European Journal of Pain 13 (2009) 458–463

Contents lists available at ScienceDirect

European Journal of Pain

journal homepage: www.EuropeanJournalPain.com

# Long-term oral lacosamide in painful diabetic neuropathy: A two-year open-label extension trial

Aziz Shaibani [a,*], Victor Biton [b], Richard Rauck [c], Brigitte Koch [d], Jeffrey Simpson [e]

[a] Nerve and Muscle Center of Texas, 6624 Fannin Suite 1670, Houston, TX 77030, USA
[b] Clinical Trials, Inc., Little Rock, AR, USA
[c] The Center for Clinical Research, Winston-Salem, NC, USA
[d] SCHWARZ PHARMA AG, UCB Group, Monheim, Germany
[e] SCHWARZ BIOSCIENCES, Inc., UCB Group, Research Triangle Park, NC, USA

ARTICLE INFO

*Article history:*
Received 5 November 2007
Received in revised form 18 April 2008
Accepted 23 May 2008
Available online 10 July 2008

*Keywords:*
Anticonvulsant drugs
Antiepileptics
Painful diabetic neuropathy
Lacosamide
Open-label trial
Long-term

ABSTRACT

*Objectives:* This open-label follow-on trial aimed to investigate long-term safety and efficacy of lacosamide in patients with painful diabetic neuropathy.
*Methods:* After 1-week baseline period, lacosamide 100 mg/day was started. Each week, based on pain and safety assessments, doses were escalated by 100 mg/day to an optimal level, up to a maximum of 400 mg/day. Patients then entered the 20-week maintenance period (dose adjusted as needed). Thereafter, patients could opt to continue lacosamide up to about 2.5 years (extension period).
*Results:* Of the 69 enrolled patients, 47 (68%) completed the 20-week maintenance period and elected to continue into the extension period; 37/69 (54%) patients were in the extension period for more than one year and 34/69 (49%) continued until study termination. The modal lacosamide dose in most patients (54%) was 400 mg/day. Headache, upper respiratory tract infection, arthralgia, sinusitis, nasopharyngitis, and back pain were the most frequently reported adverse events ($\geqslant$10% of patients). Significant reductions from baseline in Likert pain scores began during dose titration and were sustained throughout the study. Significant improvements were also seen in Neuropathic Pain Scale, Quality of Life scores, and Patient's Global Impression of Change assessment. Of 34 patients at study termination, 32 (90%) elected to continue with lacosamide treatment in another long-term open-label trial (NCT00235443).
*Conclusion:* The long-term safety profile and sustained efficacy of lacosamide observed in this trial support its continued development for treatment of painful diabetic neuropathy.


## 1. Introduction

Painful diabetic neuropathy (PDN) is one of the leading causes of neuropathic pain in humans (Vinik, 2005; Boulton et al., 2005; Schmader, 2002). PDN is a chronic, usually symmetrical, sensorimotor polyneuropathy that produces significant morbidity with negative influence on a patient's general activity, mood, mobility, work, social relations, sleep, and overall quality of life (Vinik, 2005; Schmader, 2002).

Treatment of PDN is challenging because the mechanisms involved are unclear (Campbell and Meyer, 2006), and the mechanisms of action for drugs used to treat neuropathic pain have not been fully elucidated, making it difficult to match the type of pain to the most appropriate medication. Pharmacological agents used in the management of PDN include tricyclic antidepressants, selective serotonin and norepinephrine reuptake inhibitors, opioids, and antiepileptic drugs. Generally, the available treatment options do not give total relief, are not effective in all patients, and only about one-third of patients may achieve more than 50% pain relief (Jensen et al., 2006). Anticonvulsants are becoming increasingly important in the management of neuropathic pain, with antiepileptic drugs such as lamotrigine, gabapentin, and pregabalin demonstrating an analgesic effect in diabetic neuropathy (Attal et al., 2006; Collins and Chessell, 2005; Vinik, 2005). Patients who have failed to respond to one anticonvulsant may respond to another or to two or more drugs in combination (Dworkin et al., 2003).

Lacosamide, the *R*-enantiomer of 2-acetamido-*N*-benzyl-3-methoxypropionamide, was synthesized as an anticonvulsive drug candidate. Animal model studies have shown that lacosamide has antiepileptic and antinociceptive efficacy, including efficacy in the streptozotocin-induced rat model of diabetic neuropathic pain, where it showed equivalent or greater efficacy on measures of allodynia and hyperalgesia to that of other antidepressant or anticonvulsant drugs (Beyreuther et al., 2006, 2007). It is absorbed rapidly and completely after oral administration (bioavailability ~100%)

* Corresponding author. Tel.: +1 713 795 0033; fax: +1 713 796 9302.
*E-mail address:* Nerveandmuscle@houston.rr.com (A. Shaibani).

