

Clinical Trial Results Summary  
Study EN3220-012

<b>Study Number:</b> EN3220-012	
<b>Title of Study:</b> A Randomized, Open-Label Study Comparing the Efficacy and Safety of Lidocaine Patch 5% With Celecoxib 200 mg in Patients With Pain From Osteoarthritis of the Knee	
<b>Investigators:</b> 16 investigators in the United States (US), 14 of whom enrolled patients	
<b>Study Centers:</b> Multicenter study conducted at 16 sites in the US, 14 of which enrolled patients	
<b>Publication (reference):</b> None	
<b>Study Period (years):</b> Date of First Patient Enrollment: June 11, 2004 Date of Last Patient's Last Visit: November 11, 2004	<b>Phase of Development:</b> IV
<b>Objectives:</b> The primary objective of the study was to assess the efficacy of lidocaine patch 5% compared with celecoxib 200 mg in treating pain from osteoarthritis (OA) of the knee. A secondary objective was to assess the safety and tolerability of lidocaine patch 5% compared with celecoxib 200 mg. The secondary efficacy objectives are not presented in this report.	
<p><b>Methodology:</b> This randomized, open-label, active-controlled, parallel-group study was conducted at multiple investigational sites in patients with moderate-to-severe pain from OA of one or both knees. At the screening visit (Day -14), patients provided written informed consent and completed all screening evaluations, including the identification of the index joint, i.e., the knee to be used for all OA pain assessments throughout the study. (For patients with OA of both knees, the index joint was the knee with more severe pain.)</p> <p>Patients who met eligibility criteria entered a washout period for up to 14 days and discontinued the use of all analgesic medications, chondroitin, and glucosamine. (Patients were permitted to use a stable dose of aspirin daily for cardiac prophylaxis.) Patients recorded average daily pain intensity in the index joint in a diary at bedtime. Site personnel contacted patients at least every other day (via telephone) to monitor average daily pain intensity scores, adverse events (AEs), and to ensure that analgesic medications were not being used.</p> <p>When patients' average daily pain intensity score was 5 or greater (on a scale of 0 to 10 using Question 5 of the Brief Pain Inventory [BPI]) for 3 days out of the 5 consecutive days immediately prior to the baseline visit, and they had an OA severity score of 7 or greater (on a composite scale of 0 to 24 using the Index of Severity for Osteoarthritis of the Knee), baseline procedures were conducted. After all baseline assessments were completed, eligible patients were randomly allocated to receive one of two treatments for 12 weeks: lidocaine patch 5% or celecoxib 200 mg daily.</p> <p>Patients returned to the study site at Weeks 2, 4, 6, and 8 for study assessments and again at Week 12 for end of study (EOS) assessments.</p> <p>This study was terminated early by the sponsor because of recently identified safety concerns with the COX-2 specific inhibitor class of drug. Because the study was terminated early and planned enrollment was not reached, only an abbreviated data presentation is included in this clinical study report (CSR). The abbreviated data presentation comprises descriptive statistics and analysis results for the primary efficacy endpoint; the analysis was conducted using data from completers only (i.e., 12 weeks of treatment) who met the criteria for the Intent-to-Treat and/or Efficacy Evaluable populations. Data from all patients who received at least one dose of study medication are included in the analysis of safety.</p>	

**Number of Subjects Planned and Analyzed:**

Planned: Approximately 200 patients (100 per treatment)

Entered Washout: 166 patients

Randomized to Treatment: 143 (69 lidocaine, 74 celecoxib)

Analyzed for efficacy based on:

- Efficacy Evaluable Completer Population: 63 (24 lidocaine, 39 celecoxib)
- Intent-to-Treat (ITT) Completer Population: 73 (27 lidocaine, 46 celecoxib)

Analyzed for Safety based on Treated Population: 143 (69 lidocaine, 74 celecoxib)

**Diagnosis and Main Criteria for Inclusion:** Patients 18 years of age or older who were in generally good health with unilateral or bilateral OA of the knee diagnosed according to the American College of Rheumatology (ACR) criteria based on clinical and radiographic evidence of OA (presence of osteophytes on x-ray and written evaluation) and who had a functional capacity class rating of I, II, or III according to ACR classification.

