Efficacy and Safety of Lacosamide in Painful Diabetic Neuropathy

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OBJECTIVE — To evaluate efficacy and safety of lacosamide compared with placebo in painful diabetic polyneuropathy.

RESEARCH DESIGN AND METHODS — Diabetic patients with at least moderate neuropathic pain were randomized to placebo or lacosamide 400 (in a slow or standard titration) or 600 mg/day over 6-week titration and 12-week maintenance periods. Primary efficacy criterion was intra-individual change in average daily Numeric Pain Rating Scale score from baseline to the last 4 weeks.

RESULTS — For the primary end point, pain reduction was numerically but not statistically greater with lacosamide compared with placebo (400 mg/day, $P = 0.12$; 600 mg/day, $P = 0.18$). Both doses were significantly more effective compared with placebo over the titration ($P = 0.03$, $P = 0.006$), maintenance ($P = 0.01$, $P = 0.005$), and entire treatment periods ($P = 0.03$, $P = 0.02$). Safety profiles between titration schemes were similar.

CONCLUSIONS — Lacosamide reduced neuropathic pain and was well tolerated in diabetic patients, but the primary efficacy criterion was not met, possibly due to an increased placebo response over the last 4 weeks.

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Up to one in four patients with diabetes may be affected by chronic diabetic painful neuropathy (DPN) (1,2) and suffer substantial morbidity and impaired quality of life (3). Because the current treatment options are limited, there is continued need for new therapeutic approaches (3,4). Lacosamide is an anticonvulsant with a unique mode of action, selectively enhancing slow inactivation of voltage-gated sodium channels (5–8). This trial was one of three similarly designed placebo-controlled, parallel-group trials to evaluate the efficacy of lacosamide in DPN (9,10) using 400 mg/day (two titration schemes) and 600 mg/day.

RESEARCH DESIGN AND METHODS

— This trial (SP743, ClinicalTrials.gov identifier NCT00238524), conducted December 2003 to January 2005 at 52 European sites, was approved by Institutional Review Boards and met with the International Conference on Harmonisation–Good Clinical Practice (ICH-GCP) guidelines and local laws. All patients signed written informed consent before participation.

Study population

Eligibility criteria were as follows: patients aged ≥18 years with type 1 or type 2 diabetes, symptomatic DPN for 6 months to 5 years (score ≥4 on an 11-point Numeric Pain Rating Scale [NPRS]), and A1C <12%). Exclusion criteria are described in supplemental Appendix A, which is available online at http://care.diabetesjournals.org/cgi/content/full/dc09-1578/DC1. Concomitant acetaminophen ≤2 g/day was permitted as rescue medication.

Trial design

This 18-week, double-blind, placebo-controlled trial began with a 1-week washout and a 1-week baseline period for pain assessments. Eligible patients were randomized (1:2:2) to placebo or oral lacosamide, 400 or 600 mg/day, and then entered a 6-week titration period followed by a 12-week maintenance period. To ensure blinding, trial medication and packaging were identical in appearance, and all dosing was twice daily. The 400 mg/day group was further randomized to receive slow titration (100 mg/day for 3 weeks, followed by weekly increases of 100 mg/day, to 400 mg/day target dose at week 6) or a standard titration (100 mg/day, with weekly increases of 100 mg/day, to 400 mg/day target dose for titration weeks 4–6). The 600 mg/day group followed standard titration increasing by 100 mg/day each week. No back titration was allowed.

Outcomes

The primary outcome was intra-individual change in average daily (24-h) pain score (11-point NPRS; 0 = no pain, 10 = worst possible pain) from baseline to average score over the last 4 weeks of the maintenance period. Secondary measures included within-subject change in average daily pain score from baseline to each trial period (titration, maintenance, and entire treatment). Additional secondary measures are described in supplemental Appendix A. Safety evaluations on all patients receiving one or more doses of trial medication (safety set) included adverse

