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Examining the Clinical Utility of Lacosamide

Pooled Analyses of Three Phase II/III Clinical Trials

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Abstract

Background: Lacosamide is an antiepileptic drug (AED) approved for the adjunctive treatment of partial-onset seizures in adults. Completed phase II/III clinical trials of lacosamide provide a valuable opportunity to evaluate clinically relevant aspects of the resulting large patient pool.

Objective: To provide insight into the clinical utility of lacosamide by performing *a priori*-defined and *post hoc* analyses on a large, pooled patient population.

Study Design: Pooled data from three randomized, double-blind, multicentre, placebo-controlled phase II/III trials.

Patients: Adult patients with partial-onset seizures with or without secondary generalization (N = 1294).

Intervention: Four- to six-week titration followed by 12-week maintenance treatment with lacosamide (Vimpat®) 200, 400 or 600 mg/day or placebo.

Main Outcome Measure: *A priori*-defined primary efficacy variables for the pooled analysis were change in seizure frequency per 28 days and the proportion of patients experiencing a ≥50% reduction in seizure frequency (50% responder rate) from Baseline to the Maintenance Phase; *a priori*-defined secondary efficacy variables were the proportion of patients achieving a ≥75% reduction in seizure frequency from Baseline to the Maintenance Phase (75% responder rate), the proportion of Maintenance Phase completers remaining seizure free throughout the entire Maintenance Phase and the percentage of seizure-free days during the Maintenance Phase for patients entering the Maintenance Phase. The pooled analyses of the change in seizure frequency, and 50% and 75% responder rates were performed with an intent-to-treat (ITT) approach, including all patients receiving at least one dose of trial

medication and having at least one post-baseline efficacy assessment. Similar analyses of the two primary efficacy variables and 75% responder rates were also performed using a modified ITT population (ITTm) that included ITT patients who entered the Maintenance Phase. Additional *post hoc* efficacy analyses were an evaluation of onset of efficacy and assessment of efficacy in patients grouped by prior surgical history and individual concomitant AED use. In addition, pharmacokinetic-pharmacodynamic modelling was performed, and safety data were assessed.

Results: In this pooled analysis of 1294 difficult-to-treat patients, all three dosages of lacosamide (200, 400 and 600 mg/day) showed a significant improvement compared with placebo for median percent seizure reduction (ITT and ITTm; $p < 0.05$ for 200 mg/day, $p < 0.001$ for 400 and 600 mg/day), as well as for 50% responder rate (ITT and ITTm; $p < 0.05$ for 200 mg/day, $p < 0.001$ for 400 and 600 mg/day). Evaluation of 75% responder rate in the phase II/III pooled population showed that a significantly higher proportion of patients randomized to lacosamide 400 or 600 mg/day achieved a ≥75% reduction in seizure frequency compared with placebo (ITT and ITTm; $p < 0.001$); statistical significance was not observed for lacosamide 200 mg/day (ITT and ITTm). A total of 2.7%, 3.3% and 4.8% of patients completing the Maintenance Phase in the lacosamide 200, 400 and 600 mg/day groups, respectively, experienced no seizures throughout the entire Maintenance Phase (placebo group = 0.9%). The mean change from baseline in the percentage of seizure-free days in patients entering the Maintenance Phase for the phase II/III pool was 8.0%, 11.6% and 14.7% with lacosamide 200 ($p = 0.077$), 400 ($p < 0.001$) and 600 ($p < 0.001$) mg/day groups, respectively, compared with 6.1% in the placebo group.

The onset of efficacy relative to placebo was evident by the first week of treatment with lacosamide. Efficacy was similar in lacosamide-treated patients reporting prior surgical intervention for epilepsy compared to lacosamide-treated patients with no prior surgical intervention. Lacosamide showed a reduction in seizures, regardless of the concomitant AEDs used. The preferred pharmacokinetic-pharmacodynamic model (E_{max}) supported the therapeutic dose range of lacosamide, and no additional safety concerns were identified in the phase II/III pooled analysis.

Conclusions: Results of these *a priori*-defined and *post hoc* pooled data analyses from phase II/III trials demonstrate that lacosamide effectively reduces seizures in patients at all three dosages evaluated with an early onset of efficacy, regardless of patient surgical history and concomitant AED regimen.

Introduction

Clinical trials are designed in accordance with existing regulatory guidelines. Once a drug has been evaluated in this process, the multiple, individual trials (which are often similarly designed) provide a valuable opportunity to evaluate clinically relevant aspects of the resulting large patient pool. With a sufficiently large and uniform patient population, it may be possible to reveal

aspects of the optimal clinical utility of a drug by examining outcome within distinct patient subsets or to find differences between groups of patients that are not detectable using smaller sample sizes in individual trials.[1]

Lacosamide is an antiepileptic drug (AED) approved for the adjunctive treatment of partial-onset seizures in adults.[2,3] It is believed to exert its therapeutic effects through a unique mechanism of action, selective enhancement of slow inactivation of sodium channels, and is proposed therefore to be mechanistically different from other AEDs acting on the sodium channel that primarily affect sodium channel fast inactivation.[4] The lacosamide clinical development programme included three previously reported phase II/III clinical trials (SP667, SP754 and SP755).[5-7] Each of these trials was designed with similar features (randomized, double-blind, multicentre, placebo-controlled with 12-week Maintenance Phases) and with similar patient criteria to create ideal conditions for compelling and potentially instructive pooled analyses. We present an analysis of *a priori* protocol-defined efficacy variables and a series of *post hoc* analyses using the phase II/III patient population.

Methods

Trial Design

The pooled analyses were derived from the three similarly designed randomized, double-blind, placebo-controlled trials (SP667, SP754 and SP755) evaluating adjunctive lacosamide (Vimpat®) in patients with partial-onset seizures with or without secondary generalization. Titration and dosing details are thoroughly reported in individual trial publications[5-7] and are summarized in figure 1.

