Efficacy and Safety of Lacosamide in Painful Diabetic Neuropathy

Running Title: Lacosamide in painful diabetic neuropathy

Dan Ziegler, MD, FRCPE a; Tibor Hidvégi, MD b; Irina Gurieva, MD c; Sabine Bongardt, MS d; Rainer Freynhagen, MD e; David Sen, PhD f; Kenneth Sommerville, MD f, On behalf of the lacosamide SP743 Study Group*

*Members of the SP743 study group are listed within the Acknowledgment section

a. Institute for Clinical Diabetology, German Diabetes Center at the Heinrich Heine University, Leibniz Center for Diabetes Research and Department of Metabolic Diseases, University Hospital, Düsseldorf, Germany
b. Petz Aladár County Teaching Hospital, Department of Metabolism and Diabetes, Győr, Hungary
c. Federal State Institution, Federal Bureau Medical Social Expertise, Moscow, Russia
d. Schwarz Pharma, AG, UCB Group, Monheim, Germany
e. Department of Anaesthesiology, Critical Care Medicine, Pain Therapy & Palliative Care, Pain Center Lake Starnberg, Benedictus Krankenhaus, Tutzing, Germany
f. Schwarz Biosciences, Inc., UCB Group, Research Triangle Park, NC, USA

Corresponding Author:
Prof. Dan Ziegler, FRCPE
E-mail: dan.ziegler@ddz.uni-duesseldorf.de

Clinical trial reg. no. NCT00238524; (www.clinicaltrials.gov)

Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org

Submitted 24 August 2009 and accepted 3 January 2010.

This is an uncopiedited electronic version of an article accepted for publication in Diabetes Care. The American Diabetes Association, publisher of Diabetes Care, is not responsible for any errors or omissions in this version of the manuscript or any version derived from it by third parties. The definitive publisher-authenticated version will be available in a future issue of Diabetes Care in print and online at http://care.diabetesjournals.org.
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 600mg/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 endpoint, pain reduction was numerically but not statistically greater with lacosamide compared with placebo (400mg/day, \( P=0.12 \); 600mg/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.
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). Since 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 400mg/day (two titration schemes) and 600mg/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 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 2 diabetes, symptomatic DPN for 6 months to 5 years (score ≥4 on an 11-point Numeric Pain Rating Scale [NPRS]), and HbA1c<12%). Exclusion criteria are described in Online Appendix-A which is available at http://care.diabetesjournals.org. Concomitant acetaminophen ≤2g/day was permitted as rescue medication.

Trial Design  This 18-week double-blind, placebo-controlled trial began with a 1-week wash-out and a 1-week baseline period for pain assessments. Eligible patients were randomized (1:2:2) to placebo or oral lacosamide 400 or 600mg/day, then entered a 6-week titration period (TP) followed by a 12 week maintenance period (MP). To ensure blinding, trial medication and packaging were identical in appearance, and all dosing was twice-daily. The 400mg/day group was further randomized to receive slow titration (100mg/day for 3 weeks, followed by weekly increases of 100mg/day, to 400mg/day target dose at week 6) or a standard titration (100mg/day, with weekly increases of 100mg/day, to 400mg/day target dose for titration weeks 4-6). The 600mg/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-hour) pain score (11-point NPRS; 0 = no pain, 10 = worst possible pain) from baseline to average score over the last 4 weeks of the MP. 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 Online Appendix-A. Safety evaluations on all patients receiving ≥1 dose of trial medication (safety set [SS]) included adverse event (AE) reporting, withdrawals, clinically relevant laboratory changes, 12-lead ECG, vital signs, and physical and neurological examinations. Statistical methods are described in Online Appendix-A.

RESULTS

Of 513 patients screened, 357 were randomized and received ≥1 dose of trial medication, 355 comprised the ITT population, and 246 completed the trial (CONSORT diagram shown in Online 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 (Online 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 MP (primary endpoint) were greater in both the lacosamide 400 and 600mg/day groups compared with placebo, although differences were not statistically significant, possibly related to increased placebo effect towards the end of the trial ($P=0.12, P=0.18$; Figure 1). However, both lacosamide doses were significantly more effective than placebo in reducing average daily pain scores when assessed for the TP ($P=0.03, P<0.01$) and MP ($P<0.01$), and entire treatment period (TP+MP; $P=0.03, P=0.02$; detailed description provided in Online 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 VAS, PGIC, and pain interference with sleep and activity (Online Appendix-C). Generally, pain reductions were only slightly higher in the lacosamide 600mg/day group than the lacosamide 400mg/day group and may have been impacted by higher drop-out rates and less tolerability with the 600mg/day dose.