1090-3801/$36.00 
doi:10.1016/j.ejpain.2008.05.016

with minimal protein binding (Bialer et al., 2002). Lacosamide showed no potential to induce the activity of cytochrome P450 isoforms in human hepatocytes at therapeutic concentrations (Beyreuther et al., 2007). There is a low risk of drug interaction between lacosamide and other drugs including hepatically metabolized drugs. Interaction studies with lacosamide included drugs such as carbamazepine, valproic acid, metformin, digoxin, oral contraceptives (ethinyl estradiol/levonorgestrel), and omeprazole (Horstmann et al., 2003; Kropeit et al., 2006; Schiltmeyer et al., 2005).

Lacosamide has demonstrated clinical efficacy in treating patients with neuropathic pain (McCleane et al., 2003; McCleane et al., 2005; Rauck et al., 2007). In an earlier double-blind, placebo-controlled trial in 119 patients with PDN, lacosamide demonstrated statistically significant efficacy compared with placebo in reducing pain when administered in ascending doses up to 400 mg/day (Rauck et al., 2007). Patients completing this earlier double-blind trial had the option to enroll in the present study designed to examine the safety, tolerability, and efficacy of the long-term administration of oral lacosamide, up to 400 mg/day, in patients with PDN.

## 2. Materials and methods

### 2.1. The trial plan

The trial, approved by relevant ethics committees and institutional review boards, was conducted between April 2002 and December 2004 at 29 sites throughout the United States (US). Each patient signed an informed consent form prior to participation. The trial was conducted in accordance with the Declaration of Helsinki, the US Code of Federal Regulations Part 21, and the International Conference on Harmonization Good Clinical Practice guidelines.

Patients with PDN who had completed a randomized double-blind placebo-controlled trial with lacosamide (Rauck et al., 2007) were invited to enroll in the present trial by completing eligibility assessments followed by a 1-week baseline phase. These patients were required to have stable, good, or fair glycemic control with glycosylated hemoglobin ($HbA_{1c}$) value $\leqslant$10%. Women who were pregnant, breastfeeding, or of childbearing potential and were not practicing medically acceptable birth control, were excluded from the trial. Also excluded were patients with any other condition likely to contribute to neuropathy, clinically significant electrocardiogram (ECG) abnormalities, renal impairment, and liver enzymes greater than two times the upper limit of normal. Patients taking other drugs within seven days preceding first dose of lacosamide and during the study was not permitted. These included tricyclic antidepressants, mexiletine hydrochloride, lidocaine patch, tramadol, AEDs, dextromethorphan, opioids, capsaicin, nonsteroid anti-inflammatory drugs, skeletal muscle relaxants, benzodiazepines, alpha-2-agonists (e.g., clonidine), warfarin, drugs indicated for sleep disturbance, and over-the-counter medications with centrally acting properties. Therapy that became necessary, in the investigator's opinion and at low dosage and/or for a limited time, during the course of the trial was not refused, even if listed as a therapy that was generally not permitted.

The trial began with a 1-week run-in period, during which patients received no trial medication to help establish baseline values. After completing the run-in period, patients entered the titration period on 100 mg/day (50 mg twice daily) of orally administered lacosamide. At weekly intervals, based on pain relief and safety assessment, doses were increased by 100 mg/day (50 mg twice daily), up to the optimally effective dose for the patient. The maximum allowed dose in this trial was 400 mg/day (200 mg twice daily). Thereafter, patients entered the 20-week maintenance period on their individually determined optimal dose, or the planned maximum dose of 400 mg/day. Patients returned every 4 weeks for assessment of safety and efficacy and received their medication supply. As needed, adjustment in lacosamide dose was allowed throughout the trial provided the maximum dose of 400 mg/day lacosamide was not exceeded. Following completion of the 20-week maintenance period, patients could choose to terminate treatment and enter the 2-week safety follow-up period. Alternatively, they had the option to continue lacosamide treatment in an extension period of the trial through December 2004, at which time this trial was terminated. During the extension period, patients visited the clinic every 12 weeks for assessment. Patients wishing to continue with lacosamide treatment after the extension period had the option to enroll in another long-term, open-label lacosamide trial (NCT00235443). All patients who completed the trial through the end of December 2004 were considered as having completed the trial. Safety and efficacy analyses through titration, maintenance, and extension periods included all patients who received at least one dose of lacosamide.

### 2.2. Data analyses

Safety variables, such as adverse events, withdrawals due to adverse events, occurrence of serious adverse events, clinical laboratory evaluations, 12-lead ECG readings, vital sign measurements, and physical and neurological examination findings, were analyzed descriptively. Untoward clinical events (abnormal laboratory values, physical signs, or symptoms) experienced by a patient while taking part in this clinical trial that started on or after the date of first dosing with lacosamide, or occurred within 30 days following the date of last dose of trial medication, or whose intensity worsened on or after the date of first dosing with lacosamide were categorized as treatment-emergent adverse events (TEAEs). Untoward medical occurrences that resulted in death, posed a life-threatening situation, caused persistent or significant disability/incapacity, required hospitalization, or prolonged existing inpatient hospital stay during the trial were described as serious adverse events. TEAEs, serious adverse events, and the number of patients who discontinued due to an adverse event were evaluated.