Patients

Eligibility criteria were similar across trials and included adults who had a diagnosis of epilepsy with partial-onset seizures with or without secondary generalization. Patients were required to have had at least four partial-onset seizures per 28 days on average, with no seizure-free period longer than 21 days during the 8 weeks prior to baseline and during the 8-week Baseline Phase. Patients were to be taking a stable regimen of one to three (one to two in trial SP667) concomitant AEDs with or without vagus nerve stimulation (VNS)

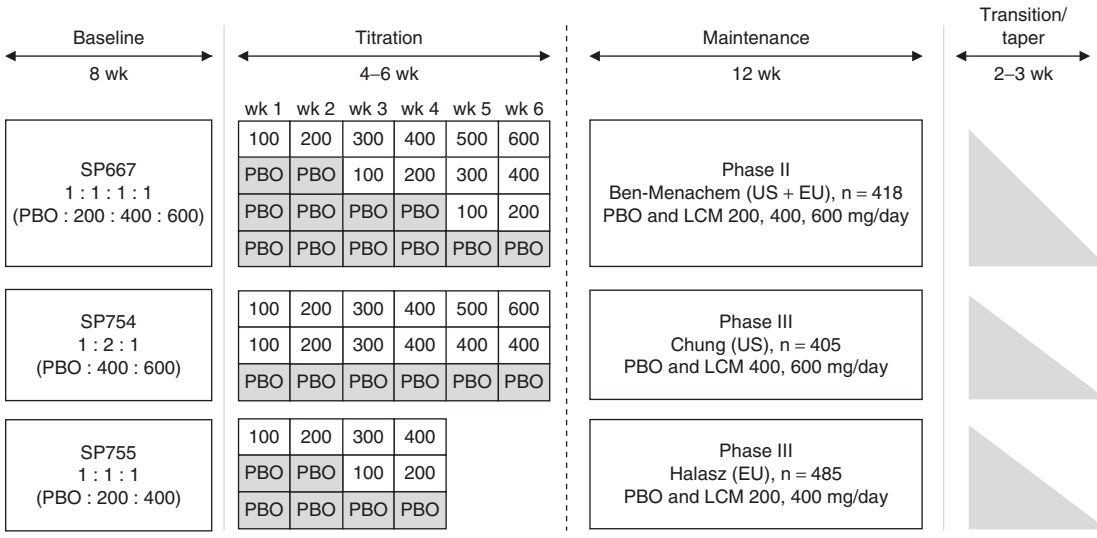

Fig. 1. Design of phase II/III randomized clinical trials of lacosamide (LCM). One back-titration of 100 mg/day was allowed at the end of titration in cases of intolerable adverse events. **PBO** = placebo.

for at least 4 weeks prior to and including baseline and throughout the trial.

Efficacy

Phase II/III A Priori-*Defined Primary and Secondary Variables*

The *a priori* protocol-defined primary variables were used for the pooled analysis. These primary variables were change in seizure frequency per 28 days from Baseline to the Maintenance Phase (presented as median percent reduction) and proportion of patients experiencing a ≥50% reduction in seizure frequency from Baseline to the Maintenance Phase (50% responder rate). In order to characterize those patients achieving the highest levels of response, additional *a priori*-defined secondary variables were also considered for the pooled analysis. These were the proportion of patients achieving a ≥75% reduction in seizure frequency from Baseline to the Maintenance Phase (75% responder rate), the proportion of patients completing the Maintenance Phase remaining seizure free throughout the entire Maintenance Phase and the percentage of seizure-free days throughout the Maintenance Phase for patients who entered the Maintenance Phase. The pooled analyses of the change in seizure frequency and 50% and 75% responder rates were performed according to the randomized treatment group assigned in individual trials using analysis of covariance (ANCOVA) and logistic regression models with an intent-to-treat (ITT) approach, including all patients receiving at least one dose of trial medication and having at least one post-baseline efficacy assessment. Similar analyses of the two primary efficacy variables and 75% responder rates were also performed using a modified ITT (ITTm) population that included ITT patients who entered the Maintenance Phase. By excluding those who dropped out during titration, the observed outcome would more accurately reflect dosing as intended by the protocol. The two primary efficacy variables were also evaluated for the ITTm in the individual trials.

Post Hoc *Analyses*

Onset of Efficacy

A *post hoc* analysis was conducted to assess response to initial lacosamide exposure compared with placebo during the Titration Phase for the two primary efficacy variables using ANCOVA and logistic regression models. Although the Titration Phases differed slightly among trials with respect to when the first dose of lacosamide was administered, the titration rate was the same in each trial (100 mg/day during the initial week of lacosamide exposure followed by weekly titration in 100 mg/day increments to the assigned target dosage). Therefore, all patients randomized to lacosamide initiated treatment with 100 mg/day during the first week of actual lacosamide exposure and with 200 mg/day during the second week of actual lacosamide exposure (see figure 1). Seizure diary data from each trial were pooled for the first and second weeks of lacosamide exposure for those patients randomized to lacosamide and the first and second weeks of trial medication exposure for those patients randomized to placebo.

By Prior Surgical History

Patient history of surgical intervention for epilepsy was considered a proxy for disease severity in a *post hoc* analysis. Patients reporting prior surgical intervention for epilepsy were placed into mutually exclusive groups based on the type of procedure: VNS only, resection only, VNS and resection only or other. Using ANCOVA and logistic regression models, the two primary efficacy variables for patients randomized to lacosamide in the 'VNS only' and 'resection only' groups were compared with the group of patients randomized to lacosamide not reporting prior surgical interventions for epilepsy. The two most common categories (VNS only and resection only) were chosen for comparison to those not reporting prior surgical history in order to have both a clearly defined patient population as well as an adequate sample size.

