Clinical Trial Results Summary
Study EN3203-008

Study Number: EN3203-008	
Title of Study: A Randomized, Double-blind Evaluation of the Analgesic Efficacy and Safety of a Low Dose Oxymorphone Immediate Release in Patients Following Ambulatory Arthroscopic Knee Surgery	
Investigators: 7 investigators	
Study Centers: 8 study centers located in the United States	
Publications (reference): none	
Study Period: April 17, 2003-June 27, 2003	**Phase of Development:** IIIb
Objectives: The primary objective was to compare the analgesic efficacy of 5 mg oxymorphone IR with placebo. The secondary objectives were to evaluate the frequency of dosing and patient satisfaction with study medication, and determine the safety of 5 mg oxymorphone IR compared to placebo.	
Methodology: This was a double-blind, randomized, placebo-controlled study to assess the safety and efficacy of oxymorphone IR in patients with mild to moderate pain following outpatient knee arthroscopy. Following surgery, patients who experienced mild to moderate pain on a categorical scale (none, mild pain, moderate pain, or severe pain) and rated their pain intensity between 30 mm and 70 mm on a 100-mm visual analog scale (VAS) were randomized to receive either oxymorphone IR or placebo for up to 8 hours. Patients were instructed to take the study medication as needed (PRN), but not more frequently than every hour for up to 8 hours after the first dose. The first dose was administered while the patient was at the study site; thereafter, patients were to self medicate at home. Patients were discharged with a diary, study medication, and rescue analgesic (Investigator's choice). Patients who wished to use rescue analgesic due to intolerable pain were discontinued. Patients were instructed to perform 30-minute and hourly pain assessments (VAS), and complete Questions 3 6 of the Brief Pain Inventory (BPI) prior to each dose and rescue. Thirty-minute and hourly pain scores; BPI scores; and dosing information (study medication and rescue) were to be recorded in the diary by patients. Physical activity was to be restricted while in the study. Patients were contacted on the evening of surgery and the morning after surgery for an assessment of study medication use and adverse events. Additionally, the morning after surgery patients were asked to provide a global assessment of pain relief. All patients returned to the study site within 7 days post-surgery for the end-of-study assessments.	
Number of Subjects Planned and Analyzed: Planned: 100 patients receiving at least 1 dose of study medication; Enrolled: 122; Safety Population: 122; Intent-to-Treat Population: 119	
Diagnosis and Main Criteria for Inclusion: Subjects males or females, 18 years of age or older, who had completed outpatient knee arthroscopy (e.g., meniscus repair, bone chip removal, exploratory scope, lateral release, synovial debridement, chondroplasty, plica) and had an initial pain intensity score of between 30 mm and 70 mm on a 100-mm Visual Analogue Scale (VAS) and a categorical pain rating of mild or moderate on a categorical scale of none, mild, moderate, or severe were eligible.	
Test Product, Dose and Mode of Administration, Batch Number(s): Oxymorphone IR 5 mg: over-encapsulated immediate release oxymorphone 5 mg administered orally for up to 8 dose; lot number: 09136.01.	
Reference Therapy, Dose and Mode of Administration, Batch Number(s): Matching placebo administered orally for up to 8 doses; lot number: 07600.01	
Duration of Treatment: 8 hours	

Criteria for Evaluation:

Efficacy: The primary efficacy variable was 8-hour Sum of Pain Intensity Difference (SPID) (VAS). The secondary efficacy variables were: 6-hour SPID (VAS); hourly pain intensity differences (VAS); pain scores from Questions 3-6 of the BPI; frequency of remedication; time to rescue medication, and global evaluation of pain relief.

Safety: Incidence of AEs, AEs resulting in discontinuation, and SAEs

Statistical Methods: Analysis of Covariance (ANCOVA), Analysis of Variance (ANOVA), Kaplan-Meier Survival method; stratified log-rank test; the Wilcoxon rank-sum test, stratified by center

SUMMARY

Efficacy Results: *Primary*: The mean SPID score at 0-8 hours was statistically significantly greater in the oxymorphone IR group compared to the placebo group (oxymorphone IR: 74.8 vs. placebo: -4.2; p=0.007). *Secondary*: The mean SPID score at 0-6 hours was statistically significantly greater in the oxymorphone IR group compared to the placebo group (oxymorphone IR: 63.9 vs. placebo: 5.5; p=0.004). Oxymorphone IR demonstrated statistically significant greater reduction in pain intensity from baseline to all timepoints post-baseline (except 7 hours) compared to placebo. The median time to rescue medication for the oxymorphone IR group was statistically significantly longer (>8 hours) compared to the placebo group (6 hours and 54 minutes). The mean number of doses taken by patients was similar in both groups (placebo group: 3.9 doses; oxymorphone IR group: 4.6 doses). Of the 29 placebo patients who completed the study, 10 (35%) received 8 doses of study medication (the maximum allowed by protocol); however, of the 48 patients in the oxymorphone IR group who completed the study, only 11 (23%) received the maximum 8 doses of study medication. For BPI Questions 3-6, pain scores were categorically moderate prior to all doses and higher prior to rescue medication across the two treatment groups. Overall, 79% of the patients in the oxymorphone IR group felt their pain relief was good, very good, or excellent compared to 59% of the patients in the placebo group with the same ratings. *Exploratory Analysis: Post hoc* exploratory analyses were performed for the subgroup of patients with moderate to severe pain intensity at baseline (oxymorphone IR: N=39; placebo: N=45). Results of the analysis for the primary endpoint revealed that the oxymorphone IR group had a statistically significantly greater ($p<0.001$) mean SPID at 0-8 hours compared to the placebo group. Similar results were observed for the secondary analyses.

Safety Results: Overall, slightly more patients (53%; 32/60) in the oxymorphone IR group reported at least one AE compared to the placebo group (45%; 28/62); this difference is reflected in the gastrointestinal and CNS body systems. The most frequently occurring AEs in the oxymorphone IR group were nausea, headache, and vomiting. The most frequently occurring AEs in the placebo group were nausea, vomiting, and headache. Only one patient in the placebo group had a serious AE, it was not fatal. None of the patients in the oxymorphone IR group and two patients (2/62, or 3%) in the placebo group withdrew due to an AE.