Original article

Epileptic Disord 2017; 19 (2): 186-94

Adjunctive lacosamide for focal epilepsy: an open-label trial evaluating the impact of flexible titration and dosing on safety and seizure outcomes

Michel Baulac [1], Safia Coulbaut [2], Pamela Doty [3], Cindy McShea [3], Marc De Backer [4], Fabrice Bartolomei [5], Mihaela Vlaicu [6]

[1] IHU-ICM and Department of Neurology, Pitié-Salpêtrière Hospital, Paris
[2] UCB Pharma, Colombes, France
[3] UCB Pharma, Raleigh, USA
[4] UCB Pharma, Brussels, Belgium
[5] Neurophysiology Clinic, University Hospital La Timone (AP-HM), Marseille
[6] IHU-ICM and Department of Neurosurgery, Pitié-Salpêtrière Hospital, Paris, France

Received August 04, 2016; Accepted March 01, 2017

Epileptic Disorders

Introduction – Phase IV, prospective, open-label, interventional trial (NCT01235403)

- The efficacy and safety of adjunctive lacosamide for the treatment of patients with focal epilepsy have been demonstrated in three pivotal Phase II/III trials[1–3].
- The objective of this trial conducted in France was to evaluate the safety and effectiveness of lacosamide under conditions that approximate a real-life setting.
- Compared with the pivotal trials, the design of the current trial allowed for some flexibility:
  - 12-week dose titration phase, starting from 100 mg/day and in 100-mg/day increments.
  - Use of intermediate doses (50, 150, 250, or 350 mg/day) at the beginning of each dose escalation step (for 1 week only) for patients deemed by the investigators to be particularly sensitive to starting new AEDs.
  - Individualised maintenance doses up to the maximum approved dose of 400 mg/day.
  - Addition or withdrawal of concomitant AEDs during the maintenance phase.
- Patients invited to take part in the trial:
  - Were >18 years of age.
  - Had a diagnosis of focal seizures, with or without secondary generalization.
  - Were experiencing 1–14 seizures per 28 days over the 3-month historical baseline period.
  - Were taking 1–3 concomitant AEDs at a stable dose (including VNS).
- After stabilization on a clinically effective dose of lacosamide for 3 weeks, patients entered a 12-week maintenance phase.
- An assessment of the characteristics of dizziness – frequency, intensity, timing of onset or worsening of dizziness episodes and impact on activities of daily living – was included.

1. Ben-Menachem E, et al. Epilepsia 2007;48(7):1308–17.
2. Halász P, et al. Epilepsia 2009;50(3):443–53.
3. Chung S, et al. Epilepsia 2010;51(6):958–67.

AED=antiepileptic drug
VNS=vagus nerve stimulation

Results – patient population, and safety and seizure outcomes

- At 6 months, of 100 patients recruited to the trial, 74 had completed and 26 had discontinued prematurely.
- Most common reasons for discontinuation – TEAEs (14 patients), withdrawal of consent (4), lack of efficacy (2), loss to follow-up (2) and 'other' (4).
- Mean age (± SD) of patients was 44.5 years (±16.2).
- Most patients were taking ≥2 concomitant AEDs at baseline (64.0%) – most frequently lamotrigine, levetiracetam, and carbamazepine.
- Median modal dose* during treatment (titration and maintenance) was 200 mg/day and mean (±SD) duration of titration to maintenance dose was 57.9 days (±32.74).

Safety outcomes – safety set (N=100)

- 64.0% of patients experienced at least one TEAE – incidence was higher during titration than during maintenance phase (55.0% vs 18.5%).
- Most frequent TEAEs (≥5% of patients) were dizziness (42.0%), headache (8.0%), and asthenia (5.0%).
- High incidence of dizziness most likely due to nocebo effect, since patients were specifically asked about this TEAE[1,2] – in most cases, dizziness episodes were described as intermittent, fluctuating in intensity, with onset or worsening within 4 hours of dosing.
- 14 patients discontinued due to TEAEs – most frequently due to dizziness (6.0%), vomiting and tremor (2.0% each).

Seizure outcomes – full analysis set (N=75)**

- Median reduction in seizure frequency (seizures/28 days) from baseline to end of maintenance was 69.7%.
- ≥50% responder rate (patients with ≥50% reduction in seizure frequency from baseline to end of maintenance) was 69.3%.
- Among 74 patients who completed the 12-week maintenance phase, 21 (28.4%) were seizure-free during the maintenance phase.
- Greater response rates observed in the current trial compared with the pivotal trials are likely due to its open-label design and inclusion of patients with less treatment-refractory epilepsy.
- Retention rate at the end of the maintenance phase (study week 24) was 73.0%.

Epileptic Disorders

1. Faasse K, Petrie KJ. Postgrad Med J 2013;89:540–6.
2. Tan K, et al. BMJ 2014;349:g5019.

* Defined as the daily dose the patients received for the longest duration
** Patients with seizure frequency data for both baseline and maintenance phases

AED=antiepileptic drug
SD=standard deviation
TEAE= treatment-emergent adverse event

Observations and conclusions

- Given strict inclusion/exclusion criteria, forced titration schedules, and fixed doses, the extent to which results of regulatory/pivotal trials are applicable to the wider patient population is limited.
- Results from Phase IV trials or well conducted observational studies with a more flexible approach can help clinicians determine how AEDs can best be used in a wider population of patients with epilepsy and decide the most appropriate dosing schedules[1].
- In this Phase IV open-label trial, conducted to resemble a real-life setting, results showed that treatment with adjunctive lacosamide was associated with effective seizure control and favourable tolerability, as indicated by the 73.0% retention rate.
- These results are similar to those of several relatively large-scale, prospective, observational studies conducted in Spain, the UK, Germany, and Australia[2–5].
- Results of this trial can help physicians adjust the dose of lacosamide based on their patients' tolerability of, and response to lacosamide.
- Insights into the frequency, intensity, and timing of the onset of dizziness in relation to taking lacosamide can also help patients minimise the impact of this adverse event on their daily activities.

1. Mohanraj R, Brodie MJ. Seizure 2003;12:413–43.
2. Villanueva V, et al. Epilepsy Behav 2012;23:298–304.
3. Stephen LJ, et al. Epilepsy Res 2014;108:1385–91.
4. Runge U, et al. Epilepsia 2015;56:1921–30.
5. Kamel JT, et al. Acta Neurol Scand 2013;127:149–53.