Within-patient changes from baseline in average daily pain scores taken from patient diary entries were based on the 11-point Likert scale (0 = no pain to 10 = worst pain ever experienced). Changes in the patient's rating of overall pain were measured by the visual analog scale (VAS) of the Short Form McGill Pain Questionnaire (SF-MPQ). The qualitative aspects of changes in pain perception were evaluated by the Neuropathic Pain Scale (NPS). The percentage of pain-free days was also assessed by lacosamide dose. Global improvement were assessed by Patient's Global Impression of Change (PGIC) and the Clinician's Global Impression of Change (CGIC) in pain based on 7-point categorical rating scales ranging from "much better" to "much worse". The impact of pain on quality of life was assessed using the Short Form-36 (SF-36) Quality of Life questionnaire, which assessed two overall composite scores for physical and mental health and eight health concepts (physical functioning, role functioning-physical, role functioning-emotional, social functioning, body pain, mental health, vitality, and general health perceptions) scored from 0 (worst possible quality of life) to 100 (best possible quality of life), with increases in scores indicating improvement in quality of life. The 11-point Likert scale of the Brief Pain Inventory was used to assess the effect of pain on sleep quality and general daytime activity on a daily basis.

Imputation of missing values was not undertaken as only reported data were used. Unless otherwise stated, measurements of efficacy are presented as mean ± SD (standard deviation) values. Post hoc, paired t-tests were performed for evaluating changes

from baseline in average daily Likert pain scale scores, NPS, and Quality of Life SF-36 scores.

## 3. Results

### 3.1. Patients

Of the 94 patients who completed the previous double-blind trial (Rauck et al., 2007), 69 patients enrolled in the current open-label extension trial (Fig. 1) and received at least one dose of trial medication. At the end of titration, 62 patients entered the 20-week maintenance period. On completion of the maintenance period, 47 patients elected to continue lacosamide in the extension phase of this trial. During the entire trial, spanning more than 2.5 years, there were 7 discontinuations during the titration period, 15 during the maintenance period, and 17 during the extension period. Thirty-four patients (49%) completed the entire trial.

The average age of patients was 56.9 years ± 10.19; 74% of subjects were <65 years of age, 26% of subjects were ⩾65 years of age, and 1% of subjects were ⩾75 years of age. There were an equal proportion of male and female subjects (49% male, 51% female) and 88% of the patients were caucasian. The median body mass index for the randomized patients was 33.0 (range 20.0–49.1). The median body weight was 92.1 kg (range 59.9–155.6). Sixty patients (87%) reported using at least one concomitant medication during the trial. Enrolled patients were not receiving lacosamide or a non-analgesic medication for neuropathic pain relief for at least three weeks preceding entry into the titration period. Twelve patients (12/69 = 17%) listed a concomitant medication taken apparently for pain. These included amitryptyline ($n$ = 1/69), gabapentin ($n$ = 2/69), hydrocodone ($n$ = 2/69), paracetamol ($n$ = 8/69), and rofecoxib ($n$ = 1/69). The mean (SD) Likert pain scale score at baseline for enrolled patients was 5.65 ± 2.53 ($n$ = 64); five patients did not submit their baseline entries.

Thirty-seven patients received lacosamide for at least one year by trial termination time in December 2004. The mean exposure to lacosamide was 450.1 days ± 314.50. The most common daily dose taken during the entire trial by 46 patients (67%) was lacosamide 400 mg/day with a mean exposure to the drug of 426.5 days ± 328.91. Generally, once an optimal dose was established, patients tended to remain on that dose. During the trial, 11 patients (16%) who were receiving 400 mg/day lacosamide had their dosage reduced to 300 mg/day. In the case of two of these 11 patients, the dosage was further reduced to 200 mg/day. Additionally, two patients who were on 300 mg/day lacosamide had their dosage reduced to 200 mg/day.

### 3.2. Tolerability

Headache (16%), upper respiratory tract infection (14%), arthralgia (12%), sinusitis (10%), nasopharyngitis (10%), back pain (10%), fatigue (9%), tremor (9%), and dizziness (9%) were amongst the more commonly reported adverse events during the entire trial. Most adverse events were either mild (62%) or moderate (30%) in intensity. The adverse events occurred most frequently during the titration period. Investigators considered 14.3% of the events to be possibly related to trial medication, the most common of such events were headache (7%), dizziness (7%), tremor (4%), fatigue (6%), and diarrhea and nausea (4%).

Nineteen patients (28%) experienced one or more serious adverse events (total 24 serious adverse events). No single serious adverse event occurred in more than one patient, with the exception of chest pain in two patients, both of which were considered unrelated to trial medication by investigator. Only 2 events (cerebrovascular accident and convulsion) were considered as possibly related to lacosamide; both occurred in the same patient at a dose of 200 mg/day lacosamide and resulted in the patient being withdrawn from the trial. Overall, laboratory values, vital signs, and physical and neurological examination findings were generally unremarkable. Major fluctuations in $HbA_{1c}$ values were not observed. Lacosamide did not affect body weight; the mean and median changes in body weight from baseline to the last visit were 0.03 kg and −0.37 kg, respectively (range −15 to 14.5 kg).

