Clinical Trial Results Summary
Study EN3202-016

Study Number: EN3202-016	
Title of Study: Evaluation of the Efficacy and Safety of Numorphan® CR (Oxymorphone HCl Controlled Release) Relative to Placebo and OxyContin® (Oxycodone HCl Controlled Release) in Subjects with Chronic Low Back Pain	
Investigators: Multicenter study with 26 investigators	
Study Center(s): 26 centers in the United States	
Publication (reference): None	
Studied Period (years): 28 February 2001 to 26 July 2002	**Phase of Development**: III
Objectives: The primary objective of this study was to evaluate the analgesic efficacy and safety of extended-release oxymorphone (oxymorphone ER) compared with placebo in subjects with moderate to severe, chronic low back pain requiring opioid pain therapy. The secondary objectives were to establish an efficacious dose range of oxymorphone ER, to compare the analgesic efficacy and safety of OxyContin with placebo, and to compare the safety of oxymorphone ER with OxyContin, in the same subjects.	
Methodology: This was a multicenter, randomized, placebo- and active drug-controlled study of oxymorphone ER in subjects with chronic low back pain. Subjects screened were generally in good health; male or female, aged 18 to 75 years; had a confirmed diagnosis of moderate to severe, chronic lower back pain; and required chronic treatment with opioids for their back pain. The study was divided into three phases: Screening, Double-Blind Dose Titration, and Double-Blind Treatment. Screened subjects who met the inclusion/exclusion criteria were randomly assigned to receive either double-blind oxymorphone ER or double-blind OxyContin during the 7-to-14-day Double-Blind Dose Titration Phase. Those subjects who attained a fixed dosage of study drug during titration proceeded to the 18-day Double-Blind Treatment Period. A fixed dose was one that was tolerated, provided adequate analgesia, and required minimal or no rescue pain medication. During double-blind treatment, approximately two-thirds of the subjects continued to receive the same, active study drug they had taken during titration, while the other one-third received placebo. Rescue medication (immediate-release [IR] morphine sulfate, 15 mg p.o. q4 to 6h) was available to the subjects throughout the study. During dose titration and the first 4 days of treatment, the use of rescue medication was unrestricted; for the remainder of the Double-Blind Treatment Phase, subjects were limited to two 15-mg doses of rescue medication per day. After completing the final study visit, eligible subjects could enter the open-label extension study and receive up to a year's treatment with oxymorphone ER.	
Number of Subjects (Planned and Analyzed): Planned: 240 subjects were planned to be randomized, with 80 subjects enrolled in each of the 3 treatment groups (oxymorphone ER, OxyContin, and placebo), in order to achieve a final population of 210. An average of about 12 subjects were to be randomized per site. Actual: 330 subjects were randomized to compensate for an unexpectedly large number of dropouts during titration. Analyzed for efficacy: 213 (modified ITT population without Site 23 data, all safety subjects who completed the titration phase and had at least one VAS pain intensity assessment during the double-blind treatment phase, excluding subjects from Site 23). Efficacy analyses were conducted both with and without Site 23 because of a drug diversion at that site. Analyzed for safety: 329 (safety population, all randomized subjects who received at least one dose of study medication).	
Diagnosis and Main Criteria for Inclusion: Subjects were generally in good health; male or female, aged 18 to 75 years, with a confirmed diagnosis of moderate to severe, chronic lower back pain. The subjects' back pain had been present for more than 15 days per month and several hours per day for a minimum of 2 months before Visit 1. In addition, subjects were on a stable dose of opioid pain medication for the management of moderate to severe, chronic low back pain for at least 3 consecutive days before Visit 1.	
Test Product, Dose and Mode of Administration, Batch Number: Over-encapsulated oxymorphone ER; 10-, 20-, and 40-mg tablets, administered p.o. q12h. Lot numbers: 05215.07, 05215.08, 05215.09.	
Duration of Treatment: 7-to-14-day dose titration followed by 18-day treatment period.	
Reference Therapy, Dose and Mode of Administration, Batch Number: Over-encapsulated OxyContin 20-, 40-, and 80-mg tablets, administered p.o. q12h. Lot numbers: 05215.13, 05215.14, 05215.15. Placebo capsules, administered p.o. q12h. Lot numbers: 05215.01, 05215.02, 05215.03. Morphine sulfate IR, administered open-label, p.o. q4 to 6h prn. Lot number: 27173.	

