Study Number: EN3202-025	
Title of Study: Double-Blind, Placebo Controlled, Parallel Group, Dose Ranging Comparison of the Efficacy and Safety of Extended Release Oxymorphone and Placebo in the Treatment of Osteoarthritis of the Knee and/or Hip	
Investigators: 33 investigators	
Study Center(s): 33 study centers located in the United States	
Publications (reference): None	
Studied period (years): Date of First Enrollment: 25 July 2001 Date of Last Enrollment: 22 March 2002	**Phase of development:** Phase III
Objectives: The primary objective was to test the analgesic efficacy dose response of oxymorphone ER at doses of 10 mg, 40 mg, 50 mg and placebo in patients with moderate to severe pain due to osteoarthritis (OA). Secondary objectives were: (1) To compare the analgesic efficacy of oxymorphone ER 10 mg, oxymorphone ER 40 mg and oxymorphone ER 50 mg with placebo in patients with moderate to severe pain due to osteoarthritis; (2) To compare the relative analgesic efficacy of oxymorphone ER 10 mg, oxymorphone ER 40 mg and oxymorphone ER 50 mg; and, (3) To compare the safety and tolerability of oxymorphone ER 10 mg, oxymorphone ER 40 mg and oxymorphone ER 50 mg with placebo.	
Methodology: Eligible patients were to have Functional Class II-IV OA of the knee and/or hip with moderate to severe pain while off treatment and were to have had a suboptimal response to acetaminophen and NSAID therapy (in the Investigator's opinion), or had previously received opioid analgesics. Eligible patients entered a 2- to 7-day washout period during which all analgesic use was discontinued. When pain in the index joint was assessed to be > 40 mm on the Arthritis Pain Intensity Visual Analogue Scale (VAS), the patient was randomized to receive one of four treatment regimens: oxymorphone ER 10 mg bid during Week 1 and Week 2; oxymorphone ER 20 mg bid during Week 1 and oxymorphone ER 40 mg bid during Week 2; oxymorphone ER 20 mg bid during Week 1 and oxymorphone ER 50 mg bid during Week 2; or placebo during Week 1 and Week 2. No dose adjustments were permissible during the study. Patients were to return to the clinic at the end of each week following randomization for efficacy and safety assessments. Study medication was discontinued at the end of Week 2. Patients whose pain did not improve or worsened, or who were unable to tolerate the study medication, could have been withdrawn from the study at any time prior to the end of Week 2. The Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index, the Arthritis Pain Intensity VAS, and the Physician's and the Patient's Global Assessment of Arthritis were to be completed at Baseline, Week 1 and Week 2 (or at withdrawal, if appropriate). Quality of life was to be assessed at Baseline, Week 1 and Week 2 (or at withdrawal, if appropriate) using the SF-36 Health Survey and a sleep questionnaire. Safety was to be assessed at each visit using a non-directed adverse events questionnaire, and by conducting clinical laboratory tests and measuring vital signs. Physical examinations and EKGs were to be conducted at Screening and at the end of Week 2 (or at withdrawal, if appropriate). In females of childbearing potential, serum pregnancy tests were to be performed at Screening and at Week 2 (or at withdrawal, if appropriate).	
Number of patients (planned and analyzed): Approximately 300 patients were to be randomized into the study to ensure that 240 patients (60 patients per treatment arm) completed the study.	

Diagnosis and main criteria for inclusion: Patients were to be males and females with OA of knee/hip as defined by Functional Class II-IV and radiographic evidence, were to have had suboptimal response to acetaminophen, COX-2 inhibitors, or NSAIDs, or were to have previously received immediate release opioid analgesics.

Duration of treatment: 2 weeks

Criteria for evaluation:

Efficacy: The primary efficacy variable was the change from baseline to the final visit in the arthritis pain intensity VAS score. Secondary efficacy variables included: changes from baseline in the WOMAC OA pain subscale score, the WOMAC OA stiffness subscale score, the WOMAC OA physical function score, and the WOMAC OA comprehensive index score; the patient's and physician's global assessments of OA, the incidence of withdrawals due to lack of efficacy, and the time to withdrawal due to lack of efficacy.

Quality of Life: Quality of life variable scores derived from the SF-36 Health Survey and individual item scores from the sleep assessment questionnaire.

Safety: Safety assessments included adverse events, clinical laboratory tests, vital signs, physical examinations and EKG recordings.

