Study Number: EN3272-301	
Title of Study: A Randomized, Double-Blind Study Comparing the Safety and Efficacy of the Lidocaine Patch 5% With Placebo in Patients With Pain From Carpal Tunnel Syndrome	
Investigators: 64 investigators (44 with enrolled patients)	
Study Centers: 76 study centers	
Publication (reference): none	
Study Period (years): November 28, 2005 – January 4, 2007	**Phase of Development:** IIIB

Objectives:

Primary Objective: To compare the efficacy of the lidocaine patch 5% with that of a placebo patch in the treatment of moderate to severe pain associated with mild to moderate carpal tunnel syndrome (CTS), as measured by the worst daily pain intensity score (using Brief Pain Inventory [BPI] Question 3) recorded on an 11-point scale (range 0 to 10).

Secondary Objectives:

- To compare the efficacy of the lidocaine patch 5% with that of a placebo patch as measured by:
  - Least and average daily pain intensities (BPI Questions 4 and 5)
  - The Levine CTS Symptom Severity Scale
  - The Pain Quality Assessment Scale (PQAS)
  - Patient and Investigator Global Impression of Change
  - Patient and Investigator Global Assessment of Treatment Satisfaction
- To compare the effects of lidocaine patch 5% with those of a placebo patch on the quality of life, as assessed by:
  - Pain interference with the quality of life (BPI Question 9)
  - The Quality of Sleep (QoS)
  - The Levine CTS Functional Status Scale
- To compare the safety and tolerability of the lidocaine patch 5% with that of a placebo patch in patients with mild to moderate CTS.

Methodology: This randomized, double-blind, placebo-controlled, parallel-group study was conducted at 76 investigational sites in the United States in patients with moderate-to-severe pain associated with mild-to-moderate CTS. The study design included a 3- to 7-day, open-label placebo run-in period followed by an 8-week, randomized, double-blind treatment period.

At the screening visit (Day –7), patients with bilateral CTS identified the "index" wrist (ie, the more painful wrist), which was subsequently to be the wrist used for all efficacy assessments throughout the study; however, patients were to treat both wrists with study drug. Patients who met eligibility criteria at the screening visit entered an open-label placebo run-in period, during which they used a placebo patch on each affected wrist. Patients participated in the placebo run-in period for a minimum of 3 days up to a maximum of 7 days, during which time they recorded daily pain intensity scores for the index wrist in an electronic diary upon awakening in the morning. Worst, average and least daily pain intensity were rated using an 11-point scale (range 0 to 10). Patients were permitted to use up to 400 mg/day ibuprofen (supplied by the patient) as rescue medication.

Patients returned for the baseline visit and were randomized to double-blind treatment as soon as the worst daily pain intensity score for the index wrist was >5 (using BPI Question 3) for 3 out of 5 consecutive days. At the baseline visit, patients were randomly assigned to receive either the lidocaine patch 5% or a matching placebo patch for 8 weeks. For patients with bilateral CTS, the same

randomized treatment was applied to both wrists during the double-blind treatment period; however, only the index wrist was assessed for efficacy. Safety assessments were conducted on both treated wrists.

During the 8-week double-blind treatment period, patients recorded daily pain intensity scores for the index wrist using the electronic diary each morning upon awakening. Patients visited the clinic at Weeks 2, 4, and 8 for additional efficacy and safety assessments. Rescue medication of up to 400 mg/day ibuprofen (supplied by the patient) was allowed on no more than 1 day/week for non-CTS pain and for not more than 2 doses/week for CTS-related pain.

Number of Subjects Planned and Analyzed:
Planned: 310 patients

Analyzed: A total of 210 patients were enrolled, randomized, and included in the safety analyses.

Diagnosis and Main Criteria for Inclusion: Males and females with a confirmed diagnosis of mild to moderate CTS in one or both wrists and worst daily pain intensity >5 (using BPI Question 3) on approximately 75% of days over the previous 3 months.

