Clinical Trial Results Summary
Study EN3202-015

Study Number: EN3202-015	
Title of Study: Double-Blind, Placebo Controlled, Parallel Group, Dose Ranging Comparison of the Efficacy and Safety of Controlled Release Oxymorphone, Controlled Release Oxycodone (OxyContin®) and Placebo in the Treatment of Osteoarthritis of the Knee and/or Hip	
Investigators: 31 investigators enrolled at least one patient	
Study Centers: Investigators enrolled patients at 31 study centers	
Publication (reference): None	
Study Period (years): 20 July 1999-10 May 2000	**Phase of Development**: III
Objectives: The primary objectives were to evaluate the analgesic efficacy of oxymorphone CR (controlled release oxymorphone) by comparing oxymorphone CR 40 mg q12h (every 12 hours) with placebo in patients with moderate to severe pain due to osteoarthritis and to compare the safety and tolerability of oxymorphone CR 20 mg q12h and oxymorphone CR 40 mg q12h with OxyContin® (controlled release oxycodone) 20 mg q12h. The secondary objectives were to compare the analgesic efficacy of oxymorphone CR 20 mg q12h with placebo, to compare the analgesic efficacy of oxymorphone CR 20 mg q12h and oxymorphone CR 40 mg q12h, to compare the analgesic efficacy of oxymorphone CR 20 mg q12h and oxymorphone CR 40 mg q12h with OxyContin 20 mg q12h, to compare the analgesic efficacy of oxymorphone CR 20 mg q12h with OxyContin 10 mg q12h, and to compare the safety and tolerability of oxymorphone CR 20 mg q12h with OxyContin 10 mg q12h.	
Methodology: This was a 6-week, randomized, double-blind, placebo controlled, parallel group, multiple center, multiple dose study with 7 visits: screening, baseline, treatment Weeks 1 - 4, and post-treatment. Following the screening visit, patients entered a 2- to 7-day washout period. When the pain in the index joint reached at least 40 mm on a visual analog scale (VAS) (baseline), patients were randomized to receive one of the 4 treatments, oxymorphone CR 20 mg q12h or 40 mg q12h, OxyContin 20 mg q12h, or placebo q12h, and began receiving study medication. To allow for optimal tolerability of the opioid study medications, the initial dose of study medication for patients randomized to receive oxymorphone CR 20 mg or 40 mg was started at 20 mg q12h. After 2 weeks of treatment, the dose was increased to 40 mg q12h for those patients randomized to the oxymorphone CR 40 mg treatment group. Similarly, the dose for patients randomized to receive OxyContin 20 mg was started at 10 mg q12h and increased to 20 mg q12h after 2 weeks. Patients continued on the assigned dose for 2 additional weeks, followed by the cessation of study medication for the final week of the study. Patients completed the Arthritis Pain Intensity VAS score daily and the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index, the Arthritis Pain Intensity VAS, the Patient's and Physician's Global Assessment of Arthritis, and nausea, drowsiness, and sleep assessments at the visits through the end of the fourth week of treatment with study medication. The Physical Dependence Survey was completed at the end of the final week of the study (post-treatment). An electrocardiogram (EKG) was done at the screening and Week 4 visits, adverse events were monitored throughout the study, physical examinations with vital signs were performed at the screening and post-treatment visits, and clinical laboratory tests were performed at each visit.	
Number of Subjects (Planned and Analyzed): Planned: 490 patients enrolled to achieve 240 evaluable patients, approximately 60 per treatment. Actual: 491 randomized. Safety analyses: 489 (all who received study medication: 119 oxymorphone-20; 121 oxymorphone-40 mg, 125 OxyContin-20; 124 placebo). Efficacy analyses: 392 (Intent-to-Treat population, all randomized patients who had efficacy data at baseline and Week 1 or later visit) and 261 (Evaluable population, all patients who achieved their randomized dose and had efficacy information recorded at the baseline and Week 3 visits).	
Diagnosis and Main Criteria for Inclusion: Patients were male or female, 40 years of age or older and in generally good health, with Grade II-IV severity osteoarthritis of the knee and/or hip who previously had a suboptimal response to acetaminophen and nonsteroidal anti-inflammatory drug therapy or had previously received opioid analgesics for osteoarthritis.	
Test Product, Dose and Mode of Administration; Batch Number: Over-encapsulated controlled release oxymorphone (oxymorphone CR) 20 mg and 40 mg tablets, administered orally every 12 hours. Lot numbers 9902090-A, 9902090-B and 9902090-C (oxymorphone 20 mg); 78K1, 78W1, and 1W51 (OxyContin 10 mg).	
Duration of Treatment: 2- to 7-day washout period followed by a 4-week treatment period cessation of study medication treatment for a 5th week.	