**Test Product, Dose and Mode of Administration, Batch Number(s):** Lidocaine patch 5% (Lidoderm<sup>®</sup>, Endo Pharmaceuticals Inc.), 1½ patches applied topically to each affected knee every 24 hours (q24h), lot number 5321

**Reference Therapy, Dose and Mode of Administration, Batch Number(s):** Celecoxib (Celebrex<sup>®</sup>, G.D. Searle & Co., Chicago, IL), one 200 mg oral capsule QD, lot number C300608

**Duration of Treatment:** 12 weeks

**Criteria for Evaluation:** For this abbreviated CSR, the primary efficacy endpoint and all safety assessments are presented.

Primary Efficacy Endpoint

- Mean change from baseline to Week 12 in Western Ontario and McMaster Universities OA Index (WOMAC) pain subscale score

Safety

- AEs
- Dermal assessment (lidocaine group only)
- Skin sensory testing (lidocaine group only)
- Clinical laboratory test results, including urinalysis
- Vital sign measurements
- Physical examination results
- Body weight
- Plasma lidocaine concentrations (lidocaine group only)

**Statistical Methods:**

Efficacy: For this abbreviated CSR, only the statistical methods used to analyze the primary efficacy endpoint are described.

The mean change from baseline to Week 12 in WOMAC pain subscale score was analyzed using analysis of covariance (ANCOVA) models with treatment and center as effects and baseline value as a covariate. The least square means and the standard errors obtained from ANCOVA models were used to estimate 95% confidence intervals (CI). Although non-inferiority conclusions

(inferior/noninferior) were planned to be derived, these were not done. The ANCOVA analyses were performed for both the Efficacy Evaluable and ITT completer populations using observed values. A completer was defined as a patient who completed 12 weeks of treatment.

Safety:

The frequency of treatment-emergent AEs (TEAEs), treatment-related TEAEs, and TEAEs by intensity were tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class. 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, body weight, physical examinations, and dermal/sensory assessments were summarized.

**SUMMARY:**

This study was designed with a treatment period of 12 weeks to evaluate the primary efficacy endpoint (the mean change from baseline to Week 12 in WOMAC pain subscale score). At study termination, only 39.1% (27/69) of patients in the lidocaine group and 62.2% (46/74) of patients in the celecoxib group had completed 12 weeks of treatment. For the purpose of this abbreviated report, only data from patients who completed 12 weeks of treatment were used in the analysis of efficacy (primary endpoint only). Because the study was terminated early, the planned enrollment was not reached and thus some assumptions of the protocol were not met; therefore, no conclusions were drawn from the efficacy results.

Efficacy Results:

- Efficacy Evaluable Completer Population (N=63):

On the basis of ANCOVA, the mean reduction in OA pain from baseline to Week 12 in the WOMAC pain subscale score (based on a composite scale ranging from 0 to 20 with a lower number indicating a better condition) was 5.93 in the group of patients who used lidocaine for the 12-week study period (n=24), and 5.12 in the group of patients who received celecoxib for the 12-week study period (n=39).

- ITT Completer Population (N=73):

The analysis results for the ITT completer population showed mean pain reductions from baseline to Week 12 in the WOMAC pain subscale of 5.72 in the group of patients who used lidocaine for the 12-week study period (n=27), and 5.21 in the group of patients who received celecoxib for the 12-week study period (n=46).

Safety Results:

At least one treatment-emergent AE was reported by 44.9% (31/69) of patients in the lidocaine group and by 55.4% (41/74) of patients in the celecoxib group. Headache, dyspepsia, pruritus, and erythema were the only treatment-related AEs occurring in at least two patients in either treatment group. Safety-related discontinuations occurred in six lidocaine-treated patients (urinary tract infection; anxiety; exacerbated pain in both feet and peripheral edema; nausea and headache; back pain; and erythema, papular and vesicular rash) and one celecoxib-treated patient (depression); most were mild or moderate in intensity and considered by the investigator to be unlikely related to study medication. Non-fatal SAEs (elevated blood glucose and right lower abdominal pain), unlikely related to treatment, occurred in two patients (both in the celecoxib group). There were no deaths reported in this study.

Three patients (1 lidocaine and 2 celecoxib) had clinically significant elevation in serum glucose levels during the study. The elevation in one patient (celecoxib group) was considered serious but unlikely related to study medication. There was little systemic absorption of lidocaine with plasma concentrations maintained well below the levels associated with cardiac activity (1500 ng/mL) or toxicity (5000 ng/mL).

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There were no clinically notable changes in vital signs and physical examinations. The lidocaine patch was well tolerated with few dermal reactions: erythema >2 occurred in one patient, papules in two patients, and vesicles in three patients.