Clinical Trial Results: A Randomized, Double-Blind, Placebo-Controlled, Trial of a Three-Day Bupivacaine Patch (ELADUR™) in Patients with Post-Herpetic Neuralgia

Wallace MS, Kudrow DB, McElveen WA, Drass MJ, Webster LR, Huddlestone JJ, Reynolds LW, Lissin DV, Langecker P.

Introduction

ELADUR™ is a flexible, rectangular shaped, skin-friendly, breathable, drug-in-adhesive matrix transdermal delivery system, 140 cm² (10 cm x 14 cm), containing amino-amide type local anesthetic (bupivacaine), designed for a 3-day duration of pain relief. The product was developed by DURECT Corporation and is intended for topical treatment of acute and chronic pain conditions. Presented data was generated in a phase II proof-of-principle trial in patients with Post-Herpetic Neuralgia (PHN).

Methodology

Study design: randomized, double-blind, placebo-controlled, cross-over, multicenter trial in patients with PHN affecting large dermatome(s) to assess safety, characteristics of the analgesic benefit of ELADUR as compared to placebo. Eligible subjects received 2 treatments in a randomly assigned sequence: one treatment with 3 ELADUR patches and one treatment with 3 placebo patches. Each treatment period lasted 3 days with a washout period of 3 to 14 days between treatment periods to allow the patient’s pain intensity to return to the baseline level (between 4 and 9 on the 11-point Pain Intensity Numeric Rating Scale) prior to application of the second set of patches. Subjects had no change in prescribed analgesic medications (including anticonvulsants and tricyclic antidepressants) for 7 days prior to randomization and received no investigational topical or systemic preparations for 30 days prior to randomization.

Sample size and demographics: 60 patients were randomized (31 to ELADUR/placebo sequence, 29 to placebo/ELADUR sequence), 55 completed treatment: 3 discontinued due to AEs and 2 due to patient decision. Mean age was 71.1 years (range 50 to 90) and there were 34 (57%) females and 26 (43%) males.

Endpoints:

- mean daily pain intensity (average of 3 daily measurements), the proportion of patients achieving at least 20% pain intensity improvement (the mean Neuropathic Pain Questionnaire (NPQ) scores, rescue medication usage, patch adherence, adverse events (AEs), clinical laboratory evaluations, vital signs, electrocardiograms (ECGs), physical examinations, and dermal response evaluation.

Statistical methods: The mean change in daily pain intensity (relative to baseline) was analyzed using a repeated-measures analysis of variance (ANOVA) based on the Grizzle model with treatment, sequence, and treatment, sequence, and period as factors. The proportion of patients achieving at least a 20% improvement in pain intensity relative to baseline, mean total NPQ scores, rescue medication (converted into morphine-equivalent dose amounts), and function of the patches (evaluated on a 0 to 7 categorical scale for patch adherence) were summarized using descriptive statistics by treatment and analyzed similarly to the primary endpoint.

Safety Results

The application of the patches was well tolerated throughout the study and no clinically significant safety concerns were identified. Adverse events were reported for 49% of patients during placebo application and 38% during ELADUR. There were no notable differences in AEs between the treatments and no AEs were classified as related to study treatment. All AEs with frequency higher than 5% are presented in the table below. Most events were mild or moderate in severity.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Placebo (n=55)</th>
<th>ELADUR (n=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>4 (7.0%)</td>
<td>3 (5.2%)</td>
</tr>
<tr>
<td>Application Site Pruritus</td>
<td>4 (7.0%)</td>
<td>3 (5.2%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (1.8%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Systemic Bupivacaine Exposure</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overall skin irritation was minimal. No patient removed ELADUR due to an adverse dermal response. Presence of bupivacaine in the applied patches did not result in increased skin irritation scores.

Conclusions

- ELADUR patches demonstrated greater analgesic activity compared to placebo patches when applied over affected dermatome(s) in patients with PHN.
- There were no differences in plasma bupivacaine concentrations between treatments for clinical laboratory evaluations, vital signs, physical examination findings, ECGs, and dermal response evaluation after the patches were removed.

Systemic Bupivacaine Exposure: No signs of cardiovascular or CNS toxicity were observed following ELADUR treatment. Bupivacaine plasma concentrations after application of 3 ELADUR patches are expected to be below 100 ng/mL, based on previous pharmacokinetic studies, i.e. at least 20 times lower than reported toxic levels (2,000 – 4,000 ng/mL).

