Clinical Trial Results Summary
Study EN3202-029

Study Number: EN3202-029	
Title of Study: An Open-Label, Long-Term Effectiveness and Safety Study of Oxymorphone Extended Release Tablets in Patients with Cancer or Neuropathic Pain, EN3202-029	
Investigators: 40 investigators, 37 of which enrolled subjects	
Study Centers: 39 centers in the United States, 36 of which enrolled subjects	
Publication (reference): Not applicable	
Study Period (years): Date of First Enrollment: August 22, 2003 Date of Last Enrollment: March 5, 2005	**Phase of Development:** Phase III
Objectives: To evaluate the analgesic effectiveness of oxymorphone ER, to evaluate the tolerability of oxymorphone ER, to evaluate the time to stabilization, to evaluate subject satisfaction with oxymorphone ER treatment, and to evaluate the safety of oxymorphone ER.	
Methodology: This was an open-label, nonrandomized study to assess the effectiveness and safety of oxymorphone ER in subjects with moderate to severe chronic (≥3 months duration) malignant and/or neuropathic pain. Two types of subjects were eligible for this study: 1) those who were suboptimally responding to their current analgesic regimens, and 2) those who were experiencing intolerable side effects from their current opioid-containing analgesic regimens and required opioid rotation. Subjects who were suboptimally responding to their current analgesic regimens, rated their pain intensity >4 on a scale from 0 to 10 using Brief Pain Inventory (BPI) Question 5, and who met all other inclusion criteria were to be entered into the study. Subjects who had intolerable side effects to one or more components of their current opioid-containing analgesic regimens and required opioid rotation and who met all other inclusion criteria were to be entered into the study. The study was divided into two periods: Titration/Stabilization Period – Following baseline assessments, subjects currently receiving an opioid(s) as part of their analgesic regimen were to be converted to treatment with oxymorphone ER based on guidelines provided. Opioid-naïve subjects were to initiate 2 days (Day 1 and Day 2) of therapy with oxymorphone ER 5 mg, every 12 hours (q12h). Thereafter, all subjects were to be titrated to a stable dose (defined as pain scores ≤4 on BPI Question 5 on 3 of 5 consecutive days while receiving the same total daily dose of study medication including rescue) with tolerable side effects. Dosing adjustments were to be made under the direction of the investigator based on a review of the subject's average daily pain scores, current daily dose of study medication, and evaluation of adverse events (AEs) reported by the subject and observed by the investigator. Subjects were instructed to call the investigator between scheduled study visits if their pain relief was unsatisfactory or if they were experiencing intolerable side effects, so that the investigator could evaluate the need for and authorize adjustments in study medication. Subjects who entered the study due to a suboptimal response to their current analgesic regimen could be discontinued from or continued on the same regimen during the Titration/Stabilization period at the discretion of the investigator. Subjects who entered the study due to intolerable side effects and the need for opioid rotation were to have the culprit drug(s) tapered and discontinued according to standard clinical practice. If a subject did not reach a stable dose within 4 weeks, the investigator was to contact the sponsor. Maintenance Period – Subjects could receive therapy for up to 12 months after the first dose of study medication; further titration was permitted. Free use of concomitant non-opioid analgesic drug(s) was permitted. However, for worsening pain, the investigator was to titrate the study medication prior to initiating any other non-opioid analgesic therapy, i.e., starting a new non-opioid analgesic or increasing the dose of a current concomitant non-opioid analgesic.	

Rescue medication in the form of oxymorphone IR 5 mg and 10 mg tablets was available for breakthrough pain throughout the study. Upon completion of the treatment period at Month 12 (or early termination), subjects were to be tapered off oxymorphone ER over a 1–2 week period or converted to an equivalent dose of a marketed opioid at the discretion of the investigator.

Number of Subjects Planned and Analyzed:

Planned: Up to 200

Enrolled: 223

Treated: 221

Analyzed for effectiveness and safety: 221 (Treated Subjects population)

Diagnosis and Main Criteria for Inclusion: Males or females, 18 years of age or older, with moderate to severe chronic malignant and/or neuropathic pain of at least 3 months' duration who were receiving a stable analgesic regimen and who either 1) were suboptimally responding to their current analgesic regimen with an initial pain intensity score of >4 on a scale from 0 to 10 using BPI Question 5, or 2) had intolerable side effects to one or more components of their current opioid-containing analgesic regimen.