Sixteen patients discontinued from this trial due to an adverse event. Nine patients withdrew due to adverse events related to gastrointestinal, nervous system, and general disorders considered unrelated to lacosamide. Investigators regarded the possibility of a causal relation to the trial medication in the case of the remaining seven patients. Of these seven patients, one patient had dizziness and nausea, one had chest pain and nausea, two had ECG changes, one had dizziness, fatigue, and tinnitus, one patient was hospitalized with possible cerebrovascular accident and convulsion (serious adverse event), and one patient had an accidental overdose

| | Number of patients enrolled and entering the Titration Period (n = 69*) | | | |
|---|---|---|---|---|
| | Lacosamide prescribed dose | | | |
| | 100 mg/day | 200 mg/day | 300 mg/day | 400 mg/day |
| **Titration Period (n – 69*)** | 69 | 61 | 53 | 45 |
| ***Discontinued (n = 7):*** *Adverse events (n = 4); Consent withdrawn (n = 3)* | | | | |
| **Maintenance Period (n = 62*)** | 1 | 14 | 18 | 40 |
| ***Discontinued: (n = 15):*** *Adverse events (n = 6); Other reasons (n = 9)* | | | | |
| **Extension Period (n = 47*)** | | | | |
| ***Discontinued (n = 17*):*** *Adverse events (n = 6*); Other reasons (n = 11*)* | | | | |
| **< 6 months (n = 4*)** | 0 | 1 | 1 | 2 |
| **6 – < 12 months (n = 5*)** | 0 | 3 | 0 | 2 |
| **12 – < 18 months (n = 21*)** | 1 | 4 | 5 | 14 |
| **≥18 months (n = 16*)** | 0 | 2 | 4 | 12 |

**Fig. 1.** Patient disposition * = number of patients participating in a particular treatment period and may be counted in more than one column.

of 800 mg/day for four days when she was admitted to the hospital due to numbness of her lips, blurred vision, dizziness, and vomiting. The condition of the patient with lacosamide overdose resolved and she was sent home in six days. Of the two patients with ECG changes who were withdrawn from this trial, one patient experienced a QTc value of 501 ms compared with the baseline value of 436 ms; the second patient developed a QRS of 124 ms and a heart rate of 55 beats/min against baseline values of 112 ms and 78 beats/min.

The mean ± SD change in QTc (Bazett formula) interval from baseline to the beginning of the maintenance period was −1.7 ms ± 16.8 ($n = 60$). At the start of the extension period, the change in QTc was 0.1 ± 16.2 ms ($n = 47$), and at the last visit the mean change was −1.2 ms ± 19.0 ($n = 68$). During the treatment period, the mean changes from baseline in PR interval ranged from 9.6 ms ± 14.2 to 14.8 ms ± 15.6. These ECG changes were not associated with cardiac-related adverse events.

### 3.3. Efficacy

Lacosamide administration was associated with sustained and significant reductions in the average daily Likert pain scale scores through all phases of treatment (Table 1). From a mean baseline Likert pain scale score of 5.65 ± 2.53, lacosamide produced an average reduction of 57% (−3.23 ± 2.26) by the end of the maintenance phase. This pattern of pain reduction was sustained through the extension period with a mean reduction of 3.10 ± 2.38 ($P < 0.001$) in Likert pain scale scores.

Significant mean reductions from baseline were recorded for each of the lacosamide 200, 300, and 400 mg/day dosages during each treatment phase and overall for the entire treatment period. Based on patient diary entries, response in the evening hours was equal in magnitude to the response in the morning.

Neuropathic Pain Scale evaluation showed that significant improvements occurred with lacosamide 400 mg/day (Table 2) in 7 of the 10 items compared with baseline. Similar level of significant improvement was recorded for all lacosamide doses considered together in seven of the ten items of the scale. Significant improvement was also seen for the domain "intensity" on lacosamide 200 and 300 mg/day doses. The mean scores in the case of NPS items "coldness" and "itchiness" were not reduced.

