Clinical Trial Results Summary
Study EN3203-009

Study Number: EN3203-009	
Title of Study: Randomized, Double-Blind, Placebo- and Active-Control, Single- and Multiple-Dose Evaluation of the Analgesic Efficacy and Safety of Oxymorphone Immediate Release (IR) Tablets in Patients with Moderate/Severe Pain Following Abdominal Surgery	
Investigators: 22 investigators, 20 of whom enrolled patients	
Study Centers: 23 study centers, 21 of which enrolled patients	
Publication (reference): None	
Study Period (years): Date of First Enrollment: September 1, 2004 Date of Last Enrollment: August 9, 2005	**Phase of Development:** III

Objectives:

Primary—To evaluate the analgesic efficacy of oxymorphone IR 10 mg and 20 mg compared with placebo after single and multiple doses of study medication in patients with moderate to severe pain following abdominal surgery.

Secondary—To evaluate the tolerability and safety of oxymorphone IR 10 mg and 20 mg after multiple doses of study medication compared with placebo and oxycodone IR 15 mg in patients with moderate to severe pain following abdominal surgery.

Methodology: This Phase III randomized, double-blind, placebo- and active-control, single- and multiple-dose study was conducted to evaluate the analgesic efficacy, tolerability, and safety of oxymorphone IR, 10 mg and 20 mg, administered every 4-6 hours compared to placebo and oxycodone IR 15 mg. Approximately 320 patients were to be randomized at up to 25 sites.

Each patient was screened and underwent an abdominal surgery. Each patient's initial pain therapy after surgery was established using an intravenous (IV) (patient-controlled analgesia [PCA] or non-PCA) or intramuscular (IM) opioid. Epidural PCA was not allowed. Postoperatively up to 30 hours after surgery, enrolled patients who were able to take oral medication discontinued all opioids and any other pain medications. Patients who rated their intensity of pain as moderate to severe on a categorical scale and ≥50 mm on a 100-mm visual analog scale (VAS) after a washout period were eligible to be randomized. Patients who met the above criterion and all inclusion/exclusion criteria were enrolled into the study and randomized to receive one of four treatment regimens. The patient was considered a screen failure if the patient could not be converted to oral pain medication within 30 hours following surgery. The patient was also considered a screen failure if the patient did not develop moderate to severe pain that was ≥50 mm on a 100 mm VAS within the required time periods.

During the Single-Dose Period (after the first dose), patients underwent efficacy and safety assessments for up to 6 hours. Patients who requested remedication ≥4 hours and before 6 hours after the initial dose or patients who completed the 6-hour Single-Dose efficacy assessments were remedicated at Hour 6 and entered the Multiple-Dose Period. Any patient who requested re-medication within the first 4 hours of the initial dose received a rescue medication of the investigator's choice and was discontinued from the study after completing the exit evaluation assessments.

During the Multiple-Dose Period, patients continued to take the same study drug that they were assigned during the Single-Dose Period. During this period, patients were instructed to take the study medication every 4-6 hours (patients could not dose sooner than every 4 hours or later than every 6 hours). They were required to complete a diary for dosing and pain assessments prior to each dose of the study medication. Patients who required re-medication sooner than every 4 hours between doses were discontinued from the study after completing the exit evaluation assessments and received a rescue medication of the investigator's choice.

Patients were treated in-hospital for the duration of the Treatment Period; those discharged prior to the end of the 48-hour Multiple-Dose Period continued treatment as outpatients until the end of the 48-hour Multiple-Dose Period. Patients who did not require additional medication within the 4-6 hour dosing window were to be discontinued from the study.

Number of Patients Planned and Analyzed:

Planned: Approximately 320 patients (80 per treatment)

Enrolled: 331

Treated: 331

Analyzed for Efficacy: 330 (oxymorphone IR 10 mg: 81; oxymorphone IR 20 mg: 81; oxycodone IR 15 mg: 83; placebo: 85) in the Intent-to-Treat Patient population

Analyzed for Safety: 331 in the All Treated Patients population

Diagnosis and Main Criteria for Inclusion: Patients 18 years of age or older who were undergoing surgery through an abdominal incision of at least 3 cm who were expected to be hospitalized for at least 36 hours and were expected to subsequently require at least 48 hours of oral opioid therapy

Test Product, Dose and Mode of Administration, Batch Number(s): Oxymorphone IR supplied as 10 mg tablets over-encapsulated with gelatin capsules, one 10 mg or one 20 mg strength capsule orally every 4-6 hours, lot number: 315125

Reference Therapy, Dose and Mode of Administration, Batch Number(s): Oxycodone IR supplied as 15 mg tablets over-encapsulated with gelatin capsules, 1 capsule orally every 4-6 hours, lot number 3651A1