Dermal response is assessed for all patients immediately after removal of the patches at the end of each study treatment. A specific numerical scoring system on a scale of 0-7 was used. A score of 0 means “no evidence of skin irritation”. A score of 7 means “strong reaction spreading beyond test site”. For the Neuropathic Pain Questionnaire (NPQ), consisting of 12 pain descriptors rated on a 0-100 scale (Kravitz SJ, Backhorst MM. 2003), the mean composite score at baseline was 45.9 for placebo and 46.0 for ELADUR. Treatment with ELADUR resulted in greater reduction of the daily NPQ score by Day 2 and 3, where mean change from baseline was -8.8 and -8.3 for placebo and -125.1 and -134.3 for ELADUR. Although the improvement was not statistically significant, a trend for greater reduction with longer ELADUR treatment is encouraging for the potential benefit of repeated applications.

Overall pain intensity was assessed using a pain intensity scale of 0-10. The change from baseline at Day 3 was -5.8 for placebo and -6.3 for ELADUR. A score of 0 means “no pain”. A score of 10 means “worst pain imaginable”. The mean pain intensity change for placebo was -5.8 and -6.3 for ELADUR. Although the improvement was not statistically significant, a trend for greater reduction with longer ELADUR treatment is encouraging for the potential benefit of repeated applications.

For the Neuraxial Pain Questionnaire (NPQ) and the Neuropathic Pain Questionnaire (NPQ), consisting of 12 pain descriptors rated on a 0-100 scale (Kravitz SJ, Bakhorst MM. 2003), the mean composite score at baseline was 45.9 for placebo and 46.0 for ELADUR. Treatment with ELADUR resulted in greater reduction of the daily NPQ score by Day 2 and 3, where mean change from baseline was -8.8 and -8.3 for placebo and -125.1 and -134.3 for ELADUR. Although the improvement was not statistically significant, a trend for greater reduction with longer ELADUR treatment is encouraging for the potential benefit of repeated applications.

Dermal response is assessed for all patients immediately after removal of the patches at the end of each study treatment. A specific numerical scoring system on a scale of 0-7 was used. A score of 0 means “no evidence of skin irritation”. A score of 7 means “strong reaction spreading beyond test site”. For the Neuropathic Pain Questionnaire (NPQ), consisting of 12 pain descriptors rated on a 0-100 scale (Kravitz SJ, Bakhorst MM. 2003), the mean composite score at baseline was 45.9 for placebo and 46.0 for ELADUR. Treatment with ELADUR resulted in greater reduction of the daily NPQ score by Day 2 and 3, where mean change from baseline was -8.8 and -8.3 for placebo and -125.1 and -134.3 for ELADUR. Although the improvement was not statistically significant, a trend for greater reduction with longer ELADUR treatment is encouraging for the potential benefit of repeated applications.

Overall pain intensity was assessed using a pain intensity scale of 0-10. The change from baseline at Day 3 was -5.8 for placebo and -6.3 for ELADUR. A score of 0 means “no pain”. A score of 10 means “worst pain imaginable”. The mean pain intensity change for placebo was -5.8 and -6.3 for ELADUR. Although the improvement was not statistically significant, a trend for greater reduction with longer ELADUR treatment is encouraging for the potential benefit of repeated applications.

For the Neuropathic Pain Questionnaire (NPQ), consisting of 12 pain descriptors rated on a 0-100 scale (Kravitz SJ, Bakhorst MM. 2003), the mean composite score at baseline was 45.9 for placebo and 46.0 for ELADUR. Treatment with ELADUR resulted in greater reduction of the daily NPQ score by Day 2 and 3, where mean change from baseline was -8.8 and -8.3 for placebo and -125.1 and -134.3 for ELADUR. Although the improvement was not statistically significant, a trend for greater reduction with longer ELADUR treatment is encouraging for the potential benefit of repeated applications.

Overall pain intensity was assessed using a pain intensity scale of 0-10. The change from baseline at Day 3 was -5.8 for placebo and -6.3 for ELADUR. A score of 0 means “no pain”. A score of 10 means “worst pain imaginable”. The mean pain intensity change for placebo was -5.8 and -6.3 for ELADUR. Although the improvement was not statistically significant, a trend for greater reduction with longer ELADUR treatment is encouraging for the potential benefit of repeated applications.