

Clinical Trial Results Summary
Study EN3202-031

Study Number: EN3202-031	
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-Naïve Patients With Chronic Low Back Pain	
Investigators: 33 investigators, 29 of whom enrolled patients	
Study Centers: 33 centers in the United States, 29 of which enrolled patients	
Publication (reference): Not applicable	
Study Period (years): Date of First Enrollment: November 22, 2004 Date of Last Enrollment: July 18, 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-naïve patients with chronic low back pain (LBP) 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-naïve chronic LBP patients • To evaluate stable dosing ranges of oxymorphone ER in opioid-naïve chronic LBP patients 	
<p>Methodology: The study consisted of a screening visit (patients had to have an initial pain intensity score of at least 50 mm on a 100-mm visual analogue scale [VAS]) followed by an Open-Label Titration Period and a 12-week Double-Blind Treatment Period. During the Open-Label Titration Period, eligible patients received daily oxymorphone ER by mouth (PO) every 12 hours (q12h) in the early morning (about 8 a.m.) and in the evening (about 8 p.m.). Initially, patients received a dose of 5 mg PO q12h for 2 days; thereafter, patients continued receiving oxymorphone ER 5 mg q12h or titrated at increments of 5-10 mg q12h every 3-7 days until stabilization was achieved. The patients had to be stabilized within 4 weeks of treatment initiation in order to be eligible to enter the double-blind, placebo-controlled Treatment Period. No rescue medication was allowed during the Open-Label Titration Period; those patients who required rescue medication were to be discontinued. All patients were administered an anti-constipation regimen that was continued throughout the study. All study medication taken by the patient and pain assessments were recorded in a patient diary 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 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 relief rated ≤ 40 mm on 100-mm 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, and 3) Reached a minimum oxymorphone ER dose of 10 mg q12h (20 mg daily) <p>Each eligible patient was randomized at the first visit (baseline/Visit 5) during which the patient met the criteria for a fixed dose and then proceeded directly into the 12-week, Double-Blind Treatment Period at the fixed dose determined during the Open-Label Titration Period. During the Double-Blind Treatment Period, patients received, in a blinded manner, either oxymorphone ER or placebo q12h in the early morning and evening with one-half of the patients receiving oxymorphone ER and one-half receiving placebo. During the Double-Blind Treatment Period, patients were allowed oxymorphone immediate release (IR) as a supplemental ‘rescue’ pain medication for breakthrough pain. The amount of</p>	

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<p>supplemental ‘rescue’ pain medication that was allowed varied: during the first 4 days of the Double-Blind Treatment Period, patients were allowed as much supplemental ‘rescue’ medication as required (5 mg of oxymorphone IR q4-6h); 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 were allowed to adjust the fixed dose of blinded study medication during the Double-Blind Treatment Period. Patients who developed intolerance or inadequate pain control to their established dose of study drug were terminated from the study. Patients kept a daily diary record of the total oxymorphone ER (or placebo) dose, as well as any oxymorphone IR (rescue medication) doses. During the Double-Blind Treatment Period, patients returned to the site for safety and efficacy assessments at Days 0, 4, 7, 14, 21, 28, 42, 56, 70, and 84 (±3 days).</p>
<p>Number of Patients Planned and Analyzed: <u>Planned:</u> A sufficient number to ensure a total of 160 patients were randomized into the Double-Blind Treatment Period <u>Enrolled:</u> 326 <u>Treated:</u> 325 in Open-Label Titration Period; 205 (105 oxymorphone ER, 100 placebo) in Double-Blind Treatment Period <u>Analyzed for Efficacy:</u> 192 (97 oxymorphone ER, 95 placebo) in Modified Intent-to-Treat (Double-Blind Treatment Period) population <u>Analyzed for Safety:</u> 325 in Open-Label Titration Period; 205 (105 oxymorphone ER, 100 placebo) in Double-Blind Treatment Period</p>
<p>Diagnosis and Main Criteria for Inclusion: Opioid-naïve males or females, 18 years of age or older, with moderate to severe chronic non-neuropathic LBP of at least 3 months duration. During the Open-Label Titration Period, patients had to reach a minimum oxymorphone ER dose of 10 mg q12h to enter the Double-Blind Treatment Period.</p>
<p>Test Product, Dose and Mode of Administration, Batch Number(s): Oxymorphone ER 5 mg, 10 mg, 20 mg, and 40 mg tablets over encapsulated with gelatin capsules administered orally every 12 hours. Patients received 2 days of therapy with oxymorphone ER 5 mg q12h and then titrated to a stabilized dose. Stabilized dose was 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 study medication. Patients had to reach a minimum oxymorphone ER dose of 10 mg q12h to enter the Double-Blind Treatment Period. During Open-Label Titration Period, lot numbers 313519 for the 5 mg tablets; 323014 for the 10 mg tablets; 323017 for the 20 mg tablets, and 316096 for the 40 mg tablets. During the Double-Blind Treatment Period, tablet lot numbers 313519 (5 mg), 323014 (10 mg), 323017 (20 mg), and 316096 (40 mg).</p>
<p>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 12045.05, 12045.06, 12045.07, and 12045.08.</p>
<p>Rescue Medication, Dose and Mode of Administration, Batch Number(s): Oxymorphone hydrochloride IR, one 5-mg tablet administered orally every 4-6 hours for breakthrough pain during the Double-Blind Treatment Period. During the first 4 days of the Double-Blind Treatment Period, patients were allowed as much rescue medication as required; thereafter, rescue medication was restricted to a maximum of 2 doses each day. The tablets were not blinded. Lot number 323008.</p>
<p>Duration of Treatment: Up to 28-day Open-Label Titration Period followed by 12-week Double-Blind Treatment Period</p>