By Concomitant Antiepileptic Drugs (AEDs)

The two primary efficacy variables were descriptively evaluated in a *post hoc* analysis by individual concomitant AED use such that patients could be assigned to as many as three different subgroups (i.e. one for each of the up to three concomitant AEDs). These data are presented only for those patients in the phase II/III pool who were randomized to lacosamide 400 mg/day,

as this was the dosage included in all three trials. Efficacy variables were analysed using an ITT approach.

Pharmacokinetic-Pharmacodynamic Model

Pharmacokinetic-pharmacodynamic (PK-PD) models were applied to evaluate the correlation between plasma lacosamide concentration over time and reduction of daily seizures over time based upon the pooled data. The pharmacokinetic parameter of interest was the individual lacosamide exposure, quantified by the area under the plasma concentration-time curve (AUC) within a dose interval of 12 hours under steady-state conditions ($AUC_{\tau,ss}$). The daily number of partial seizures in individuals was chosen as the pharmacodynamic variable. Three models (linear PK-PD model, E_{max} model [where E_{max} is the maximum daily number of seizures] and $E_{max}100$ model [with the additional condition to have a maximum effect of 100%]) were tested to find the most appropriate model to describe the effect (the relative difference of daily number of seizures) as a function of the approximated AUC in a dose interval at steady-state conditions.

Safety

A complete report of the safety profile observed in this large pooled patient population is currently in preparation,[8] and safety assessments described here are limited to incidence of treatment-emergent adverse events (TEAEs) and TEAEs leading to discontinuation. These safety assessments were analysed and are briefly described for the safety set, which included all patients who took at least one dose of study medication.

Results

Demographic and Baseline Characteristics in the Pooled Patient Population

A total of 1294 patients received at least one dose of trial medication and had at least one post-baseline efficacy assessment, and comprised the ITT population. Of these, 1116 patients completed titration and entered the Maintenance Phase, comprising the ITTm population. The percentages of patients completing the trial were 88% (placebo), 83% (lacosamide 200 mg/day), 78% (lacosamide 400 mg/day) and 62% (lacosamide 600 mg/day). Individual trial contributions are noted in figure 2.

Patient demographic and baseline characteristics are summarized in table I. On average, patients were 38.6 years of age and slightly more than half were female (51%). Patients in these trials had a mean time since diagnosis of more than 2 decades. Most patients (77%) reported using four or more lifetime AEDs, and 45% reported seven or more lifetime AEDs. Most patients (84%) were receiving two to three concomitant AEDs, mainly carbamazepine (35%), lamotrigine (31%) and levetiracetam (29%). In addition, median baseline seizure frequency per 28 days ranged from 11.0 to 13.5.

Efficacy Results

Phase II/III A Priori-*Defined Primary and Secondary Variables*

In individual trials, the lacosamide 400 and 600 mg/day dosage groups were significantly different from placebo for both primary efficacy variables (median percent reduction in seizure frequency and 50% responder rate) in all trials using these dosages (table II; ITT and ITTm).[5,7,9-11] Median percent reduction in seizure frequency for the lacosamide 200 mg/day dosage was significantly greater than placebo in the phase III trial, SP755 (ITT and ITTm).[6] In the phase II trial (SP667),[5] the percent reduction over placebo for 200 mg/day was similar to SP755 and was significantly different from placebo in the ITTm analysis but not for the ITT analysis. Although lacosamide 200 mg/day showed a consistent effect over placebo on the responder rate analysis, the 50% responder rates with lacosamide 200 mg/day did not reach statistical significance in the two trials that included this dosage (SP667 and SP755)[5,6] in either the ITT or ITTm analyses (table II).

The proportions of patients achieving a ≥75% reduction in seizure frequency were evaluated in individual trials, though statistical comparisons to placebo are only available for trial SP754,[7] in which the 75% responder rate from Baseline to Maintenance Phase was significantly higher in

