

Clinical Trial Results Summary
 Study EN3202-032

Study Number: EN3202-032	
Title of Study: An Open-Label Titration Followed by a Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy, Tolerability, and Safety of Oxymorphone Extended Release Tablets in Opioid-Experienced Patients with Chronic Low Back Pain	
Investigators: 32 investigators, 30 of whom enrolled patients	
Study Centers: 32 centers in the United States, 30 of which enrolled patients	
Publication (reference): None	
Study Period (years): Date of First Enrollment: October 13, 2004 Date of Last Patient Visit: August 19, 2005	Phase of Development: Phase III
<p>Objectives:</p> <p><u>Primary</u>—To compare the analgesic efficacy of oxymorphone extended release (ER) to placebo in opioid-experienced chronic non-neuropathic low back pain (LBP) patients during the Double-Blind Treatment Period.</p> <p><u>Secondary</u>—</p> <ul style="list-style-type: none"> • To evaluate the tolerability and safety of oxymorphone ER. • To evaluate the dosing titration regimen of oxymorphone ER in opioid-experienced chronic LBP patients. • To evaluate stable dosing ranges of oxymorphone ER in opioid-experienced chronic LBP patients. 	
<p>Methodology: The study consisted of a screening visit followed by an open-label Titration Period and a 12-week double-blind Treatment and Evaluation Period (Treatment Period). Prior to study entry, each patient had to be receiving a stable dose of prescribed opioid pain medication (for at least 2 weeks prior to screening) for the management of moderate to severe chronic non-neuropathic LBP. During the open-label Titration Period (up to 28 days), eligible patients began open-label treatment with oxymorphone ER PO q12h. Each patient's initial oxymorphone ER dose was approximately equivalent to his or her individual pre-study opioid requirements. Each patient then titrated to a stabilized dose. During the open-label Titration Period, patients also were provided with open-label immediate release (IR) oxymorphone (5 mg PO q4-6h prn) to be used as supplemental 'rescue' pain medication for breakthrough pain. All patients were administered an anti-constipation regimen, which continued throughout the study. Each patient recorded in a patient diary all study medication, including rescue medication, taken and pain assessments and reported to the investigator on a daily basis to allow for upward titration of the study drug as required for appropriate analgesia.</p> <p>The goal of the open-label Titration Period was to determine for each patient a fixed dose of study medication that was tolerated and achieved adequate, clinically meaningful analgesia. The open-label Titration Period ended and the dose of study medication was considered fixed when the patient:</p> <ol style="list-style-type: none"> 1) Achieved adequate pain relief (average pain intensity had to be rated ≤ 40 mm on 100-mm visual analogue scale [VAS]) while receiving the same dose of study medication for 3 of 5 consecutive days immediately prior to randomization 2) Tolerated the dose for 3 of 5 consecutive days immediately prior to randomization 3) Did not require more than 2 doses of oxymorphone IR per day as a supplemental 'rescue' pain medication for 3 of 5 consecutive days immediately prior to randomization 4) Reached a minimum oxymorphone ER dose of 10 mg q12h (20 mg daily). 	

Following randomization, eligible patients proceeded directly to the 12-week double-blind Treatment Period. During the Treatment Period, patients received, in a blinded manner, either oxymorphone ER or placebo, q12h at the fixed dose determined during the open-label Titration Period. One-half of the patients received oxymorphone ER, and one-half received placebo. During the first 4 days of the Treatment Period, patients were allowed unlimited supplemental 'rescue' medication as required (5 mg of oxymorphone IR q4-6h prn); thereafter, rescue medication was restricted to a maximum of 2 doses each day (maximum of 5 mg oxymorphone IR twice daily). Neither investigators nor patients could adjust the fixed dose of blinded study medication during the Treatment Period. Patients who developed intolerance or inadequate pain control to their established dose of study drug were to be terminated from the study. During the Treatment Period, patients kept a daily diary record of the total oxymorphone ER (or placebo) dose, as well as oxymorphone IR (rescue medication) doses. Patients returned to the site for assessment of safety and efficacy at Days 4, 7, 21, 28, 42, 56, 70, and 84.

