Clinical Trial Results Summary
Study EN3220-009

Study Number: EN3220-009	
Title of Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of Lidocaine Patch 5% Alone, Gabapentin Alone, and Lidocaine Patch 5% and Gabapentin in Combination for the Relief of Pain in Patients with Diverse Peripheral Neuropathic Pain Conditions	
Investigators: 6 investigators	
Study Centers: 12 centers in the United States	
Publication (reference): None	
Study Period (years): Date of First Enrollment: January 6, 2003 Date of Last Patient Visit: June 19, 2003	**Phase of Development:** Phase IV
Objectives: Primary: To assess the comparative efficacy and safety of Lidoderm® monotherapy versus gabapentin monotherapy in a diverse group of peripheral neuropathic pain patients. Secondary: To assess the comparative efficacy and safety of the combination group versus each of the monotherapy groups and to assess the efficacy and safety of Lidoderm (lidocaine patch 5%) versus placebo in a diverse group of peripheral neuropathic pain patients.	
Methodology: At the screening visit (Visit 1), patients began the 2- to 14-day washout period, during which the following medications were discontinued: muscle relaxants, benzodiazepines, anticonvulsants, tricyclic antidepressants, opioid analgesics, antivirals, topical analgesics (e.g., Capsaicin), dextromethorphan, and non-steroidal anti-inflammatory drugs (NSAIDs). During the washout period, patients recorded their average daily pain intensity in a diary and returned to the clinic for their baseline visit once their pain had reached >4/10 on an 11-point scale. At the baseline visit (Visit 2), eligible patients were randomized into one of four treatment groups: placebo capsules + placebo patch (Placebo Group), placebo capsules + Lidoderm patch (Lidocaine Group), Gabapentin capsules 1800 mg/day + placebo patch (Gabapentin Group), or Gabapentin capsules 1800 mg/day + Lidoderm patch (Combination Group). Patients were treated for 5 weeks, the first week of which was used to titrate patients up to 1800 mg/day of gabapentin as specified in the product labeling. The Placebo and Lidocaine Groups received a sham dose increased during the same study period. Patients returned to the clinic weekly during the 5-week treatment period for measurements of efficacy, quality of life (QOL), and safety.	
Number of Subjects Planned and Analyzed: Planned: Approximately 60 patients (15 per treatment arm) Enrolled: 62 patients (16 Placebo, 14 Lidocaine, 16 Gabapentin, and 16 Combination) Intent-to-Treat Population (for efficacy analyses): 60 patients (15 Placebo, 13 Lidocaine, 16 Gabapentin, and 16 Combination) Treated Population (for safety analyses): 62 patients (16 Placebo, 14 Lidocaine, 16 Gabapentin, and 16 Combination)	
Diagnosis and Main Criteria for Inclusion: Males or females, 18 years of age or older, with a diagnosis of postherpetic neuralgia (PHN), diabetic neuropathy (DN), complex regional pain syndrome (CRPS), carpal tunnel syndrome, HIV neuropathy, idiopathic sensory neuropathy, or other peripheral neuropathy. During the baseline week, patients reached an average daily pain rating greater than 4 on	

the 0-to-10 numerical pain rating scale (Question 5 of the Brief Pain Inventory [BPI]), they entered the Titration Phase of the study.

Test Product, Dose and Mode of Administration, Batch Number(s):

Lidoderm (lidocaine patch 5%), up to four patches applied topically once daily (q24h) to the area of maximal peripheral pain; lot number 51292

Other Therapy, Dose and Mode of Administration, Batch Number(s):

Gabapentin 300 mg capsules for oral dosing at a dose of 1800 mg/day; lot number 08232.02 (capsule lot no. 10302V)

Reference Therapy, Dose and Mode of Administration, Batch Number(s):

Placebo to match lidocaine patch; up to four patches applied topically once daily (q24h) to the area of maximal peripheral pain; lot number 51291

Placebo capsules to match gabapentin for oral dosing; lot number 08232.01

Duration of Treatment: 5 weeks

Criteria for Evaluation:

Efficacy: Average daily pain intensity (BPI Questions 3, 4, 5, and 6), Pain Quality Assessment Scale (PQAS), Investigator and Patient Global Impression of Change, and allodynia testing.

Safety: Adverse events (AEs), dermal assessments/sensory testing, clinical laboratory tests, vital sign measurements, and physical/neurological examination.

QOL: Symptom Checklist, pain interference with QOL (BPI Question 9), Patient Global Impression of Treatment Satisfaction, disability assessment, and Percent Pain Relief (BPI Question 8)

Statistical Methods:

Efficacy: Endpoints from BPI and PQAS were analyzed using analysis of covariance (ANCOVA) model with treatment as effect and baseline as the covariate. Arithmetic mean change from baseline and p-values from the ANCOVA were presented for these parameters. For Patients who discontinued early, the last observation was carried forward for the analysis. Descriptive statistics were performed for Patient and Investigator Global Impression of Change and allodynia testing.

Safety: The frequency of treatment-emergent AEs (TEAEs), treatment-related TEAEs, and TEAEs by intensity were tabulated by MedDRA® term and body system. Serious adverse events (SAEs) and discontinuations due to AEs were summarized. All clinical laboratory measurements were summarized by mean values, changes from baseline, and shift changes. Vital signs, physical/neurological examinations, and dermal/sensory assessments were summarized.