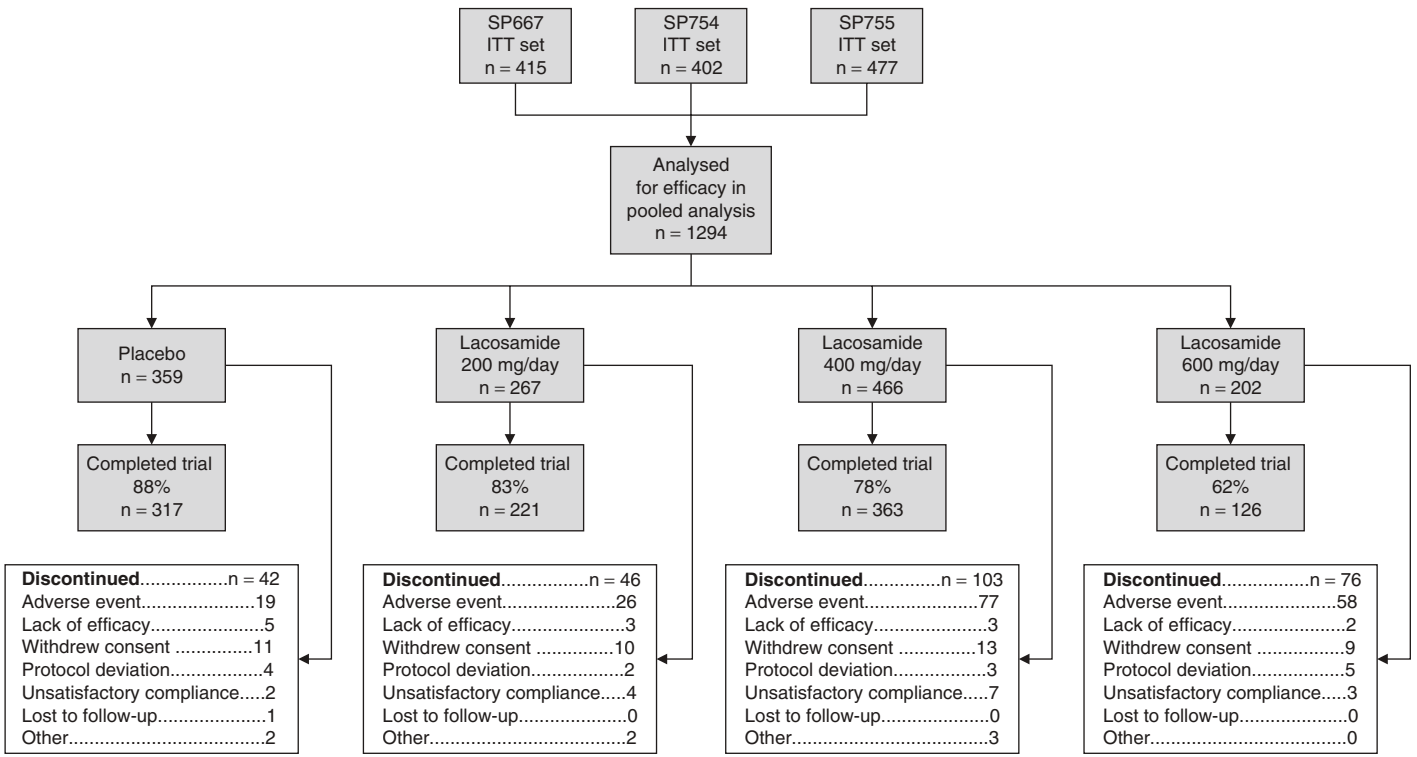

Fig. 2. Phase II/III pooled population: pooling strategy and patient disposition. Individual trial flow diagrams are available in the primary publications.[5-7] Patients could provide more than one reason for trial discontinuation. **ITT** = intent-to-treat.

Table I. Phase II/III pooled population: demographic and baseline characteristics (intent-to-treat [ITT])

	Placebo (n = 359)	Lacosamide (mg/day)			Total (N = 1294)
		200 (n = 267)	400 (n = 466)	600 (n = 202)	
Age (mean, y)	38.5	38.1	39.2	38.1	38.6
Female (%)	48.5	49.8	52.4	54.5	51.1
Time since diagnosis (mean ± SD, y)	23.4 ± 12.6	23.8 ± 12.5	23.9 ± 13.2	23.5 ± 13.0	23.7 ± 12.8
Lifetime AEDs (% of patients)					
1–3	21.7	22.8	23.6	15.8	21.7
4–6	32.9	30.7	32.0	33.7	32.2
7+	44.6	44.9	43.8	50.0	45.2
missing	0.8	1.5	0.6	0.5	0.9
Number of concomitant AEDs (% of patients)					
1	16.7	12.4	16.7	14.9	15.5
2	58.8	62.9	59.9	74.3	62.4
3	24.5	24.7	23.4	10.9	22.0
Most common[a] concomitant AEDs (% of patients)					
carbamazepine	34.8	42.7	31.5	34.2	35.2
lamotrigine	32.3	25.8	33.9	30.2	31.2
levetiracetam	28.7	25.8	30.7	29.7	29.0
valproate	25.9	27.3	21.2	19.8	23.6
topiramate	22.8	26.2	22.5	15.8	22.3
Median baseline seizure frequency per 28 days	11.0	12.2	11.0	13.5	11.5
Patients reporting a history of surgical intervention (% of patients)	Placebo (n = 116)	Total lacosamide (n = 310)			Total (N = 426)
VNS only	50.0	45.8			46.9
resection only	24.1	32.9			30.5
VNS and resection only	12.1	8.1			9.2
other	13.8	13.2			13.4

a Represents the top five most commonly used concomitant AEDs.

AEDs = antiepileptic drugs; **VNS** = vagus nerve stimulation.

both dosage groups included in that trial (400 mg/day, 20.4%, p = 0.005 and 600 mg/day, 21.6%, p = 0.007) compared with placebo (7.7%; ITT). In trial SP667,[5] 75% responder rates were 11.2%, 22.4% and 16.2% with lacosamide 200, 400 and 600 mg/day, respectively, compared with placebo (6.3%). In trial SP755,[6] 75% responder rates were 15.0% and 15.2% in the lacosamide 200 and 400 mg/day groups respectively, compared with placebo (11.9%).

In the pooled analyses, all three lacosamide dosages (200, 400 and 600 mg/day) showed a significant improvement compared with placebo for median percent seizure reduction (ITT and ITTm) as well as for 50% responder rate (figures 3 and 4a). Evaluation of 75% response in the phase II/III pooled population showed that a significantly higher proportion of patients randomized to lacosamide 400 or 600 mg/day achieved a ≥75% reduction in seizure frequency compared with placebo; statistical significance was not observed for lacosamide 200 mg/day (ITT and ITTm; figure 4b).

