



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

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The American Pain Society, 27th Annual Meeting
Tampa, FL, USA
Poster # 273, May 8, 2008, 4:45-6:15 PM

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 use per application. ELADUR 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 effect and utility 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. Study 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.

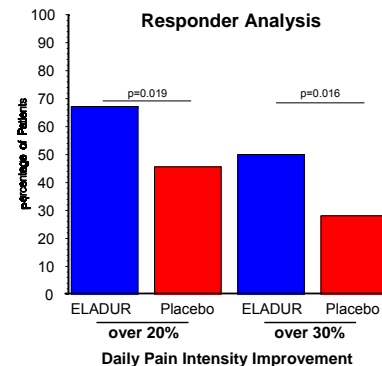
Sample size and demographics: 60 patients were randomized (31 to ELADUR/placebo sequence, 29 to placebo/ELADUR sequence), 55 completed treatment; 3 discontinued due to AEs and 2 due to patient decision. Mean age was 71.1 years (range 50 to 90) and there were 34 (57%) females and 26 (43%) males.

Endpoints: mean daily pain intensity (average of 3 daily measurements), the proportion of patients achieving at least 20% pain intensity improvement, the mean total 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 functionality 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.

Analgesic Activity

A reduction of **mean daily pain intensity** was observed in favor of ELADUR treatment compared with placebo. This improvement was sustained across all study days. The proportion of patients achieving at least 20% pain intensity improvement on any treatment day was significantly higher for ELADUR treatment than for placebo, 67.2% (39/58) compared with 45.6% (26/57) in the ITT population ($p = 0.019$). A proportion of patients with greater than 30% improvement of daily pain intensity was also significantly greater for ELADUR ($p=0.016$). Both responder analyses are presented in the graph below, demonstrating an added benefit of bupivacaine in the patch formulation after a single application.



For the **Neuropathic Pain Questionnaire (NPQ)**, consisting of 12 pain descriptors rated on 0-100 scale (Krause SJ, Backonja MM. 2003), the mean composite score at baseline was 459.4 for placebo and 460.4 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 -86.8 and -84.3 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.

Application of ELADUR or placebo patches did not result in increase of daily pain and did not require a change of stable daily dose of analgesic medications.

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.

System Organ Class	Placebo (n=57)	Eladur (n=58)
APPLICATION SITE ERYTHEMA	12 (21.1 %)	11 (19.0 %)
APPLICATION SITE PRURITUS	4 (7.0 %)	3 (5.2 %)
ERYTHEMA	4 (7.0 %)	5 (8.6 %)
HEADACHE	4 (7.0 %)	3 (5.2 %)
DIZZINESS	3 (5.3 %)	1 (1.7 %)

Two patients experienced serious AEs (SAEs), atrial fibrillation and a road traffic accident; both SAEs occurred on placebo treatment and were considered unrelated to study drug. Three patients discontinued due to AEs, one during placebo treatment due to dizziness, another during placebo treatment due to headache, and one during ELADUR treatment due to mental status changes and frustration. There were no clinically relevant findings or differences 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".

	Placebo (n=55)	ELADUR (n=58)
Mean	0.9	0.6
Median	1	0
SDEV	0.93	0.82
P-value	NS	

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.

Patch Adherence and Wearability

Patch adherence to the skin was evaluated by 0-7 categorical scale, where 0= fully unadhered and 7= fully adhered patch. The mean patch adherence scores were similar with both treatments and decreased slightly over time.

	Mean Placebo (n=57)	Mean Eladur (n=58)	Difference in Means Eladur-Placebo (95% CI)
Day 1	6.43	6.20	-0.05 (-0.44, +0.20)
Day 2	5.92	5.77	-0.10 (-0.50, +0.30)
Day 3	5.60	5.25	-0.35 (-0.90, +0.23)

ELADUR patches were well adhered during normal activities which included daily showers. No significant mass transfer effects were noted (residual adhesive on skin). No patches fell off or needed to be reapplied.

Conclusions

- ELADUR patches demonstrated greater analgesic activity compared to placebo patches when applied over affected dermatome(s) in patients with PHN.
- The difference between treatments in the proportion of patients with $\geq 20\%$ and $\geq 30\%$ pain improvement was statistically significant in favor of ELADUR.
- A reduction of pain by a single application of ELADUR was observed and sustained across all study days.
- ELADUR demonstrated good dermal compatibility. The 3-day wearing period on the affected sensitive skin areas was well tolerated and resulted in no significant skin irritation. Therefore, continuous ELADUR therapy with flexible application schedule appears feasible.
- Excellent adherence qualities were observed as patients were able to undertake normal daily activities, including exposure to water during showers.
- Further studies are planned to investigate multiple repeated applications of ELADUR.

For information regarding ELADUR clinical development, please contact:

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