QOL: BPI Question 9, the Patient Global Assessment of Treatment Satisfaction, and Percent Pain Relief (BPI Question 8) were summarized. BPI Question 9 was analyzed similarly to the BPI Questions 3, 4, 5, and 6: an ANCOVA model with treatment as the effect with baseline as the covariate. The Global Assessment of Treatment Satisfaction was summarized descriptively by presenting the number and percentage of patients' responses in each treatment group. Percent Pain Relief (BPI Question 8) was analyzed similarly to BPI Question 9. The Symptom Checklist and disability assessments were summarized descriptively.

SUMMARY:

Efficacy Results:

There were no statistically-significant differences between treatment groups for the Intent-to-Treat (ITT) population in any of the efficacy parameters other than the PQAS score for the "Itchy" and "Dull" qualities. For the "Itchy" quality, there was a statistically significantly (p-value=0.045) greater improvement for the Combination Group (-2.6) versus the Lidocaine Group (–0.7) in the mean change from baseline to Day 35. For the same time period, there also was a statistically significantly (p-value=0.043) greater improvement in the Combination Group (–2.8) versus the placebo group (–1.5) for the "Dull" quality.

The mean change in daily pain intensity (from study visit data) from baseline (Day 0) to Day 35 (end of study) ranged from –2.8 (Lidocaine) to –4.4 (Combination) for Worst Pain, from –1.1 (Gabapentin) to -2.9 (Placebo) for Least Pain, –2.3 (Gabapentin) to –3.1 (Combination) for Pain on Average, and –2.2 (Lidocaine) to –2.9 (Combination) for Pain Now.

The Combination Group showed the greatest improvement from baseline at all time points for each PQAS composite score with mean changes from baseline to Day 35 (end of study) ranging from –42 (Placebo) to –58 (Combination) for PQAS 18, from –48 (Placebo) to –65 (Combination) for PQAS 20, and from –10 (Placebo and Lidocaine) to -14 (Combination) for PQAS 4.

A larger percentage of investigators rated change in pain as either minimally, much, or very much improved in the Lidocaine Group (93%) than in the Combination (82%), Gabapentin (79%), or Placebo (64%) Groups. A similar pattern was seen for patient assessments.

In allodynia testing, the greatest improvement from baseline to the end of study was seen in the Lidocaine Group (mean change of -1.5) compared with the Placebo (-0.4), Gabapentin (-0.8), and Combination (-0.6) Groups. At the end of study, most patients reported no change in skin sensation in all treatment groups (range: 56% in the Gabapentin Group to 80% in the Placebo Group).

Safety Results:

Overall, 61 (98.4%) of 62 patients reported at least one TEAE. The percentages of patients with AEs were similar across treatment groups. Across the treatment groups, the most frequently reported TEAEs were fatigue, dizziness (excluding vertigo), weakness, somnolence, dry mouth, appetite decreased, nausea, confusion, and vision blurred. These events all occurred at similar frequencies in each of the groups, except vision blurred, which was less frequent in the Lidocaine Group (2/14 patients, 14.3%) compared with the other groups (8/16 patients, 50.0% in the Placebo and Combination Groups and 12/16 patients, 75.0% in the Gabapentin Group). Most patients had AEs that were considered treatment related.

No deaths occurred in this study. One SAE (hemorrhagic stroke) was reported by Patient 001-023 (Lidocaine Group). Of the 62 treated patients, 16 (25.8%) discontinued due to AEs, including 1 (6.3%) in the Placebo, 3 (21.4%) in the Lidocaine, 6 (37.5%) in the Gabapentin, and 6 (37.5%) in the Combination Groups.

No clinically important changes or trends in laboratory tests, vital signs, physical examinations, neurological examinations, dermal assessments, or sensory assessments occurred during the study.

Quality of Life Results:

On the Symptom Checklist, the symptoms most frequently rated ≥2 were fatigue and drowsiness in all groups. The percentage of patients rating these symptoms ≥2 generally decreased over the course of the study in each group. At Weeks 1 and 2, the mean scores for both of these symptoms were somewhat higher in the Lidocaine, Gabapentin, and Combination Groups compared with the Placebo Group; however, mean scores were similar in all groups at Weeks 3, 4, and 5.

On the BPI Question 9, statistically significantly greater improvement was seen in the mean change from baseline to the end of study for walking ability in the Lidocaine Group (-3.5) compared with the Gabapentin Group (-1.4; p-value =0.033).

At Week 5, a greater percentage of patients reported being either "Satisfied" or "Very Satisfied" regarding their treatment in the Lidocaine and Combination Groups (69% in each group) than in the Placebo Group (64%) or Gabapentin Group (65%).

At each post-baseline disability assessment, most patients reported having either no disabilities or mild disabilities. In each group, the percentage of patients reporting no disabilities increased over the course of the study.

The percent pain relief (as assessed by BPI Question 8) increased from baseline to the end of study in all treatment groups with the greatest increase in pain relief seen in the Combination Group (mean change of 50.0% at end of study) compared with the Placebo (26.4%), Lidocaine (39.2%), and Gabapentin (43.6%) Groups.