Placebo, 1 capsule orally every 4 to 6 hours, lot number 11355.01

Duration of Treatment: 48 hours

Criteria for Evaluation:

Efficacy

- Current pain intensity
- Current pain relief
- Average pain intensity
- Time to first perceptible pain relief and meaningful pain relief
- Patient global evaluation of study medication
- Physician global evaluation of study medication

Tolerability and Safety

- Adverse events (AEs)

Statistical Methods:

Efficacy: The primary analysis was based on the primary efficacy endpoint, time to discontinuation due to all causes. It was estimated using Kaplan-Meier method and analyzed using log-rank test. Pairwise comparisons were performed and p-values were evaluated using the Step-down procedure. For the secondary analyses, mean average pain and mean current pain intensity scores during dosing intervals were calculated for each patient first, and then analyzed using analysis of covariance model (ANCOVA) with treatment and center as effects, and baseline pain intensity as covariate. Additionally, average pain intensity and current pain intensity scores were summarized and graphed by treatment group and the number of doses taken. Both patients' and investigators' global evaluations of the study medication were analyzed using the stratified rank-sum test procedure, stratified by center. For the secondary endpoints during the Single-Dose Period (0-6 hours post first dose), namely SPID_6 and TOTPAR_6, 6-hour sum

of pain intensity difference and total pain relief (VAS and categorical), ANCOVA was used with effects for treatment, center, and baseline pain intensity as covariate. Pair-wise comparison between oxymorphone IR 10 mg and 20 mg and placebo was carried out using contrast statements. Time to first perceptible and time to meaningful pain relief were estimated using Kaplan-Meier method and analyzed using log-rank test.

Tolerability: Tolerability was measured by the number and percentage of patients who discontinued from the study due to treatment-emergent AEs.

Safety: The safety of oxymorphone IR 10 mg and 20 mg was evaluated by comparing the incidence rates of AEs, serious adverse events (SAEs), and discontinuations due to AEs between the oxymorphone IR treatment groups and the oxycodone IR group. All AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA). AEs were considered treatment-emergent if they occurred after the start of study drug. SAEs were considered treatment-emergent if they occurred after the start of study drug or within 15 days after the last dose of study drug. AEs were summarized by the number and percentage of patients who experienced at least one treatment-emergent adverse event (TEAE). TEAEs were summarized overall, by body system, by body system and preferred term, by relationship to study medication, and by intensity. Treatment-emergent SAEs and AEs resulting in discontinuation were summarized separately. Data listings were provided for all AEs.

SUMMARY:

Efficacy Results: *Primary*: The primary test of efficacy in this study was to determine whether the analgesic efficacy of oxymorphone IR is maintained over repeated dosing. It was assumed that if the analgesic efficacy is not maintained, patients would discontinue treatment over time. Therefore, the primary efficacy endpoint was defined as time to discontinuation due to all causes. The median time to discontinuation was statistically significantly shorter in the placebo group than the 10 mg and 20 mg oxymorphone IR groups and the oxycodone IR 15 mg group. There was no difference in time to discontinuation between the oxymorphone IR groups and the oxycodone IR group. *Secondary*: The mean average and current pain intensity during the Multiple-Dose Period were statistically significantly lower in the oxymorphone IR 10 and 20 mg groups compared to the placebo group; there were no significant differences between the oxymorphone and oxycodone groups. The mean categorical SPID within 6 hours after the first dose was statistically significantly higher in the oxymorphone IR 10 mg and 20 mg groups than in the placebo group; there were no differences between oxymorphone and oxycodone groups. None of the active treatment groups differed from placebo in time to first perceptible or meaningful pain relief, measures that evaluate the onset of analgesia after the first dose. It should be noted that in repeated dosing, when steady state was achieved, the average pain intensity was considerably lower in the active treatment groups compared to placebo.

Tolerability Results: Tolerability was assessed by unacceptable adverse events that caused patients to discontinue the treatment. The incidence of discontinuations due to AEs was generally low and comparable for all treatment groups.

Safety Results: The incidence of adverse events was similar among the three active treatment groups and larger than the incidence observed in the placebo group. In all treatment groups, the most frequently reported AEs were nausea (13-28%), pruritus (4-13%), vomiting (4-16%), and headache (7-12%). The incidence of these AEs was similar in the active treatment groups and generally larger than in the placebo group. No deaths occurred in this study. Of the 14 reported SAEs, five (occurring in three patients) were considered drug related by the investigators; all others were considered to be unlikely related to the study medication. The following three patients reported SAEs that were possibly or probably related to study medication: one patient who received oxymorphone IR 20 mg (nausea and vomiting), and two patients who received oxycodone IR 15 mg (ileus; nausea and vomiting).