Among patients in the phase II/III trials who completed the Maintenance Phase, 2.7% (6/225), 3.3% (12/366) and 4.8% (6/124) in the lacosamide 200, 400 and 600 mg/day groups, respectively, experienced no seizures throughout the entire Maintenance Phase (placebo group = 0.9% [3/326]).[12] When calculating seizure freedom with a more

Table II. Primary efficacy variables: individual trial results (intent-to-treat [ITT] and modified ITT [ITTm])[5-7]

Trial, treatment group	ITT			ITTm		
	n	median percent seizure reduction[a]	50% responder rate[b] (%)	n	median percent seizure reduction[a]	50% responder rate[b] (%)
SP667						
Placebo	96	10	21.9	91	12.2	23.1
Lacosamide 200 mg/day	107	26	32.7	95	31.5*	34.7
Lacosamide 400 mg/day	107	39**	41.1**	89	45.7**	48.3**
Lacosamide 600 mg/day	105	40**	38.1*	70	48.8**	48.6**
SP754						
Placebo	104	20.8	18.3	98	20.8	17.3
Lacosamide 400 mg/day	201	37.3**	38.3**	168	39.6**	41.7**
Lacosamide 600 mg/day	97	37.8**	41.2**	72	47.5**	48.6**
SP755						
Placebo	159	20.5	25.8	148	25.4	27.0
Lacosamide 200 mg/day	160	35.3*	35.0	149	35.6*	34.9
Lacosamide 400 mg/day	158	36.4*	40.5**	136	43.0*	44.9**

a p-values reflect the percent reduction over placebo and are based on log-transformed seizure frequency from pairwise analysis of covariance models with terms for treatment, pooled site and baseline seizure frequency.

b p-values are based on pairwise treatment logistic regression model with terms for treatment and pooled site.

* $p < 0.05$, ** $p < 0.01$.

conservative 'pragmatic ITT' approach using the ITT to determine the denominator,[13] percentages were 0.8% (3/359, placebo), 2.2% (6/267, lacosamide 200 mg/day), 2.6% (12/466, lacosamide 400 mg/day) and 3.0% (6/202, lacosamide 600 mg/day). The mean change from baseline in the percentage of seizure-free days in patients entering the Maintenance Phase for the phase II/III pool was 8.0%, 11.6% and 14.7% with lacosamide 200 ($p = 0.077$), 400 ($p < 0.001$) and 600 ($p < 0.001$) mg/day

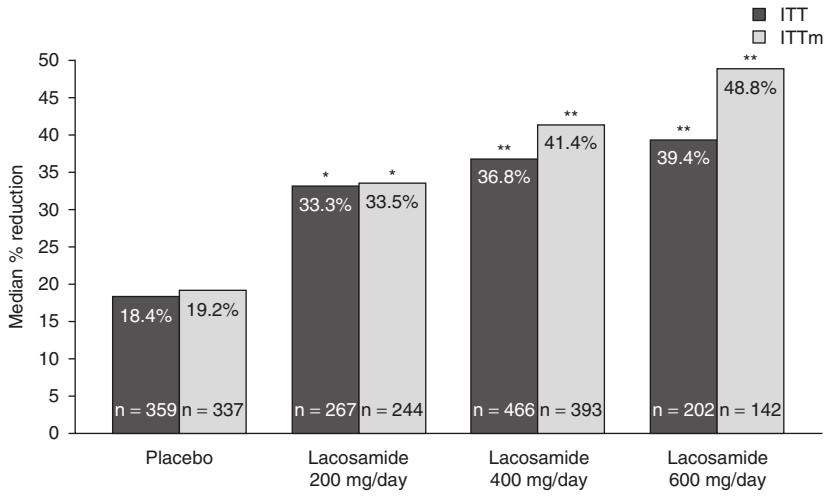

Fig. 3. Phase II/III pooled population: median percent reduction in seizure frequency per 28 days from Baseline to Maintenance Phase (intent-to-treat [ITT] and modified ITT [ITTm]). p-values represent the percent reduction over placebo and are based on log-transformed seizure frequency from pairwise analysis of covariance models with terms for treatment, trial, pooled site and baseline seizure frequency. * $p < 0.05$, ** $p < 0.001$.

groups, respectively, compared with 6.1% in the placebo group.

Post Hoc *Analyses*

Early Onset of Efficacy

Some patients prematurely discontinued during titration and prior to receiving lacosamide in the titration schedule. Therefore, the onset of action analysis included 913 lacosamide-treated and 358 placebo patients in the week 1 analysis and 904 lacosamide-treated and 357 placebo patients in the week 2 analysis. A significant difference in the median percent reduction in seizure frequency was observed during the first week (33.0% vs 19.4%) with lacosamide 100 mg/day and during the second week (34.0% vs 20.0%) with lacosamide 200 mg/day compared with placebo (figure 5). Efficacy appeared to be maintained during the subsequent weeks of lacosamide exposure regardless of randomization group (data