Test Product, Dose and Mode of Administration, Batch Number(s): Oxymorphone ER 5 mg, 10 mg, 20 mg, and 40 mg tablets administered orally every 12 hours. Subjects currently receiving an opioid(s) as part of their analgesic regimen were converted to treatment with oxymorphone ER based on guidelines provided, and opioid naïve subjects received 2 days of therapy with oxymorphone ER 5 mg q12h. All subjects then titrated to a stabilized dose. Stabilized dose was defined as having an average daily pain score ≤4 on BPI Question 5 on 3 of 5 consecutive days while receiving the same total daily dose of study medication (including rescue medication). Lot numbers 313519 for the 5 mg tablets; 316094 and 323014 for the 10 mg tablets; 316095 for the 20 mg tablets, and 310184 and 310182 of the 40 mg tablets.

Rescue Medication, Dose and Mode of Administration, Batch Number(s): Oxymorphone hydrochloride IR, 5 mg and 10 mg tablets administered orally as needed as supplemental rescue medication for breakthrough pain. Lot numbers 315123 for the 5 mg tablets and 315125 for the 10 mg tablets.

Reference Therapy, Dose and Mode of Administration, Batch Number(s): Not applicable

Duration of Treatment: Up to 12 months from the first dose of study medication.

Criteria for Evaluation:

Effectiveness

- Average daily pain intensity (Question 5 of the BPI Questionnaire) during the Titration/Stabilization period (from diary data)
- Questions 3, 4, 5, 6, 8, and 9 of the BPI Questionnaire (from visit data)
- Pain Quality Assessment Scale (PQAS)
- Average daily dose of oxymorphone ER (from diary data)
- Average daily dose of rescue medication (from diary data)
- Total daily dose of oxymorphone ER and rescue medication (from diary data)
- Time to stabilization
- Incidence rate of discontinuation due to AEs during the Titration/Stabilization period
- Subject/investigator global assessment of pain relief
- Treatment satisfaction

Safety

Adverse events

Statistical Methods:

Effectiveness: For BPI and PQAS, the significance of the mean change from screening was assessed by paired t-test. Medians and 95% confidence intervals (95% CIs) for the time to stabilization and time to discontinuation due to AEs were estimated by using the Kaplan-Meier survival method. PQAS scores, percentage of subjects who discontinued due to AEs, exposure, global assessment results, and treatment satisfaction results were summarized.

Safety: Treatment-emergent adverse events (TEAEs) were tabulated by Medical Dictionary for Regulatory Activities (MedDRA) term and system organ class (SOC) and summarized using by descriptive statistics. AEs were also summarized by relationship to study medication and intensity. Serious AEs (SAEs) and AEs leading to discontinuation were tabulated separately.

SUMMARY:

Effectiveness

Subjects were able to titrate to a stabilized dose and maintain pain control for the duration of the study as evidenced by the following:

- Overall, 62.4% (138/221) of Treated Subjects reached stabilization with a median time to stabilization of 27 days (95% CI 22, 28 days).
- The average daily dose of oxymorphone ER increased over time; as expected, increases were more pronounced in the cancer subjects, who were experiencing disease progression.
- Average daily pain intensity (BPI Question 5) showed consistent statistically significant improvements from screening after the first 4 days of treatment. Additionally, statistically significant improvements from screening were seen for all other BPI items at all visits except at Week 1 for Question 4 (pain at its least) and Question 8 (percent pain relief).
- Mean PQAS-4, PQAS-18, and PQAS-20 composite scores decreased statistically significantly from screening to Month 12/early termination.
- At the end of the study, the majority of subjects rated their overall pain relief with oxymorphone as good to excellent. The physicians' global assessment was generally consistent with subjects' assessment.

Safety

- During the study, 11/221 (5.0%) Treated Subjects died; all but one of these subjects were cancer pain patients who died of disease progression (which was unrelated to study medication).
- A total of 47/221 (21.3%) Treated Subjects experienced at least one SAE, the most frequently reported of which were malignant neoplasm progression and pneumonia NOS in both treatment periods. All but 6 of the reported SAEs were considered by the investigators to be unlikely related to the study medication.
- A total of 86/221 (38.9%) Treated Subjects discontinued due to AEs, including 53/221 (24.0%) subjects during the Titration/Stabilization period and 33/138 (23.9%) subjects during the Maintenance period. The most frequently reported events that led to discontinuation were mostly opioid-related side effects: nausea, constipation, vomiting NOS, dizziness, pruritus, malignant neoplasm progression, and somnolence.

- Overall, 199/221 (90.0%) Treated Subjects reported at least one AE during the study, including 160/221 (72.4%) subjects during the Titration/Stabilization period and 117/138 (84.8%) subjects during the Maintenance period. The most frequently reported AEs were opioid-related side effects and included nausea, constipation, vomiting NOS, dizziness, somnolence, and headache during both periods. In addition, depression was a frequently reported event during the Maintenance period (13/138 subjects, 9.4%).