AEs occurring in $\geq 5\%$ of lacosamide-treated patients included dizziness, fatigue, nausea, vertigo, headache, and vomiting; except for fatigue, these appeared to be dose-related (Online Appendix Table D1). Changes in laboratory variables, vital signs, body weight, and findings from physical and neurological examinations revealed no issues of clinical concern. AE incidence was similar between the 400mg/day slow and standard titration groups during the TP (slow, 46% [35/77]; standard, 49% [36/73]). AEs resulting in withdrawal occurred at an incidence of 13.0% versus 8.2% for the 400mg/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, lacosamide 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 MP, with almost a quarter of the placebo group experiencing a $\geq 50\%$ reduction in pain score in the last 4 weeks, may have contributed to the lack of statistical significance in the primary endpoint. High placebo responses are not unusual in neuropathic pain studies (11-14). Due to 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 MP, the differences were not statistically significant, possibly related to a marked increase in placebo response during the last 4 weeks of the trial.

**ACKNOWLEDGMENTS**

The authors acknowledge the contributions made by members of the SP743 multicenter trial team: 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, Lodz, Poland; W. Fryze, Gdansk, Poland; M. Arciszewska, Bialystok, Poland; E. Semetkowska-Jurkiewicz, Gdansk, Poland; M. Polaszewska-Musznyska, Bydgoszcz, Poland; J. Skowron, Częstochowa, Poland; D. Cheta, Bucharest, Romania; N. Hancu, Cluj-Napoca, Romania; C. Ionescu-Tirgoviste, Bucharest, Romania; G. Negrișanu, 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, United Kingdom; D. Price, Swansea, United Kingdom; K. Simpson, Leeds, United Kingdom; and G. Rayman, Ipswich, United Kingdom.

Barbara Stegmann, MD, PhD, Brigitte Koch, PhD, Stephan Thierfelder, PhD, Christine Rauschkolb, MD, PhD, and David Sen, PhD, assisted with the design of the trial and provided clinical and statistical oversight. On behalf of the sponsor, Jennifer Kemp, PhD, and Heather Bell, MSc, helped draft the manuscript and Andrea Eggert, PharmD, BCPP and Allison Coppola provided editorial assistance. Prescott Medical Communications Group provided editorial and formatting assistance. SCHWARZ PHARMA AG, UCB Group, Monheim, Germany provided the trial supplies, and SCHWARZ BIOSCIENCES, GmbH, UCB Group, Monheim, Germany sponsored and funded the trial.

Disclosure: In the past three years, Dr. Ziegler has received research support, consulting, or speaking fees from Lilly, Boehringer, Pfizer, Meda, Merck, Bayer, Nycomed, Grünenthal, Sanofi-Aventis, Eisai, Mundipharma, and Schwarz Pharma/UCB Group and Dr. Freyhagen from Grünenthal, Jansen-Cilag, Lilly/Boehringer, Mundipharma, Organon, Pfizer, and Schwarz Pharma/UCB Group. Kenneth Sommerville, MD is presently Vice President of Clinical Development at King Pharmaceuticals and has been in the position since March, 2008. King Pharmaceuticals is a publicly traded US corporation actively engaged in the development and sale of specialty branded pharmaceutical products, including products indicated for the treatment of pain. Dr. Sommerville was an employee of the sponsor through the duration of the trial. Dr. Gurieva has received research support, consulting, or speaking fees from Lilly, Pfizer, Meda, Pliva, Woervag Pharma, Nycomed, Sanofi-Aventis, and Schwarz Pharma/UCB Group. Dr. Hidvegi has no conflicts to disclose. Sabine Bongardt, MS, and David Sen are employees of the sponsor.

Figure Legends
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).
REFERENCES
Figure

Trial SP 743: Numeric Pain Rating Scale

Mean Change from Baseline

OC
- Placebo
- 400 mg/day LCM
- 600 mg/day LCM

P < .01

Weeks
BL  2  4  5  6  10  14  18

Titration  Maintenance

End MP
Last 28 days MP