Statistical methods: The primary efficacy analysis was based on the comparison of least squares mean changes (LSmeans) from baseline to the final visit in the arthritis pain intensity VAS score in each of the oxymorphone groups with the LSmean change in the placebo group for intent-to-treat (ITT) patients. Intent-to-treat was defined as all randomized patients who took at least one dose of study medication and had a baseline and at least one post-baseline primary efficacy measurement. The dose response relationship was evaluated using Tukey's modified linear trend test. Similar methods were used to analyze the secondary efficacy variables. These analyses were also repeated for evaluable patients (defined as all randomized patients who took at least one dose of study medication and had a baseline and at least one post-baseline primary efficacy measurement during the second week of the double-blind period). Rates and timing of withdrawal due to lack of efficacy were compared using Cochran-Mantel-Haenszel chi-square tests and log-rank tests. Quality of life assessments (SF-36 physical and mental comprehensive index scores and sleep assessments) were analyzed using the same methods described for the primary efficacy variable. All treated patients were included in summaries and analyses of safety data. Incidence rates for all adverse events (AEs) and for treatment-related AEs were calculated by body system and MedDRA preferred term for each treatment group. Serious AEs were identified and listed. Incidence rates for AEs resulting in withdrawal from the study were calculated by body system and preferred term for each treatment group. Descriptive statistics for laboratory test results were presented for baseline, Week 1, and Week 2/final visit data. Changes from baseline were analyzed within treatment groups using t-tests. Shift tables (baseline to "worst" post-baseline value) were also provided for laboratory test results. Descriptive statistics were used to summarize vital signs by visit. Shift tables for overall EKG assessments and results of physical examinations were provided.

SUMMARY:

Rates of withdrawal from the study were generally dose related, with the highest rates of withdrawal occurring in the oxymorphone 40 mg and oxymorphone 50 mg groups. In all treatment groups, withdrawals from the study for any reason occurred most frequently during Week 1, when patients were receiving either oxymorphone ER 10 mg or 20 mg bid. Adverse events were the most frequent reason for withdrawal from the oxymorphone groups, and the overall rates of withdrawal for this reason were generally dose-related. Rates of withdrawal due to AEs during Week 1, during which patients in the oxymorphone 40 mg and 50 mg groups received oxymorphone 20 mg, were also generally dose related. Lack of efficacy was the most frequent reason for withdrawal from the placebo group. Not unexpectedly, all but one of these withdrawals occurred during Week 1.

Efficacy: Oxymorphone 40 mg and oxymorphone 50 mg were statistically significantly superior to placebo in relieving pain due to OA as measured by the primary efficacy endpoint, i.e., the change from baseline in the arthritis pain intensity VAS score at the final visit in ITT patients. This conclusion was also supported by the statistically significant linear dose-response relationship seen for the primary efficacy endpoint. No difference between the oxymorphone 10 mg group and the placebo group was found for the primary efficacy endpoint. Patients in the oxymorphone 10 mg group showed a clinically meaningful improvement in pain intensity; however, the absence of a statistically significant difference was due, at least in part, to the large response in the placebo group. Oxymorphone 40 mg and oxymorphone 50 mg were statistically significantly superior to placebo among ITT patients at the final visit for all secondary efficacy endpoints except one (patient's global assessment of OA in the oxymorphone 50 mg group). Oxymorphone 10 mg was statistically significantly superior among ITT patients at the final visit for the WOMAC pain and physical function subscale scores and for the WOMAC composite index score. In general, the analyses of efficacy endpoints for evaluable patients in the oxymorphone 40 mg and 50 mg groups at the final visit showed a similar pattern of results seen for the ITT patients at the final visit. Analyses of efficacy endpoints for evaluable patients in the oxymorphone 10 mg group showed clinically meaningful but no statistically significant differences from the placebo group. Analyses of efficacy data at Week 1, during which patients in the oxymorphone 40 mg and oxymorphone 50 mg groups received oxymorphone 20 mg, were generally consistent with the results seen in the oxymorphone 40 mg and 50 mg groups at the final visit. In contrast to final visit results, however, analyses of Week 1 data showed that oxymorphone 10 mg was statistically significantly superior to placebo on all efficacy endpoints except the patient's global assessment of OA.

Quality of Life: The quality of life, as assessed by the SF-36 and sleep quality assessments, was significantly improved in the oxymorphone 40 mg and 50 mg groups when compared to the placebo group. Improvements were also seen in the oxymorphone ER 10 mg group. Statistically significant improvements over placebo were observed in the physical health composite index of the SF-36, and the trouble falling asleep and frequency of using sleep medication variables. Numerically superior results were observed for the remaining quality of life parameters.

Safety: The safety profile of oxymorphone ER, as evaluated by AE incidence rates, laboratory test results, vital signs, EKGs, and physical examinations, was consistent with that typically seen with opioid medications. The most frequently occurring adverse events in the oxymorphone treatment groups were nausea, vomiting, constipation, dizziness, somnolence, headache and pruritus. A dose response relationship was seen in the incidence rates (overall and by week) for these frequently occurring, opioid-related AEs, with higher incidence rates occurring at higher oxymorphone doses. No clinically meaningful changes were seen in laboratory test results, vital signs, or EKGs.