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
- Evaluation of compliance and study medication usage

Safety–

- Adverse events (AEs) (throughout the study)
- Vital signs (at each study visit)
- Adjective Rating Scale for Withdrawal (ARS) assessed at screening and during the first 4 weeks of the Double-Blind Treatment Period
- Clinical Opiate Withdrawal Scale (COWS) assessed during the first 4 weeks of Double-Blind Treatment Period

Statistical Methods:

Efficacy: Efficacy results are reported for the Modified Intent-to-Treat (MITT) Population. The primary efficacy endpoint was the change from baseline in average pain intensity (VAS) to the final visit. Analysis of covariance (ANOVA) 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 for treatment groups. Least squares mean 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. The dose level was 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 was analyzed using the rank-sum test procedures, stratified by center.

Safety: Treatment-emergent adverse events (TEAEs) were tabulated by Medical Dictionary for Regulatory Activities (MedDRA) term and system organ class (SOC) 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 from screening and change from baseline to final visit were summarized. COWS and ARS total scores and item scores were summarized by visit.

SUMMARY:

Efficacy Results:

- In both the MITT (ITT excluding major protocol violators) and ITT (All Treated Patients) analyses, the mean increase in average pain intensity from baseline to last assessment was statistically significantly higher in the placebo group than in oxymorphone ER group. Sensitivity analyses based on missing data handling rules for discontinuations due to AEs yielded similar results with statistically significant p-values ($p < 0.0001$).

- 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. In fact, the oxymorphone ER patients did not increase the amount of rescue medication over time. The durability of effect is indicative of lack of tolerance being developed during at least 12 weeks of treatment.
- 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 (81.4%) had pain reduction of $\geq 30\%$ than placebo patients (51.7%); the difference was statistically significant ($p < 0.0001$).
- 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 fair.

Safety Results:

- Approximately 69% 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., constipation, somnolence, nausea and dizziness.
- Modestly more patients in the oxymorphone ER group (58.1%) experienced at least one AE in the Double-Blind Treatment Period than in the placebo group (44.0%). Overall, the incidence rates of opioid-related AEs were low; and with the exception of vomiting and constipation, the incidence rates of other opioid-related AEs such as nausea and dizziness were similar between the two treatment groups.
- No deaths occurred in the study. Overall, six SAEs were reported, one in the Open-Label Titration Period and 5 in the Double-Blind Treatment Period (two oxymorphone ER and three placebo patients). None of the SAEs were judged by the investigators to be drug related.

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.