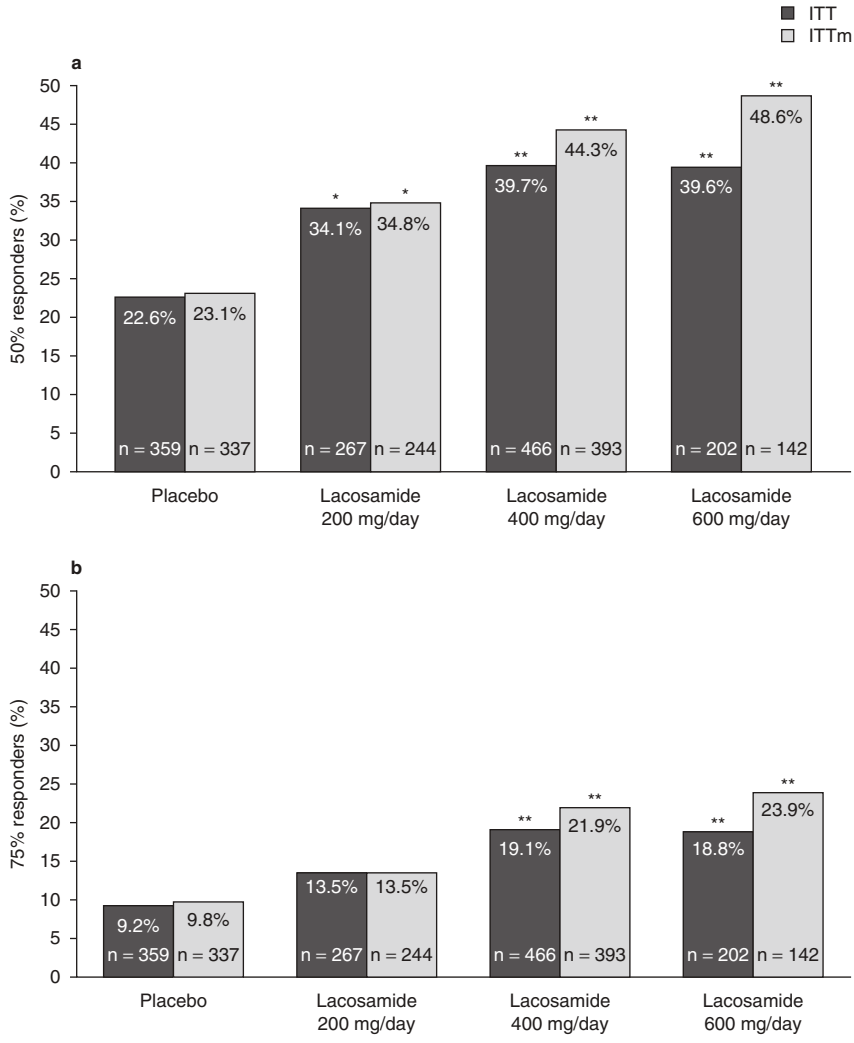

Fig. 4. Phase II/III pooled population: 50% and 75% responders (intent-to-treat [ITT] and modified ITT [ITTm]). p-values are based on a pairwise treatment logistic regression model with terms for treatment, trial and pooled site. * $p < 0.05$, ** $p < 0.001$ vs placebo.

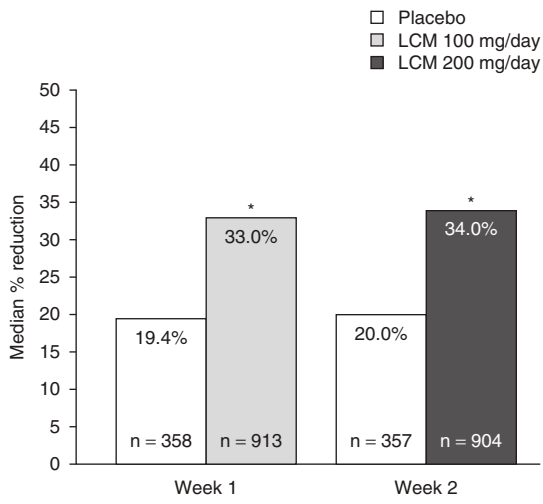

Fig. 5. Median percent reduction in seizure frequency during first 2 weeks of actual lacosamide (LCM) exposure. p-values reflect the percent reduction over placebo and are based on log-transformed seizure frequency from an analysis of covariance model with terms for treatment, trial, pooled site and baseline seizure frequency. Placebo group consists of all placebo-treated subjects in weeks 1 and 2.
* $p < 0.01$ compared with placebo.

not shown). Similar results were observed for 50% responder rates (data not shown).[14]

Efficacy Results by Previous Surgical History

Prior surgical intervention for epilepsy was reported in a total of 426 patients (33%, table I). Patients who had undergone surgery had a greater median seizure frequency per 28 days at baseline compared with those without surgery (16.4 vs 10.0). Nearly double the number of patients who had undergone surgery (67%) had tried seven or more lifetime AEDs compared with patients without surgical intervention (34%). VNS and resection were the most common forms of surgical intervention (47% vs 31%, respectively). Using the total lacosamide group (all dosages), no differences were observed for median percent reduction in seizure frequency in either VNS- or resection-only patients when compared with patients receiving lacosamide with no prior surgical intervention (39% vs 36% VNS only compared with no surgical intervention [$p = 0.62$] and 32% vs 36% for resection only compared with no surgical intervention [$p = 0.99$]). Similar results were observed in the total lacosamide group when analysing 50% responder rates (40% vs 38% for VNS-only patients [$p = 0.62$] and 39% vs 38% for resection-only patients [$p = 0.98$] vs those with no prior surgical interventions).[15]

Efficacy Results by Use of Selected Concomitant AEDs

Since most patients (84%) were taking one or more concomitant AED, subgroups in the concomitant AED analysis were not mutually exclusive, and a patient could be represented in up to three different AED subgroups. When analysed by concomitant AED, lacosamide treatment showed a reduction in seizures, regardless of the concomitant AED used. Evaluation of 50% responder rates in these concomitant AED subgroups is shown in figure 6. An evaluation of median percent seizure reduction showed similar results (data not shown).[16]

Pharmacokinetic-Pharmacodynamic Model: Serum Concentration-Effect Relationship

A total of 3055 records from 615 patients were evaluable and were included in the PK-PD analysis. Of these 615 patients, 222 patients were from trial SP667, 194 were from trial SP754 and 199 were from trial SP755. The E_{max} model was identified as the most appropriate PK-PD model to describe the relationship between AUC and seizure frequency change (table III). Individual variability was high in all tested PK-PD models, including the E_{max} model (arithmetic mean of $E_{max} = 71\%$, standard deviation = 30%, range: 0.06–100%; AUC_{50} [$AUC_{\tau,ss}$ necessary for half of maximum decrease in partial seizure frequency] = 35.9 μg/mL • h, standard deviation = 185.6, range: 0–3998 μg/mL • h).