Number of Patients Planned and Analyzed:

Planned: A sufficient number of patients were to be enrolled in the open-label Titration Period to ensure a total 120 patients were randomized into the Treatment Period of the study

Enrolled: 251

Treated: 250 during open-label Titration Period, 142 during Treatment Period

Analyzed for Efficacy: 138 (69 oxymorphone ER, 69 placebo)

Analyzed for Safety: 250 in Titration Period, 142 (70 oxymorphone ER, 72 placebo) in Treatment Period

Diagnosis and Main Criteria for Inclusion: Males or females, 18 years of age or older, who had demonstrated stabilization on prescribed doses of opioids (for at least 2 weeks prior to screening) for treatment of moderate to severe chronic non-neuropathic LBP. During the Titration Period, patients had to reach a minimum oxymorphone ER dose of 10 mg q12h to enter the double-blind Treatment Period.

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

Oxymorphone ER 10 mg, 20 mg, and 40 mg tablets administered orally every 12 hours; tablets were over encapsulated with gelatin capsules for administration during the double-blind Treatment Period. Each patient received oxymorphone ER at an initial dose approximately equivalent to his or her pre-study opioid requirements and then titrated to a stabilized dose (defined as having average pain relief rated ≤ 40 mm on 100-mm VAS on 3 of 5 consecutive days while receiving the same total daily dose of oxymorphone ER). Patients had to reach a minimum stabilized oxymorphone ER dose of 10 mg q12h to enter the double-blind Treatment Period. Each patient's oxymorphone ER dose remained the same throughout the Treatment Period. Tablet lot numbers during both periods were 316094 for the 10 mg tablets; 316095 for the 20 mg tablets, and 316096 for the 40 mg tablets. Capsule lot numbers during the Treatment Period were 10976.04 for the 10 mg capsules; 10976.02 for the 20 mg capsules; and 10976.06 and 12679.01 for the 40 mg capsules.

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

Matching placebo capsules administered orally every 12 hours during the double-blind Treatment Period. Lot numbers 10976.07 (matching 10 mg capsules), 10976.01 (matching 20 mg capsules), and 10976.05 (matching 40 mg capsules).

Rescue Medication, Dose and Mode of Administration, Batch Number(s):

Oxymorphone hydrochloride IR for oral administration; during the open-label Titration Period and the first 4 days of the Treatment Period, patients were allowed one 5-mg tablet every 4-6 hours as needed for breakthrough pain. Thereafter, rescue medication was restricted to a maximum of 2 doses each day. The tablets were not blinded. Lot number 315123.

Duration of Treatment: Up to 28-day Titration Period followed by 12-week Double Blind Treatment Period

Criteria for Evaluation:

Efficacy—

- Average pain intensity (VAS) in the past 24 hours
- Patient’s global assessment of pain medication
- Physician’s global assessment of pain medication
- Pain Quality Assessment Scale (PQAS)
- Evaluation of compliance and study medication usage

Safety—

- Adverse Events (AEs)
- Vital signs
- Adjective Rating Scale for Withdrawal (ARS) assessed at screening and during the first 4 weeks of the Treatment Period
- Clinical Opiate Withdrawal Scale (COWS) assessed during the first 4 weeks of the Treatment Period

Statistical Methods:

Effectiveness: Efficacy results are reported for the All Treated Patients (Double-Blind, Efficacy) population. The primary efficacy endpoint was the change from baseline in average pain intensity (VAS) to the final visit. Analysis of covariance was performed with treatment and center as effects, and screening and baseline average pain intensity as covariates. The OM option was used in estimating the least squares means (LSmeans) for treatment groups. LSmean and 95% confidence interval of the treatment difference were calculated.

As the randomization was stratified by patient’s dose level (high vs. low), an additional analysis was performed with the dose level added to the primary analysis model to check whether it was significant. The stratified primary efficacy endpoint was summarized by gender, race, and age groups.