Based on changes from baseline in overall pain score assessed using a visual analog scale (VAS), improvement with lacosamide occurred at all tested doses. The mean reduction for the all patients

**Table 2**
Changes from baseline in Neuropathic scale

| Neuropathic pain scale items | Lacosamide | | | |
|---|---|---|---|---|
| | 200 mg/day | 300 mg/day | 400 mg/day | All doses |
| *Intensity* | | | | |
| Mean ± SD | −2.1 ± 2.4 | −3.8 ± 3.3 | −2.2 ± 3.0 | −2.2 ± 2.9 |
| *n* = | 9 | 6 | 32 | 50 |
| *P* value | 0.028 | 0.036 | <0.001 | <0.001 |
| *Sharpness* | | | | |
| Mean ± SD | −2.1 ± 2.6 | −2.7 ± 3.4 | −2.0 ± 2.9 | −1.9 ± 2.9 |
| *n* = | 8 | 6 | 32 | 49 |
| *P* value | 0.057 | 0.116 | <0.001 | <0.001 |
| *Hotness* | | | | |
| Mean ± SD | −1.3 ± 2.8 | −1.3 ± 4.0 | −1.5 ± 2.9 | −1.2 ± 3.0 |
| *n* = | 9 | 6 | 32 | 50 |
| *P* value | 0.189 | 0.449 | 0.007 | 0.0056 |
| *Dullness* | | | | |
| Mean ± SD | −1.3 ± 1.8 | −3.0 ± 3.6 | −1.3 ± 3.1 | −1.4 ± 2.9 |
| *n* = | 9 | 6 | 32 | 50 |
| *P* value | 0.0573 | 0.099 | 0.027 | 0.002 |
| *Coldness* | | | | |
| Mean ± SD | −1.0 ± 2.1 | 0.2 ± 3.9 | −0.6 ± 2.5 | −0.6 ± 2.5 |
| *n* = | 9 | 6 | 32 | 50 |
| *P* value | 0.195 | 0.92 | 0.161 | 0.119 |
| *Sensitivity* | | | | |
| Mean ± SD | −1.2 ± 3.0 | −2.3 ± 3.5 | −1.8 ± 2.8 | −1.5 ± 2.9 |
| *n* = | 9 | 6 | 32 | 50 |
| *P* value | 0.255 | 0.164 | 0.001 | <0.001 |
| *Itchiness* | | | | |
| Mean ± SD | −0.6 ± 1.2 | −0.7 ± 3.1 | −0.5 ± 2.3 | −0.5 ± 2.1 |
| *n* = | 9 | 6 | 32 | 50 |
| *P* value | 0.215 | 0.625 | 0.252 | 0.092 |
| *Unpleasantness* | | | | |
| Mean ± SD | −1.3 ± 2.4 | −3.5 ± 3.4 | −2.2 ± 2.5 | −2.0 ± 2.6 |
| *n* = | 9 | 6 | 32 | 50 |
| *P* value | 0.134 | 0.053 | <0.001 | <0.001 |
| *Intensity of deep pain* | | | | |
| Mean ± SD | −1.7 ± 2.3 | −2.8 ± 3.4 | −2.4 ± 2.7 | −2.2 ± 2.6 |
| *n* = | 9 | 6 | 32 | 50 |
| *P* value | 0.066 | 0.099 | <0.001 | <0.001 |
| *Intensity of surface pain* | | | | |
| Mean ± SD | −2.2 ± 2.2 | −2.7 ± 3.1 | −1.4 ± 2.4 | −1.6 ± 2.5 |
| *n* = | 9 | 6 | 32 | 50 |
| *P* value | 0.017 | 0.087 | 0.002 | <0.001 |

SD = standard deviation.
*P*-values are from paired t-tests and are not adjusted for multiplicity.

**Table 1**
Changes from baseline in Likert pain scale scores

| Likert pain scale scores | | Lacosamide | | | |
|---|---|---|---|---|---|
| | | 200 mg/day | 300 mg/day | 400 mg/day | All doses |
| Titration phase | Mean ± SD | −2.16 ± 1.32 | −3.77 ± 1.37 | −2.62 ± 1.79 | −2.62 ± 1.75 |
| | *n* = | 13 | 12 | 34 | 62 |
| | *P* value | <0.001 | <0.001 | <0.001 | <0.001 |
| Maintenance phase | Mean ± SD | −2.27 ± 1.31 | −4.16 ± 1.98 | −3.27 ± 2.55 | −3.23 ± 2.26 |
| | *n* = | 13 | 12 | 31 | 56 |
| | *P* value | <0.001 | <0.001 | <0.001 | <0.001 |
| Extension phase | Mean ± SD | −2.44 ± 2.32 | −3.78 ± 2.55 | −3.19 ± 2.40 | −3.10 ± 2.38 |
| | *n* = | 10 | 6 | 26 | 42 |
| | *P* value | 0.009 | 0.015 | <0.001 | <0.001 |
| Entire treatment period | Mean ± SD | −2.31 ± 2.02 | −3.79 ± 2.40 | −3.15 ± 2.27 | −2.94 ± 2.31 |
| | *n* = | 13 | 12 | 34 | 62 |
| | *P* value | 0.001 | <0.001 | <0.001 | <0.001 |

Baseline Likert pain scale score was 5.65 ± 2.53 ($n = 64$).
SD = standard deviation.
*P*-values are from paired t-tests and are not adjusted for multiplicity.

at the end of titration was 34.8 ± 21.9, at the end of maintenance was 37.7 ± 21.3, and at the end of extension was 36.5 ± 25.1. Over the entire treatment period, the reduction in the visual analog scale score was 34.2 ± 24.7 compared with baseline.