Safety

A thorough examination of the safety profile observed in this large pooled patient population is currently in preparation.[8] Key results are summarized here. Four TEAEs occurred in the Treatment Phase (Titration and Maintenance Phases) at an incidence of ≥10% in the lacosamide total group (all dosages) and greater than placebo (dizziness [31% vs 8%], headache [13% vs 9%], nausea [11% vs 4%] and diplopia [11% vs 2%]);

all of these with the exception of headache appeared to be dose related. All occurred with a lower incidence during the Maintenance Phase compared with the Titration Phase. In addition to those TEAEs listed above, vomiting, fatigue, coordination abnormal (ataxia), blurred vision, tremor and nystagmus occurred at an incidence of ≥10% in the lacosamide 600 mg/day treatment group only. No overall dose effect among the lacosamide groups was observed for the incidence of serious TEAEs (lacosamide 200 mg/day [8%], 400 mg/day [7%], 600 mg/day [3%]); the incidence was 4% in patients randomized to placebo. Three serious TEAEs occurred at an overall rate of greater than or equal to 1% in any treatment group: dizziness (1.5% for lacosamide 600 mg/day vs 0% for all other groups), nystagmus (1.0% for lacosamide 600 mg/day vs 0% in all other groups) and convulsion (1.1% for lacosamide 200 and 400 mg/day, 0% for lacosamide 600 mg/day vs 0.8% for placebo).

The percentage of patients discontinuing treatment due to a TEAE in the Treatment Phase was 5% with placebo and 17% with lacosamide (8%, 17% and 29% for lacosamide 200, 400 and 600 mg/day). TEAEs leading to discontinuation with an incidence of greater than 5% in any treatment group were dizziness and coordination abnormal (ataxia), which were both associated with the 600 mg/day group.

Discussion

The pooled analysis of these three phase II/III randomized, double-blind, placebo-controlled trials demonstrates that lacosamide 200, 400 and

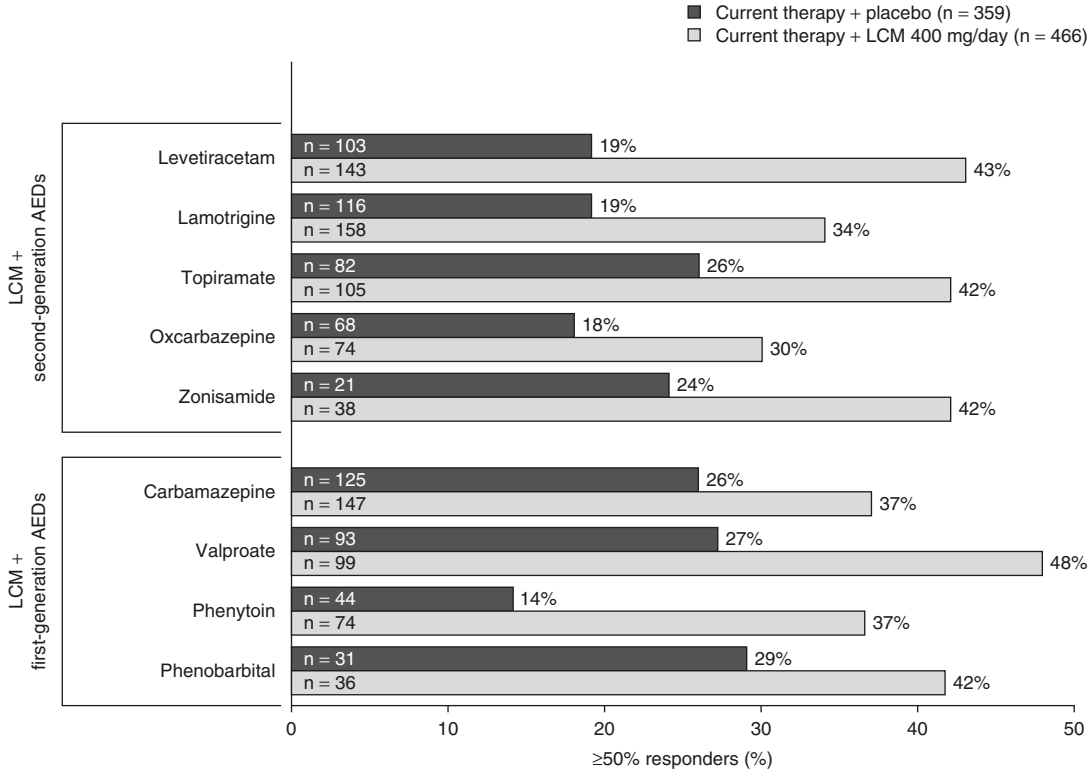

Fig. 6. 50% responder rates with lacosamide (LCM) by concomitant antiepileptic drug (AED) use. LCM was taken twice daily in equally divided doses. Intent-to-treat population. Most patients were taking more than one concomitant AED; therefore, these groups may not be mutually exclusive.

Table III. Achievable decrease of the daily number of seizures (%) in relation to area under the plasma concentration-time curve within a dose interval of 12 hours under steady-state conditions ($AUC_{\tau,ss}$) and daily lacosamide dose[a]

Decrease of daily number of seizures, E(AUC) % of baseline	Decrease of daily number of seizures, E(AUC) % of E_{max}	Corresponding $AUC_{\tau,ss}$ (μg/mL • h)	Daily dose to achieve corresponding $AUC_{\tau,ss}$ (mg bid)
22.5	31.7	16.7	50
34.2	48.1	33.3	100
35.1	50	35.9	110
41.3	58.2	50	150
46.1	65.0	66.7	200
49.6	69.9	83.3	250
52.2	73.6	100	300

a Calculated based on the results of the E_{max} model.

bid = twice daily; **E(AUC)** = decrease of daily number of seizures in percentage as function of area under the plasma concentration-time curve.

600 mg/day significantly reduced seizures compared with placebo.