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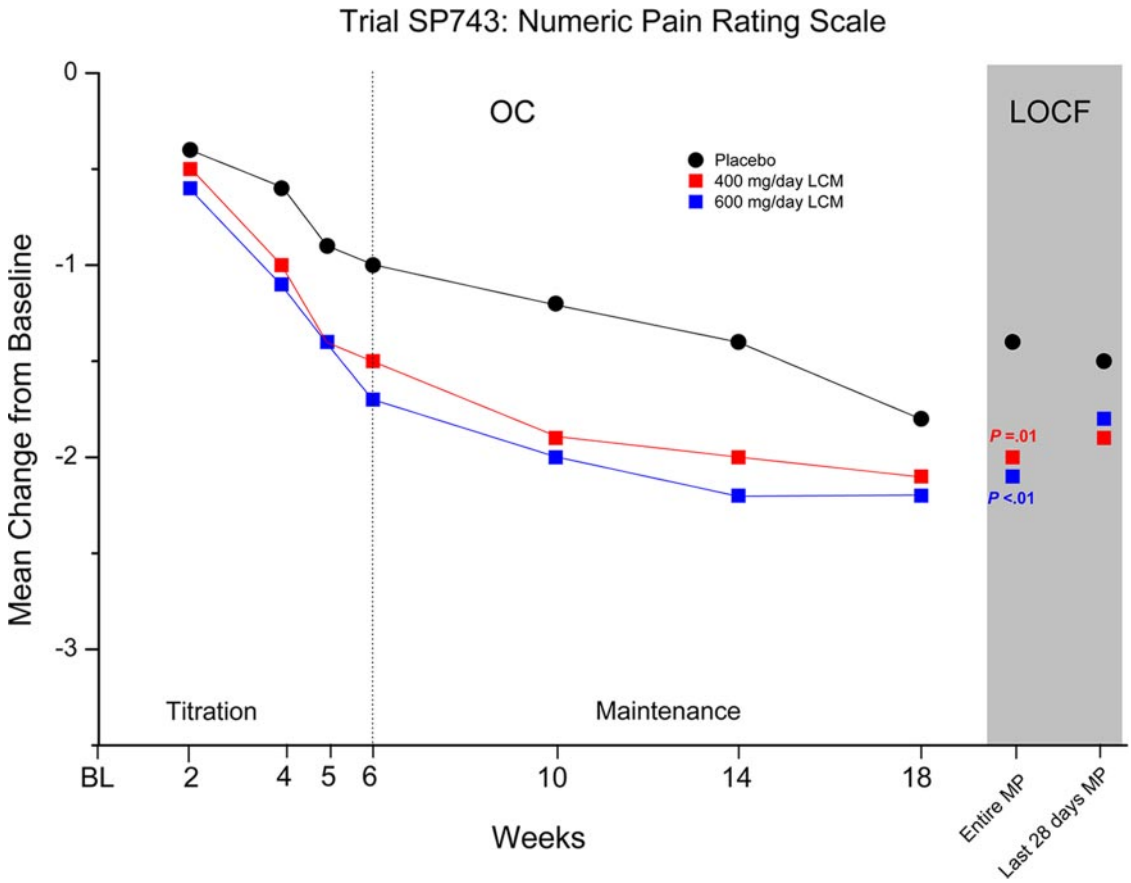

Figure 1—*Mean change from baseline in average daily pain score at each trial visit (weeks 2, 4, 5, 6, 10, 14, and 18) for observed cases (OC: patients still in the trial at the time of the clinic visit or during that visit interval) and last observation carried forward (LOCF). BL, baseline; LCM, lacosamide; MP, maintenance period.*

event reporting, withdrawals, clinically relevant laboratory changes, 12-lead electrocardiogram, vital signs, and physical and neurological examinations. Statistical methods are described in supplemental Appendix A.

RESULTS — Of 513 patients screened, 357 were randomized and received one or more doses of trial medication, 355 comprised the ITT population, and 246 completed the trial (CONSORT diagram shown in supplemental Appendix Figure B1). All groups showed similar demographic and baseline characteristics, although numerically, more patients in the placebo group reported severe pain (NPRS ≥8) at baseline (supplemental Appendix Table B1). Medical history and concomitant diseases were similar across treatment groups and were as expected in a DPN population. Concomitant medication use was similar across groups.

Reductions in average daily pain scores from baseline to the last 4 weeks of the maintenance period (primary end point) were greater in both the lacosamide 400 and 600 mg/day groups compared with placebo, although differences were not statistically significant, possibly related to increased placebo effect toward the end of the trial ($P = 0.12$, $P = 0.18$; Fig. 1). However, both lacosamide doses were significantly more effective than placebo in reducing average daily pain scores when assessed for the titration period ($P = 0.03$, $P < 0.01$) and maintenance period ($P = 0.01$, $P < 0.01$), and entire treatment period (titration period + maintenance period; $P = 0.03$, $P = 0.02$; detailed description provided in supplemental Appendix Table C1).