At the end of three months of treatment with lacosamide, 61% (34/56) of patients reported feeling "much better" as assessed by Patient's Global Impression of Change in pain (PGIC), compared with baseline. At the end of the 20-week maintenance phase, 59% of patients continued to report feeling "much better". Of the 52 patients completing the PGIC assessment at termination visit, 43 patients (83%) reported feeling mildly, moderately, or much better throughout the trial. Clinical Global Impression of Change in pain (CGIC) evaluation by investigators showed that at the end of the maintenance period 58% (26/45) of patients were assessed as being "much better" than at baseline.

Reductions in the mean Likert scale rating for patient's perception of pain interference with average sleep, compared with baseline, were 2.63 ± 1.72 at the end of titration, 3.18 ± 2.30 at the end of maintenance, 3.12 ± 2.37 at the end of the extension phase, and 2.93 ± 2.32 over the entire treatment period. Analysis of Likert scale rating of patient's perception of pain interference with activity showed a reduction of 2.43 ± 1.83 at the end of titration, 2.97 ± 2.33 at the end of maintenance, 2.87 ± 2.59 at end of extension, and 2.78 ± 2.42 for the entire treatment period.

Significant improvement in the SF-36 Quality of Life scores (Table 3) occurred in the domain "bodily pain" ($P < 0.001$) on all doses of lacosamide. Large improvements were also seen in SF-36 domains of "physical functioning" ($P = 0.027$), and "vitality" ($P = 0.02$). Improvement in the domain "social functioning" was significant in the 400 mg/day modal dose group ($P = 0.018$).

## 4. Discussion

Prolonged exposure to lacosamide, up to a mean of 450.1 days ± 314.50, in patients with chronic painful diabetic peripheral neuropathy did not give rise to any evidence of drug-related long-term safety issues of clinical concern. The most frequently reported adverse events were headache, upper respiratory tract infection, arthralgia, sinusitis, nasopharyngitis, and back pain. These are often encountered in patients with multiple chronic disorders when followed up over a long period. Most reports of adverse events were mild or moderate in intensity. Dizziness, somnolence, weight gain, and peripheral edema are often seen with AEDs (Vinik, 2005; Wong et al., 2007; Gidal, 2006; Freynhagen et al., 2005; Raskin et al., 2004; Putzke et al., 2002). In this trial, the incidence of somnolence was low and there was no overall change in body weight. AEDs associated with weight gain are gabapentin, pregabalin, valproic acid, and vigabatrin and possibly, carbamazepine (Ben-Menachem, 2007). Lacosamide appears to be a weight-neutral AED. Adverse events most commonly reported in shorter duration (10- to 20-week) double-blind trials with lacosamide in painful diabetic peripheral neuropathy included headache, dizziness, nausea, fatigue, and tremor (Rauck et al., 2007; Wymer et al., 2007). Chronic therapy with lacosamide in this trial was not associated with any new type of side effect.

Lacosamide generally had no clinically important effects on laboratory or vital sign variables. As with other AEDs that have been reported to increase PR interval, such as pregabalin and lamotrigine, a small increase in PR interval was seen with lacosamide. Similar changes have been reported in other lacosamide trials (Bialer et al., 2007). The potential risk of the small increase in PR interval appears to be small and was not associated with cardiac-related adverse events. Evaluation of ECG data did not show any clear tendency for lacosamide to prolong QTc interval or cause associated effects on repolarization. Earlier, in a QTc trial conducted in healthy human subjects receiving multiple oral doses of 400 mg/day or 800 mg/day lacosamide, no evidence of association between lacosamide and QTc prolongation or morphological changes was observed (Thomas et al., 2007).

Pain reduction on lacosamide began early in the titration period and was sustained throughout the (over 2-year) trial duration. The

