Epilepsy & Behavior 52 (2015) 119–127

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

# Safety and tolerability of lacosamide as adjunctive therapy for adults with partial-onset seizures: Analysis of data pooled from three randomized, double-blind, placebo-controlled clinical trials

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ARTICLE INFO

*Article history:*
Received 2 June 2015
Revised 4 September 2015
Accepted 4 September 2015
Available online 27 September 2015

*Keywords:*
Lacosamide
Partial-onset seizures
Safety
Tolerability

ABSTRACT

*Objective:* The objective of this study was to describe *a priori* protocol-defined analyses to evaluate the safety and tolerability of adjunctive oral lacosamide (200–600 mg/day) in adults (ages 16–70 years) with partial-onset seizures (POS) using data pooled from three similarly designed randomized, double-blind, placebo-controlled trials (SP667, SP754 [NCT00136019], SP755 [NCT00220415]).
*Methods:* Patients with POS (≥2 years' duration, ≥2 previous antiepileptic drugs [AEDs]) uncontrolled by a stable dosing regimen of 1–3 concomitant AEDs were randomized to treatment with lacosamide at doses of 200 mg/day, 400 mg/day, or 600 mg/day, or placebo. Studies comprised a 4- to 6-week titration phase to target dose followed by a 12-week maintenance phase. Safety outcomes included treatment-emergent adverse events (TEAEs) of particular relevance to patients with POS, overall TEAEs, and discontinuations due to TEAEs. *Post hoc* analyses included evaluation of TEAEs potentially related to cognition and TEAEs leading to discontinuation analyzed by concomitant AEDs.
*Results:* One thousand three hundred eight patients were randomized to and received treatment; 944 to lacosamide and 364 to placebo. Most patients (84.4%) were taking 2 or 3 concomitant AEDs. The most common drug-associated TEAEs (reported by ≥5% of patients in any lacosamide dose group and with an incidence at least twice that reported for placebo during the treatment phase) were dizziness (30.6% for lacosamide *vs* 8.2% for placebo), nausea (11.4% *vs* 4.4%), and diplopia (10.5% *vs* 1.9%). Common drug-associated TEAEs generally appeared to be dose-related, and the incidence of each was lower during the 12-week maintenance phase than during the titration phase. Most TEAEs were either mild or moderate in intensity; severe TEAEs were predominantly observed with lacosamide 600 mg/day. No individual serious TEAE occurred in ≥1% of all lacosamide-treated patients. Treatment-emergent adverse events led to discontinuation in 8.1%, 17.2%, and 28.6% of the lacosamide 200-, 400-, and 600-mg/day groups, respectively (*vs* 4.9% of placebo). Few TEAEs were related to rash, weight loss/gain, changes in clinical chemistry parameters, or psychiatric disturbances, or were seizure-related. The odds of reporting any potential cognition-related TEAE *vs* placebo increased with dose and were similar between lacosamide doses of 200 and 400 mg/day and placebo (odds ratio 1.3, 95% confidence interval 0.7–2.4). Discontinuations due to TEAEs based on most commonly used AEDs taken in combination with lacosamide (all doses combined) were carbamazepine (15.3% [51/334] *vs* 3.9% [5/129] placebo), lamotrigine (19.2% [56/291] *vs* 4.3% [5/117]), and levetiracetam (10.1% [28/278] *vs* 3.9% [4/103]).
*Conclusions:* The safety and tolerability profile of adjunctive lacosamide in this detailed evaluation was similar to that observed in the individual double-blind trials. Adjunctive lacosamide was associated with TEAEs related to the nervous system and gastrointestinal tract, predominantly during titration.
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## 1. Introduction

The antiepileptic drug (AED) lacosamide is approved at dosages up to 400 mg/day as monotherapy or adjunctive therapy in adults (17 years or older) with partial-onset seizures (POS) in the United States [1] and as adjunctive therapy in adults (16 years or older) with POS in the European Union [2] and other countries. Lacosamide has simple pharmacokinetics for oral and intravenous administration [3–6].

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http://dx.doi.org/10.1016/j.yebeh.2015.09.006
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Orally administered lacosamide is rapidly and completely absorbed with steady-state plasma levels occurring after 3 days of twice-daily administration [3]. The pharmacokinetic parameters of lacosamide are dose-proportional (orally administered 100–800 mg/day) and show low intra- and intersubject variability [3]. Lacosamide is minimally bound to plasma proteins (<15%) [4,7] and is eliminated from the systemic circulation primarily by renal excretion [3]. Lacosamide has shown no clinically relevant drug–drug interactions with other AEDs [8–13], midazolam [2,14], warfarin [15], oral contraceptives [16], omeprazole [17], digoxin [18], and metformin [19].

The safety and efficacy of lacosamide as adjunctive therapy for adults with POS have been evaluated in detail, including in three phase II/III randomized, double-blind, placebo-controlled clinical trials and their respective long-term open-label extension trials [10–12,20,21]. Results from these pivotal double-blind trials demonstrated that adjunctive lacosamide significantly reduced the frequency of POS in patients with epilepsy and was associated with an acceptable safety profile [10–12]. However, the evaluation of drug safety is a continuous process and depends on input from various sources, including standard registration trials, long-term extension studies, observational studies, and safety monitoring efforts. Pooled data analyses from multiple clinical trials are another means to assess drug safety.