In this pooled analysis, the uniform patient populations and similar study designs were conducive for evaluating the clinical utility of lacosamide since all three trials used dosage regimens and formulations described within the product label (lacosamide 200 or 400 mg/day); a dosage of lacosamide 600 mg/day was also evaluated in two of the three phase II/III trials (SP667 and SP754). As a whole, patients included within the analysis represent a difficult-to-treat population, as indicated by their epilepsy treatment history and baseline seizure frequency. In spite of this, lacosamide significantly reduced seizures relative to placebo at all dosages studied for both primary variables using both the ITT and ITTm populations in the pooled analysis.

A recent epidemiological study has demonstrated an inverse relationship between probability of response to a newly administered AED and greater disease severity, defined by a higher number of prior AEDs, a longer duration of epilepsy and more frequent seizures at baseline.[17] Despite the treatment challenges predicted for difficult-to-treat patients, the efficacy results observed here for this large pooled population are consistent with what has been observed in individual lacosamide trials[5-7] and are comparable to those seen with established and second-generation AEDs.[18-22] Though predicted by epidemiological data to have the poorest likelihood for response, significantly more patients receiving the two highest lacosamide dosages in the phase II/III pool met the strictest response criteria (75% responder rate) compared with placebo. Furthermore, among patients completing the Maintenance Phase, a dose-response trend for seizure freedom was observed. It is acknowledged that the results presented here for the phase II/III pool are from trials with a 12-week Maintenance Phase and are not equivalent to seizure-freedom status sustained over the course of longer term (≥1 year) treatment. Mean changes in the percentage of seizure-free days suggest that, compared with placebo, lacosamide 400 and 600 mg/day may provide an additional 42.3 and 53.7 seizure-free days, respectively, over a year of treatment. Safety data for the phase II/III pool were consistent with previous observations in individual trials,[5-7] and no additional safety concerns were identified in the pooled analysis.

Results were presented for the two *a priori*-defined primary efficacy variables for both ITT and ITTm. The ITT served as the basis for regulatory submissions for lacosamide. Based on the ITT analysis, the lacosamide 400 and 600 mg/day groups demonstrate similar efficacy on both primary efficacy variables. The ITTm analysis allows evaluation of subjects who tolerated lacosamide and entered the Maintenance Phase. Since the ITTm does not include patients who discontinued during titration, it is not unexpected that a dose response was more evident for both primary efficacy variables for the ITTm across all dosages. The ITTm analysis suggests that lacosamide

600 mg/day may provide additional benefit for patients who are able to tolerate this dosage.

In the pooled analysis of lacosamide phase II/III data, efficacy was demonstrated during the first (100 mg/day) and second (200 mg/day) weeks of actual lacosamide exposure when compared with placebo. This analysis circumvented confounding factors of differential titration schedules since data were combined for first and second weeks of actual exposure (when all patients were receiving either lacosamide 100 or 200 mg/day). The magnitude of effect of these seizure reductions observed during the first 2 weeks of lacosamide exposure appeared to be maintained during subsequent weeks. As a clinical note, individual patients may require higher dosages or longer duration of treatment to fully evaluate the therapeutic potential of lacosamide.

Lacosamide is currently approved as an adjunctive therapy. Insight into differential patient outcome (increased seizure reduction and/or improved tolerability) based upon prior or current treatments would provide valuable clinical guidance. A *post hoc* pooled analysis presented here showed that lacosamide was equally effective in those reporting prior surgical interventions for epilepsy compared to those with no prior surgical history. This is notable as patients with surgical interventions often represent a particularly difficult-to-treat population, as evidenced by the AED treatment history and baseline seizure frequency of lacosamide phase II/III patients with prior surgical interventions for epilepsy.

With respect to differential patient outcome based upon concomitant AEDs, the preliminary investigation presented here did not distinguish among individual AEDs since too few patients were taking only one other AED in addition to lacosamide. In addition, the sample sizes in the less common AED subgroups were small. Recognizing these limitations, these results showing efficacy with lacosamide regardless of existing AED use, support the use of lacosamide as an adjunctive therapy across a broad range of AEDs. These results, though intriguing, do not specifically address the impact that an overlapping mechanism of action may have on patient outcome. Therefore, additional, more refined analyses grouping patients based upon primary mechanism of action of their concomitant AEDs have been completed and are reported within this issue of *CNS Drugs* (see Sake et al., pages 1055-1068). Future evaluation of patient outcome with adjunctive lacosamide based upon the mechanism of action of individual concomitant AEDs is warranted.

The PK-PD modelling on the phase II/III pooled data supports the therapeutic dose range of lacosamide; however, individual variability was high. Based on the distribution of the daily number of seizures in the phase II/III pool, a wide range of parameter values for AUC_{50} and E_{max} was not unexpected. The high variability in the pharmacodynamic parameter should be considered when interpreting the current PK-PD modelling results. Overall, the current PK-PD results support the therapeutic range of lacosamide dosages (200–600 mg/day) that has been shown to be effective as an adjunctive treatment for reducing partial seizure frequency. The therapeutic serum concentration range has not been established for lacosamide. Therefore, routine monitoring is not recommended, though certain clinical situations (e.g. suspected non-compliance) may warrant this for an individual patient.

Conclusions

Lacosamide is a new AED with a favourable tolerability profile and a rapid onset of anticonvulsant effects. The pooled analysis of these three phase II/III randomized, double-blind, placebo-controlled trials demonstrates that lacosamide 200, 400 and 600 mg/day significantly reduces seizures in patients with uncontrolled partial-onset seizures. Efficacy was demonstrated during the initial weeks of lacosamide treatment and appeared to be maintained during subsequent weeks. Furthermore, seizure reduction in a difficult-to-treat patient population was observed with lacosamide, regardless of prior surgical history and the specific concomitant AEDs used.

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