Reference Therapy, Dose and Mode of Administration; Batch Number: Over-encapsulated controlled release oxycodone (OxyContin, Purdue Pharma) 20 mg tablets; placebo capsules, administered orally every 12 hours. Batch GUS 00488 (sections .01 - .06), GUS 00698 (sections .001- .006), and GUS 00802 (sections .001 - .016).

Criteria for Evaluation:

Efficacy: The primary efficacy measure was the Arthritis Pain Intensity VAS score from patient visits. The secondary efficacy measures were the Arthritis Pain Intensity VAS score from daily patient diary; WOMAC Osteoarthritis Index Pain, Stiffness, and Physical Function Subscale Scores, and Composite Index; Patient's Global Assessment of Osteoarthritis, Physician's Global Assessment of Osteoarthritis, incidence of patient withdrawal due to lack of osteoarthritis efficacy, Patient's Sleep Assessment, and SF-36 Health Survey (8 domains and Physical Health and Mental Health Composite Indices).

Safety: Safety assessments were adverse events, EKG, physical examinations, clinical laboratory tests, vital signs, nausea assessment, and drowsiness assessment.

Statistical Methods: Analysis of Covariance (ANCOVA); Cochran-Mantel-Haenszel (CMH); Kaplan-Meier Survival method; log-rank and Wilcoxon tests; chi-square test; Fisher's exact test; Kruskal-Wallis test.

SUMMARY

EFFICACY RESULTS: The primary efficacy objective was achieved in this study: the oxymorphone-40 was superior to placebo as assessed by actual change from baseline to Week 3 in Arthritis Pain Intensity in the population of primary interest, ie, ITT population (all randomized patients who had Arthritis Pain Intensity data at baseline and Week 1 visit). In addition, oxymorphone-40 was superior to placebo at Week 4 (last visit). When the analysis was based on the ITT_2 population (all randomized patients who had Arthritis Pain Intensity data at baseline and at least one post-baseline assessment), oxymorphone-20 differed significantly from placebo at Weeks 3 and 4. OxyContin-20 did not differ from placebo at either Weeks 3 or 4. For most of the secondary efficacy measures, including Patient's Global Assessment, oxymorphone 20 and 40 were superior to placebo at Weeks 3 and/or 4, while OxyContin-20 was comparable to placebo on all components of WOMAC Index and only differed from placebo on quality of life (SF-36), Physician Global and sleep assessments.

SAFETY RESULTS: The overall rates of adverse events were statistically significantly different across the treatment groups. At least 1 adverse event was reported for 109 (90%) in the oxymorphone-40 group, 113 (95%) patients in the oxymorphone-20 group, 109 (87%) in the OxyContin-20 group, and 71 (57%) in the placebo group. In all treatment groups most adverse events were of either mild or moderate intensity. In the active treatment groups, 11 - 14% of the adverse events were judged to be severe compared to 6% in the placebo group. In the active treatment groups, 65 - 79% of all adverse events had a suspected or probable relationship to treatment compared to 43% in the placebo group. No patients died. Five (5) patients (2 oxymorphone-40, 1 oxymorphone-20 and 2 OxyContin-20) had serious adverse events. These adverse events did not result in treatment discontinuation. One hundred forty (140) patients discontinued treatment because of adverse events; 57 (47%) in the oxymorphone-40 group, 46 (39%) in the oxymorphone-20 group, 31 (25%) in the OxyContin-20 group, and 6 (5%) in the placebo group. The majority of these patients discontinued treatment because of gastrointestinal disorders (principally nausea and/or vomiting) or nervous system disorders (principally dizziness). Between the screening/baseline and end of treatment evaluations there were no clinically meaningful differences among the treatment groups in changes in laboratory test values, vital signs, physical examination findings, or EKGs. Changes from baseline in the mean nausea and drowsiness VAS at the end of each week of treatment were significantly greater for each active treatment compared to placebo.

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