment was demonstrated in 3 pivotal Phase 2b/3 studies.[22–24] The most frequently reported treatment-emergent adverse events in these studies were associated with the central nervous system (dizziness and headache) and gastrointestinal tract (nausea), while fatigue and somnolence were reported at lower rates across doses of 200–600 mg/day.[22–24] To date, effects of lacosamide on sleep have not been formally assessed via objective assessment such as polysomnography (PSG); therefore, this study sought to evaluate whether lacosamide has any impact on objective and subject-rated measures of sleep.

Evaluating the effects of AEDs on sleep in healthy subjects has the benefit of distinguishing drug effects on sleep with fewer confounding variables. These individuals, unlike patients with epilepsy, do not take concomitant AEDs, experience seizures, or have co-morbidities that could affect sleep parameters. This evaluation was conducted in healthy subjects utilizing overnight PSG (7–8 h). The primary objective was to evaluate the effects of lacosamide 300 mg/day (the mid-range approved dose) on wake after sleep onset (WASO) in healthy subjects after 3 weeks of exposure. Secondary objectives included evaluating the effect of lacosamide on additional objective sleep measures, subject-reported measures of sleep quality, and tolerability.

2. Materials and methods

This was an open-label study conducted at 3 clinical sites in the US (ClinicalTrials.gov identifier: NCT01530386; SP1031). This study was conducted in accordance with the applicable regulatory and International Conference on Harmonisation Good Clinical Practice requirements and local laws. All subjects provided written informed consent prior to participation in the study.

2.1. Subjects

Healthy men and women aged 18–50 years with body weight (body mass index [BMI] $\geq$18 kg/m^2 and $\leq$28 kg/m^2) and good sleep hygiene with normal bedtime between 9:00 PM and 1:00 AM were eligible for inclusion. Subjects had no clinically relevant cardiovascular, renal, gastrointestinal, hepatic, metabolic, endocrine, neurological, or psychiatric abnormalities, and were in general good health.

Key exclusion criteria were history of or a PSG during screening revealing primary sleep disorders such as sleep apnea syndrome (including moderate-to-severe obstructive sleep apnea or an apnea-hypopnea index [AHI] >8) or narcolepsy, have a known hypersensitivity to any component of lacosamide, or taking concomitant medications within 2 weeks prior to the first day of dosing (except non-steroidal anti-inflammatory drugs, oral contraceptives, and non-psychoactive supplements; short-term use of medications for symptomatic relief was permitted but not within 3 days prior to the PSG). In addition, subjects who were smokers, had a history of alcohol or drug abuse or test positive on alcohol breath test or urine drug screen, were pregnant or nursing, or consumed >400 mg of caffeine/day or 40 g alcohol/day; had clinically relevant hematology or clinical chemistry parameters, physical examination or vital signs, or cardiac condition; or had a lifetime history of suicide attempt or suicidal ideation in the past 6 months, or any medical or psychiatric condition that, in the opinion of the investigator, could have jeopardized or would have compromised the subject's ability to participate in this study were excluded.

2.2. Study design

The study consisted of a screening period of up to 21 days, a 22-day treatment period, and a taper/safety follow-up. Screening was conducted over 3 visits: at Visit 1 (Day −21 [21 days before first administration of treatment]), subjects were evaluated for eligibility for enrollment into the study; Visit 2 (Day −2) consisted of the initial pre-treatment overnight PSG for an adaptation night of recording; and Visit 3 (Day −1) was the second pre-treatment overnight PSG followed by additional subjective sleep assessments the morning after as baseline sleep measurements.

Subjects began lacosamide treatment (Day 0) after completing the second pre-treatment overnight PSG during Visit 3. Lacosamide was provided as 50 mg and 100 mg tablets using the commercial formulation (UCB Pharma, Smyrna, GA). Tablets were taken in equally divided doses approximately 12 h apart, with the evening dose 2–3 h before bedtime. The initial dose was lacosamide 100 mg/day (lacosamide 50 mg twice daily) for 7 days, increased weekly by 100 mg/day to a target dose of lacosamide 300 mg/day [150 mg twice daily]). Dose reductions were not allowed; subjects who could not tolerate the lacosamide 300 mg/day dose were withdrawn.

After subjects had maintained a dose of lacosamide 300 mg/day for a period of 7 continuous days, Visit 4 (Day 21) was conducted, which included the first of the post-treatment overnight stays with PSG. On Visit 5 (Day 22), the second post-treatment overnight was conducted and subjects began a 2-day taper during which time they were to decrease the dose of lacosamide by 100 mg/day. Subjects returned for a safety follow-up at Visit 6 (Day 30).

2.3. Assessments

Overnight in-laboratory PSG recordings were conducted using standard methods for 7–8 h. Scoring of PSG tracings were performed in strict accordance with the criteria of the American Academy of Sleep Medicine Manual for Scoring Sleep by a central reader.[25,26] The international 10–20 electrode placement system was used for recording an electroencephalogram (ECG; F3, F4, C3, C4, O1, O2, M1, M2), electro-oculography (E1, E2), chin electromyogram, leg electromyogram, ECG, respiratory effort (chest and abdomen), pulse oximetry, and airflow (nasal pressure transducer and thermistor). Sleep staging, respiratory events (e.g., apneic events, hypopneic events), periodic limb movements, and arousals were scored at 30-s epochs on a high-resolution monitor. Hypopneas were scored according to rule VII.4.B (3%).[25]

Readings from the second night of the PSG were used for analysis. PSG recordings for the second overnight PSG assessment were initially scored by a certified scorer at the investigative site, so as to immediately determine the subject's eligibility to enroll in the treatment period of the study before they were sent to the central reader. Data from each first overnight assessment was considered as an adaptation to the sleep laboratory; therefore, sites were not required to score or send these files to the central reader for review unless the second overnight assessment was inadequate or not valid for evaluation.

The primary pharmacodynamic variable was change in WASO from baseline to the end of treatment as measured by PSG. WASO is a measure of sleep disruption and fragmentation, which may be associated with effect of seizures and medications in patients with epilepsy.[5,10] WASO was defined as the total time that was scored as awake in a PSG occurring between sleep onset and final wake up. Secondary PSG assessments were total sleep time (TST), sleep efficiency, percentage of sleep spent in each sleep stage (1, 2, 3, and