Time to early discontinuation due to lack of efficacy was estimated using the Kaplan-Meier survival method. Treatment comparison was performed using the log-rank test. Patient’s and physician’s global assessments of pain medication were summarized categorically by visit were analyzed using the rank-sum test procedures, stratified by center. For PQAS, the changes from screening to baseline and baseline to final visit for each composite score were summarized.

Safety: Treatment-emergent adverse events were tabulated by Medical Dictionary for Regulatory Activities (MedDRA) term and system organ class and summarized descriptively. AEs were also summarized by relationship to study medication and severity. Serious adverse events (SAEs) and AEs leading to discontinuation were tabulated separately. Vital sign measurements and change from screening (during Titration Period) and change from baseline (during Treatment Period) by visit were summarized. COWS and ARS total scores and item scores were summarized by visit.

SUMMARY:

Efficacy Results:

- The mean increase in average pain intensity from baseline to last assessment was statistically significantly ($p < 0.0001$) higher in the placebo group than in the oxymorphone ER group. Sensitivity analyses yielded similar results.

- The average pain intensity over time indicated durability of analgesic effect during the 12-week double-blind Treatment Period. This finding is particularly important given the fact that the fixed dose was not to be changed and only two doses of rescue were allowed. The durability of effect is indicative of lack of tolerance being developed during at least 12 weeks of treatment.
- Substantially more placebo patients discontinued early during the double-blind Treatment Period than oxymorphone ER patients. As expected, the difference between the two treatment groups was due to a much higher early dropout rate in the placebo group, compared to oxymorphone ER, due to lack of efficacy ($p < 0.0001$).
- Both patient and physician global assessment of the study medication indicated substantially higher ratings of good to excellent for oxymorphone ER than for placebo during the double-blind Treatment Period. It should be noted that the majority of patients, prior to entering the study, rated their current analgesic medication as poor to good.
- Results from the PQAS, which measures the type of pain, were consistent with the VAS pain intensity results, with placebo patients experiencing statistically significantly larger increases in mean scores compared to oxymorphone patients ($p < 0.0001$).

Responder Analysis

- A responder analysis was performed to assess the magnitude of change in pain intensity from screening to last visit. Ordinarily, a change of $\geq 30\%$ constitutes a clinically meaningful improvement in pain relief. In this study, substantially more oxymorphone ER patients (79.7%) had pain reduction of $\geq 30\%$ than placebo patients (34.8%); the difference was statistically significant ($p < 0.0001$).

Adverse Events

- Approximately 70% of patients experienced at least one AE during the open-label Titration Period. The most prevalent AEs were those associated with opioid therapy, e.g., nausea, constipation, headache somnolence, and vomiting.
- Slightly more patients in the oxymorphone ER group (44.3%) experienced at least one AE in the double-blind Treatment Period than in the placebo group (37.5%). Overall, the incidence rates of individual AEs were very low and “pain exacerbated” and constipation were the only two AEs with incidence rates above 5%.
- One patient died in the Titration Period due to respiratory failure secondary to pneumonia, which was considered as unrelated to the study medication. No deaths occurred in the double-blind Treatment Period. Overall, eight SAEs were reported, six in the open-label Titration Period and two (both oxymorphone ER) in the double-blind Treatment Period. Most of the SAEs were judged by the investigators to be unrelated (unlikely or not related) to the study medication.

Opioid Withdrawal Assessment

- In order to evaluate opioid withdrawal symptoms, particularly in placebo patients, two scales were used during the first 4 weeks of the double-blind Treatment Period; a period in which the prevalence of symptoms characteristic of opioid withdrawal is expected to be highest for patients randomized to placebo. In general, the mean ratings from the COWS (completed by the investigator) and the ARS (completed by the patient) at each visit were similar in both the oxymorphone ER and placebo groups. These findings, along with the fact that only a few patients discontinued due to opioid-withdrawal AEs (discussed above) indicate that the rescue medication dosing design during the double-blind Treatment Period served as an effective tapering method to minimize withdrawal symptoms and also prevent possible unblinding to the treatment.