**Table 3**
Changes from baseline in Quality of Life Scores at last visit

| SF-36 Quality of Life Domains | | Lacosamide | | | |
|---|---|---|---|---|---|
| | | 200 mg/day | 300 mg/day | 400 mg/day | All doses |
| Physical functioning Baseline 49.3 ± 24.6 (n = 67) | Mean ± SD | 4.1 ± 12.4 | 9.1 ± 13.4 | 3.2 ± 16.8 | 4.4 ± 15.1 |
| | n = | 11 | 11 | 37 | 62 |
| | *P* value | NS | 0.48 | NS | 0.027 |
| Role – physical Baseline 49.3 ± 24.6 (n = 67) | Mean ± SD | 1.6 ± 27.5 | 5.7 ± 24.3 | 5.1 ± 22.6 | 4.6 ± 23.1 |
| | n = | 12 | 11 | 37 | 63 |
| | *P* value | NS | NS | NS | NS |
| Bodily pain Baseline 41.9 ± 17.9 (n = 67) | Mean ± SD | 14.0 ± 17.9 | 15.2 ± 16.9 | 10.4 ± 16.7 | 11.1 ± 17.0 |
| | n = | 12 | 11 | 37 | 63 |
| | *P* value | 0.02 | 0.014 | < 0.001 | < 0.001 |
| General health Baseline 50.7 ± 20.7 (n = 66) | Mean ± SD | −1.3 ± 10.4 | 0.4 ± 14.7 | −0.5 ± 13.8 | −0.3 ± 12.9 |
| | n = | 12 | 11 | 36 | 62 |
| | *P* value | NS | NS | NS | NS |
| Vitality Baseline 44.6 ± 23.2 (n = 66) | Mean ± SD | 2.6 ± 15.4 | 11.4 ± 15.3 | 6.1 ± 20.2 | 5.5 ± 18.4 |
| | n = | 12 | 11 | 36 | 62 |
| | *P* value | NS | 0.033 | NS | 0.02 |
| Social functioning Baseline 65.7 ± 27.6 (n = 67) | Mean ± SD | 1.0 ± 22.3 | −1.1 ± 17.2 | 9.5 ± 23.3 | 5.4 ± 21.8 |
| | n = | 12 | 11 | 37 | 63 |
| | *P* value | NS | NS | 0.018 | 0.056 |
| Role – emotional Baseline 70.3 ± 30.8 (n = 67) | Mean ± SD | −7.6 ± 14.0 | 2.3 ± 22.4 | 7.0 ± 23.4 | 2.8 ± 21.7 |
| | n = | 12 | 11 | 37 | 63 |
| | *P* value | NS | NS | NS | NS |
| Mental health Baseline 71.8 ± 21.2 (n = 66) | Mean ± SD | −3.8 ± 19.3 | −3.3 ± 16.1 | 3.3 ± 17.1 | 0.7 ± 17.1 |
| | n = | 12 | 11 | 36 | 62 |
| | *P* value | NS | NS | NS | NS |

SD = Standard Deviation.
*P*-values are from paired t-tests and are not adjusted for multiplicity.

efficacy results are supported by the significant clinical benefits measured by changes in VAS, sleep and general activity, Neuropathic Pain Scale scores, PGIC, CGIC, and quality of life assessment. Results derived from NPS in this study indicate that lacosamide may have a beneficial effect on multiple pain sensations associated with diabetic neuropathic pain with 7 of the 10 NPS items showing significant improvement from baseline. The SF-36 quality of life assessment suggests that lacosamide may help patients in a number of domains with significant improvement over baseline recorded in "bodily pain," "physical functioning," and "vitality."

Overall, the side effect profile observed in this 2-year trial was comparable to that observed in the earlier double-blind 10-week duration trial (Rauck et al., 2007). The long-term open-label design of this trial mimics clinical practice with dose adjustments permitted as needed. The results support the thesis that lacosamide attenuates the pain of diabetic peripheral neuropathy, is well-tolerated, helps improve some domains of quality of life variables, and is suitable for long-term use in patients with painful diabetic peripheral neuropathy.

## 5. Sponsorship

The authors acknowledge the contributions that Barabara Stegman, MD, PhD; Kenneth Sommerville, MD; Christine Rauschkolb, MD, PhD; Patrick Liu, PhD; David Sen, PhD; Cindy Garrison; and Wendy Frye made in assisting with the design of the trial and providing clinical and statistical oversight. Jennifer Kemp, PhD, and Jyoti Nandi, MD, PhD, assisted with medical writing services, and Allison Coppola provided editorial assistance on behalf of SCHWARZ BIOSCIENCES, UCB Group, RTP, NC, USA.

SCHWARZ BIOSCIENCES, UCB Group, RTP, NC, USA provided the trial supplies, sponsored, and funded the trial.

## Acknowledgements

The authors wish to acknowledge all members participating in this SP665 study who contributed materially to the total data generated for this trial and which form the basis for the contents of this manuscript by their participation and, caring for patients according to the approved protocol: M. Backonja, Madison, WI; D. Cantrell, Irving, TX; B.B. Cleeremans, Irvine, CA; S.E. Clevinger, Ocala, FL; J.A. Dicke, Baltimore, MD; K.R. Edwards, Bennington, VT; G. Gerard, Toledo, OH; R.J. Graf, Tacoma, WA; R.P. Hull, Huntsville, AL; L.C. Kirby, Peoria, AZ; E.C. La Cava, Kirkland, WA; L. Loman, New Port Richey, FL; M.A. McClanahan, Fredericksburg, VA; E. Michna, Boston, MA; M.D. Mollen, Phoenix, AZ; J.T. Perkins, Crestview Hills, KY; R.W. Richter, Tulsa, OK; C.N. Sang, Boston, MA; S.L. Schwartz, San Antonio, TX; J.J. Shelmet, Lawrenceville, NJ; R.P. Singer, Plantation, FL; R.J. Tanenberg, Greenville, NC; R.L. Weinstein, Walnut Creek, CA; J. Wymer, Albany, NY; A.A. Zayed, Anniston, AL; and L. Zemel, Denver, CO.

The authors acknowledge the contribution made by participating patients and their families.