The three double-blind lacosamide trials had similar study designs and patient populations, thus, allowing a valuable opportunity for data pooling. The pooling of data from the three trials facilitates a more detailed evaluation of treatment effect than that from individual trials. Efficacy analyses on pooled data are published [22], confirming and extending the results of the individual trials. Notably, adjunctive lacosamide significantly reduced overall seizure frequency compared with placebo treatment, regardless of concomitant AEDs or patients' epilepsy surgical history [22]. An additional *post hoc* analysis suggested that adjunctive lacosamide treatment demonstrated seizure reduction compared with placebo regardless of the inclusion of "traditional" sodium channel blockers, which were included in the concomitant AED regimen of 82% of patients [23]. This *post hoc* analysis also showed that lacosamide was well tolerated by most patients taking either sodium channel-blocking AEDs or nonsodium channel-blocking AEDs and suggested that lacosamide may have potential for improved tolerability when added to an AED regimen that did not include traditional sodium channel blockers, especially at higher lacosamide doses [23].

Here, we present the results of *a priori* protocol-defined and *post hoc* safety analyses of data pooled from the three pivotal double-blind, placebo-controlled lacosamide trials. Though data have been reported elsewhere [22–24], the current analyses go beyond previous reports to provide a more detailed description of the safety profile of lacosamide, including additional safety information of particular interest, such as rash, psychiatric effects, seizure-related adverse events (AEs), weight change, and clinical laboratory changes. In addition, *post hoc* analyses investigated AEs potentially related to cognition and AEs leading to discontinuation analyzed by concomitant AEDs.

## 2. Methods

### 2.1. Trial design

Safety analyses were performed on data pooled from three similarly designed randomized, double-blind, placebo-controlled trials (SP667 [10], SP754 [NCT00136019] [11] and SP755 [NCT00220415] [12]) that evaluated the safety and efficacy of adjunctive lacosamide treatment in adults with uncontrolled POS. The SP667 trial was conducted in Europe and the United States, SP754 in the United States, and SP755 in Europe and Australia. Detailed methods are published elsewhere [10–12]. All studies were conducted in accordance with the Declaration of Helsinki. The trial protocol, amendments, and informed consent documentation were reviewed by national regulatory authorities in each country and relevant ethics committees or Institutional Review Boards for each site. Before trial participation, all patients gave written informed consent.

In each trial, patients were randomized to receive fixed dosages of lacosamide or placebo twice-daily in equally divided doses (Fig. 1). In all trials, a single 100 mg/day dose reduction was allowed at the end of the titration phase for patients experiencing intolerable AEs.

### 2.2. Patient eligibility

Patients aged 16–70 years (18–65 years in SP667) with a diagnosis of focal epilepsy and who had experienced POS (with or without secondary generalization) for 2 years or longer despite therapy with two or more AEDs (concurrently or sequentially) were recruited. To be eligible for randomization, patients were required to have an average

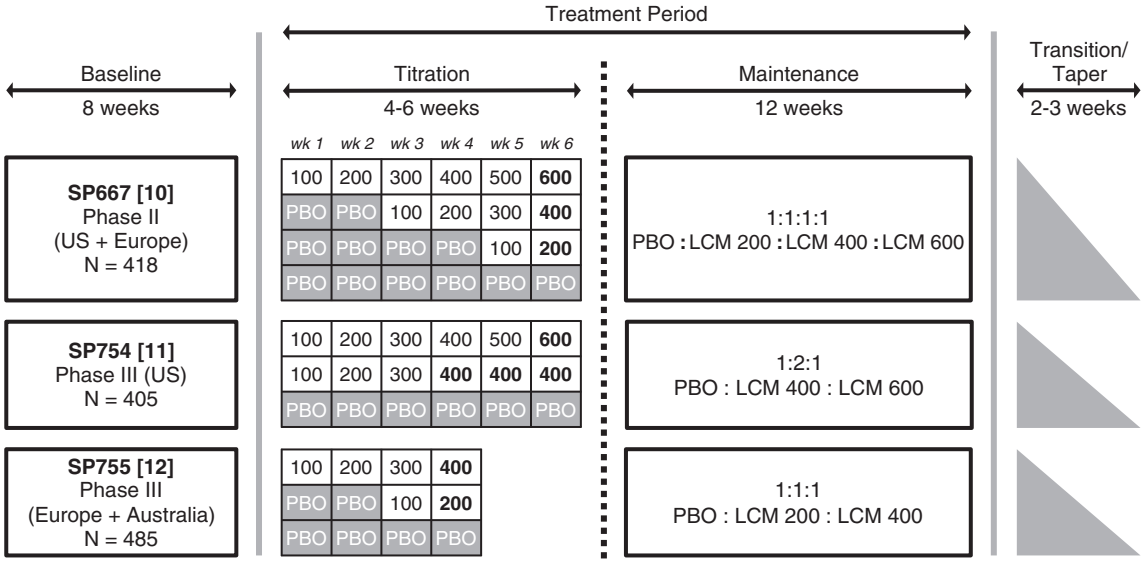


**Fig. 1.** Design of the double-blind, placebo-controlled clinical trials of lacosamide for the adjunctive treatment of adults with partial-onset seizures. One back-titration of 100 mg/day was allowed at the end of titration in cases of intolerable adverse events. PBO, placebo; LCM, lacosamide.
Modified from Chung S. et al. [22].

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