Test Product, Dose and Mode of Administration, Batch Number(s): Lidoderm® (lidocaine patch 5%), 1 patch applied topically to the volar aspect of each affected wrist daily, 2-4 hours before bedtime, Lot number 24092

Reference Therapy, Dose and Mode of Administration, Batch Number(s): Placebo patch, 1 patch applied topically to the volar aspect of each affected wrist daily, 2-4 hours before bedtime, Lot number 24061

Duration of Treatment: 8 weeks

Criteria for Evaluation:

Safety: Adverse events (AEs), discontinuations due to AEs, physical examination results, vital signs, clinical laboratory tests, electrocardiograms (ECGs), Muscle Weakness examination, Nerve Conduction Velocity Testing (NCVT), dermal sensory testing, and dermal assessments

Efficacy: The primary efficacy endpoint that was to be assessed was the mean worst daily pain intensity score by using BPI Question 3.

Statistical Methods:

Safety: All treated patients were included in the safety analyses. Adverse events were coded by system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA, version 6.1). The number and percentage of patients experiencing at least one AE were summarized overall, by SOC, and by preferred term. Serious adverse events (SAEs) and discontinuations due to AEs were summarized separately. Nerve conduction tests were summarized by means, standard deviations, medians, minimums and maximums, and change from screening. Muscle Weakness examinations and skin sensory tests were summarized by percentage and change from baseline. Dermal assessments were summarized by percentage. Vital signs were summarized by means, standard deviations, medians, minimums and maximums, and change from baseline. The results of clinical laboratory tests and physical examinations were presented in a listing.

Efficacy: The planned primary analysis planned was an analysis of covariance (ANCOVA) comparing the mean worst daily pain intensity scores between the two treatment groups.

SUMMARY:

Safety Results: Overall, 10/210 (4.8%) patients experienced at least 1 treatment-emergent adverse event (TEAE) during the placebo run-in period. During the double-blind treatment period, 37/104 (35.6%) patients in the lidocaine patch 5% group and 36/106 (34.0%) patients in the placebo patch group experienced at least 1 TEAE. The most frequently reported TEAEs overall during the placebo run-in

period were those associated with the nervous system (2/210; 1.0%) and skin and subcutaneous tissue body systems (2/210; 1.0%). The most frequently reported TEAEs overall during the double-blind treatment period were infections and infestations (11/104 or 10.6% in the lidocaine patch 5% group and 12/106 or 11.3% in the placebo patch group) and general disorders and administration site conditions (16/104 or 15.4% in the lidocaine patch 5% group and 5/106 or 4.7% in the placebo patch group). There were no serious TEAEs reported during the placebo run-in period. During the double-blind treatment period, 2/104 (1.9%) patients in the lidocaine patch 5% group and 1/106 (0.9%) patients in the placebo patch group experienced at least 1 SAE. Six of 104 (5.8%) patients in the lidocaine patch 5% group and 4/106 (3.8%) patients in the placebo patch group discontinued due to AEs.

There was little change from screening on the NCVTs and little change from baseline on the Muscle Weakness examination. A majority of patients at baseline and end of study (EOS) were able to detect pinprick and light touch in the dermal sensory evaluations.

In the dermal assessments, 8/104 (7.7%) patients in the lidocaine patch 5% group and 3/106 (2.8%) patients in the placebo patch group experienced papules. Vesicles were reported by 2/104 (1.9%) patients in the lidocaine patch 5% group and 1/106 (0.9%) patients in the placebo patch group. No patients experienced erythema graded >2 on the cutaneous AE categoric scale. Edema graded >2 did not occur in any patient in the lidocaine patch 5% group and occurred in only 2/106 (1.9%) patients in the placebo patch group.

Only 1 patient in the lidocaine patch 5% group had a clinically significant laboratory test that resulted in the patient's removal from the study. The patient had an elevated creatinine clearance before study drug was administered that was significantly higher than the normal range. The same patient also had an ECG result of a slight inferior repolarization disturbance that was considered to be of clinical significance. No other clinically significant changes in laboratory results, vital signs, or the physical examination were observed.

Efficacy Results: A planned per protocol blinded interim analysis was performed to verify that the selected sample size was sufficient to demonstrate a difference in the study population between the two groups. This methodology was employed because there is no literature to support expected effect sizes or interindividual variability in this condition, as placebo-controlled, 8-week studies had not been previously performed.

The results of this blinded interim analysis indicated that the sample size that would be required to show a statistically significant difference between the two treatments groups was far larger than was initially expected. Due to the results of the interim analysis and the fact that the screen failure rate was higher than was initially anticipated, the study was terminated early and no final efficacy analysis was performed.