## References

Attal N, Cruccu G, Haanpää M, Hansson P, Jensen TS, Nurmikko T, et al. EFNS guidelines on pharmacological treatment of neuropathic pain. Eur J Neurol 2006;13(11):1153–69.

Ben-Menachem E. Weight issues for people with epilepsy – a review. Epilepsia 2007;48(Suppl 9):42–5.

Beyreuther B, Callizot N, Stöhr T. Antinociceptive efficacy of lacosamide in a rat model for painful diabetic neuropathy. Eur J Pharmacol 2006;539(1-2):64–70.

Beyreuther BK, Freitag J, Heers C, Krebsfänger N, Scharfenecker U, Stöhr T. Lacosamide: a review of preclinical properties. CNS Drug Rev 2007;13(1):21–42.

Bialer M, Johannessen SI, Kupferberg HJ, Levy RH, Loiseau P, Perucca E. Progress report on new antiepileptic drugs: a summary of the Sixth Eilat Conference (EILAT VI). Epilepsy Res 2002;51:31–71.

Bialer M, Johannessen SI, Kupferberg HJ, Levy RH, Perucca E, Tomson T. Progress report on new antiepileptic drugs: a summary of the eighth Eilat Conference (EILAT VIII). Epilepsy Res 2007;73(1):1–52.

Boulton AJ, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, et al. Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care 2005;28:956–62.

Campbell JN, Meyer RA. Mechanisms of neuropathic pain. Neuron 2006;52(1):77–92.

Collins SD, Chessell IP. Emerging therapies for neuropathic pain. Expert Opin Emerging Drugs 2005;10(1):95–108.

Dworkin RH, Backonja M, Rowbotham MC, Allen RR, Argoff CR, Bennett GJ, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. Arch Neurol 2003;60:1524–34.

Freynhagen R, Strojek K, Griesing T, Whalen E, Balkenohl M. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. Pain 2005;115:254–63.

Gidal BE. New and emerging treatment options for neuropathic pain. Am J Manag Care 2006;12(9 Suppl):S269–78.

Horstmann R, Bonn R, Cawello W, Doty P, Rudd D. SPM 927 does not interact with valproic acid and carbamazepine. Epilepsia 2003;44(suppl 9):97. Abstract.

Jensen TS, Backonja MM, Hernández Jiménez S, Tesfaye S, Valensi P, Ziegler D. New perspectives on the management of diabetic peripheral neuropathic pain. Diab Vasc Dis Res 2006;3(2):108–19.

Kropeit D, Scharfenecker U, Schiltmeyer B, Koch B, Rudd D, Cawello W, et al. Lacosamide has low potential for drug–drug-interaction. J Pain 2006;7(4):S63. Abstract.

McCleane G, Koch B, Rauschkolb C. Does SPM 927 have an analgesic effect in human neuropathic pain? An open label study. Neurosci Lett 2003;352:117–20.

McCleane G, Koch B, Rauschkolb C. A report of continuing analgesia after 12 months treatment with SPM 927 in six subjects with neuropathic pain. J Neuropathic Pain Symptom Palliation 2005;1(1):25–8.

Putzke JD, Richards JS, Kezar L, Hicken BL, Ness TJ. Long-term use of gabapentin for treatment of pain after traumatic spinal cord injury. Clin J Pain 2002;18:116–21.

Raskin P, Donofrio PD, Rosenthal NR, Hewitt DJ, Jordan DM, Xiang J, et al. Topiramate vs placebo in painful diabetic neuropathy: analgesic and metabolic effects. Neurology 2004;63:865–73.

Rauck RL, Shaibani A, Biton V, Simpson J, Koch B. Lacosamide in painful diabetic peripheral neuropathy: a phase 2 double-blind placebo-controlled study. Clin J Pain 2007;23:150–8.

Schiltmeyer B, Kropeit D, Cawello W, Hammes W, Horstmann R. No interaction between lacosamide and metformin. In: 11th World Congress on Pain, August 21–26, Sydney, Australia; 2005.

Schmader KE. Epidemiology and impact on quality of life of postherpetic neuralgia and painful diabetic neuropathy. Clin J Pain 2002;18:350–4.

Thomas D, Zisowsky J, Horstmann R. Lacosamide demonstrates no potential for QTc-prolongation. Eur J Pain 2007;11(1):84–5. Abstract.

Vinik A. Clinical review: use of antiepileptic drugs in the treatment of chronic painful diabetic neuropathy. J Clin Endocrinol Metab 2005;90:4936–45.

Wong MC, Chung JW, Wong TK. Effects of treatments for symptoms of painful diabetic neuropathy: systematic review. BMJ 2007;335(7610):87.

Wymer J, Ziegler D, Sommerville K, Bongardt S, Shaibani A. Lacosamide in patients with painful diabetic neuropathy: a summary of adverse events in four double-blind randomized clinical trials. In: Tenth international conference on the mechanisms and treatment of neuropathic pain, Salt Lake City, Utah; 2007.