In addition to the consistency of effect on NPRS scores through the total treatment period with lacosamide, persistent and clinically relevant effects were observed for the secondary efficacy measures such as patients' perceptions of pain using the Visual Analog Scale (VAS), the Patients' Global Impression of Change (PGIC), and pain interference with sleep and activity (supplemental Appendix C). Generally, pain reductions were only slightly higher in the lacosamide 600 mg/day group than the lacosamide 400 mg/day group and may have been affected by higher dropout rates and less tolerability with the 600 mg/day dose.

Adverse events occurring in ≥5% of lacosamide-treated patients included dizziness, fatigue, nausea, vertigo, headache, and vomiting; except for fatigue, these adverse events appeared to be dose related (supplemental Appendix Table D1). Changes in laboratory variables, vital signs, body weight, and findings from physical and neurological examinations revealed no issues of clinical concern. Adverse event incidence was similar between the 400 mg/day slow and standard titration groups during the titration period (slow, 46% [35/77]; standard, 49% [36/73]). Adverse events resulting in withdrawal occurred at an incidence of 13.0% versus 8.2% for the 400 mg/day standard and slow titration groups, respectively.

CONCLUSIONS — In this trial, lacosamide did not result in statistically significant pain reductions over placebo for the primary outcome. However, lacos-

amide showed a durability of effect that was sustained and significantly greater than placebo through the titration, maintenance, and entire treatment periods. Persistent and clinically relevant effects were also observed for the secondary efficacy measures (PGIC, VAS, and pain interference with sleep and activity). Titration schemes did not affect tolerability.

The increased placebo response observed at the end of the maintenance period, with almost a quarter of the placebo group experiencing a ≥50% reduction in pain score in the last 4 weeks, may have contributed to the lack of statistical significance in the primary end point. High placebo responses are not unusual in neuropathic pain studies (11–14). Because of the relatively long titration, this trial is among the longest conducted in patients with DPN. In trials of DPN, placebo response does not plateau, but increases over time, such that longer trials are at greater risk for decreased separation of drug effect from placebo (14).

In conclusion, lacosamide resulted in numerically greater pain reductions over placebo, but for the primary efficacy variable of change in average pain score from baseline to the last 4 weeks of maintenance period, the differences were not statistically significant, possibly related to a marked increase in placebo response during the last 4 weeks of the trial.

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APPENDIX — Members of the SP743 multicenter trial team include the following: C. Mathieu, Leuven, Belgium; L. Van Gaal, Antwerp, Belgium; F. Duyck, Roeselare, Belgium; A. Verhaegen, Merksem, Belgium; B. Vets, Bonheiden, Belgium; J. Hovorka, Prague, Czech Republic; R. Mazanec, Prague, Czech Republic; D. Dolezil, Ostrava-Poruba, Czech Republic; P. Valensi, Bondy, France; C. Le Devehat, Nevers, France; L. Geffray, Lisieux, France; J. von Hubbenet, Hamburg, Germany; J. Jansen, Berlin, Germany; C. Klein, Künzing, Germany; T. Drescher, Stuhr-Brinkum, Germany; A. Herzner, Hamburg, Germany; R. Bodenschatz, Mittweida, Germany; A. Pfeiffer, Berlin, Germany; R. Nischik, Leipzig, Germany; B. Bergtholdt, Berlin, Germany; E. Boenninghoff, Beckum, Germany; H. Stahl, Leipzig, Germany; A. Holst, Hamburg, Germany; P. Franz, Berlin, Germany; R. Lehmann, Berlin, Germany; G. Jermendy, Budapest, Hungary; G. Winkler, Budapest, Hungary; V. Spallone, Roma, Italy; G. Comi, Milan, Italy; J. Banga, Utrecht, the Netherlands; A. Mikolajczyk-Swatko, Lodz, Poland; W. Fryze, Gdansk, Poland; M. Arciszewska, Bialystok, Poland; E. Semetkowska-Jurkiewicz, Gdansk, Poland; M. Polaszewska-Muszynska, Bydgoszcz, Poland; J. Skowron, Częstochowa, Poland; D. Cheta, Bucharest, Romania; N. Hancu, Cluj-Napoca, Romania; C. Ionescu-Tirgoviste, Bucharest, Romania; G. Negriçsanu, Timisoara, Romania; N. Verbovaya, Samara, Russia; A. Zalevskaya, St. Petersburg, Russia; A. Ametov, Moscow, Russia; I. Dedov, Moscow, Russia; M. Ansiferov, Moscow, Russia; F.J. Salvador Rodriguez, Pamplona, Spain; A. Baksi, Newport, U.K.; D. Price, Swansea, U.K.; K. Simpson, Leeds, U.K.; and G. Rayman, Ipswich, U.K.

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