Criteria for Evaluation:
Efficacy: The modified ITT population without Site 23 was the population used for efficacy analyses in the report. The primary efficacy variable was the change in pain intensity from baseline to final visit, assessed by using a VAS score at 4 hours after dosing. The secondary measures of efficacy were the percent change from baseline in pain intensity, mean daily pain intensity (categorical) at 4 hours after the morning dose, pain relief from daily pain assessments at 4 hours after the morning dose, change from baseline in the worst daily pain from daily pain assessments, Brief Pain Inventory (BPI: pain intensity, pain relief, and pain interference items), subject's global assessment of pain medication, physician's global assessment of pain medication, time to treatment failure (discontinued because of lack of efficacy), amount of rescue medication used, and concentrations of oxymorphone in plasma.

Safety: Safety assessments were adverse events (AEs), physical examinations, vital signs, clinical laboratory tests, and opioid side effects.

Statistical Methods: Analysis of covariance (ANCOVA), analysis of variance (ANOVA), stratified rank-sum test, Kaplan-Meier method, log-rank test, McNemar's test, Kruskal-Wallis test, Fisher's exact test, chi-square test, Spearman correlation coefficient, shift tables, summary statistics.

SUMMARY:
EFFICACY RESULTS: The results of the efficacy analyses strongly support the efficacy of treatment with oxymorphone ER for the relief of chronic, low back pain. The primary efficacy analysis, change from baseline until the final visit in the VAS pain intensity score (modified ITT population without Site 23), showed a statistically superior effect of oxymorphone ER over placebo ($p=0.0001$). Statistically significant results favoring oxymorphone ER over placebo were obtained for most of the secondary efficacy variables as well: percent change from baseline in VAS pain intensity ($p=0.0032$), categorical pain intensity ($p=0.0001$), pain relief ($p=0.0006$), change from baseline in the worst daily pain ($p=0.0001$), BPI (9 out of 12 items, $p\leq0.0309$), subject's global assessment of pain medication ($p=0.0001$), physician's global assessment of pain medication ($p=0.0001$), time to treatment failure because of lack of efficacy ($p=0.0001$), and amount of rescue medication used (during the first week of treatment, $p=0.0068$).

Steady-state plasma concentrations of oxymorphone ER were achieved, on average, by the end of the titration period, with peak concentrations almost twice the concentrations at trough. However, the magnitude of peak-to-trough change in pain intensity was much less than the magnitude of change in plasma concentration, and therefore the concentration-effect correlation coefficients were low.

Comparisons of OxyContin with placebo in all the efficacy analyses performed for oxymorphone ER produced nearly identical results. The primary efficacy analysis and most of the secondary analyses gave statistically significant results favoring OxyContin over placebo.

SAFETY RESULTS: The incidence, severity, and relationship to study drug of AEs did not differ meaningfully between oxymorphone ER and OxyContin during the titration phase or among oxymorphone ER, OxyContin, and placebo during the treatment phase. During the titration phase, at least one AE was reported for 41% of subjects receiving oxymorphone ER and 39% of subjects receiving OxyContin. The most commonly reported AEs during titration were in the body systems nervous system disorders (19% of all subjects), gastrointestinal disorders (10%), and psychiatric disorders (7%). During the treatment phase, at least one AE was reported for 20% of subjects receiving oxymorphone ER, for 23% of subjects receiving OxyContin, and for 18% of subjects receiving placebo. The most commonly reported AEs during treatment were in the body systems nervous system disorders (7%), musculoskeletal/connective tissue/bone disorders (3%), and infections/infestations (3%). No AE in either phase of the study was life threatening; the majority were mild to moderate (73%).

No subjects died during the study. A total of six subjects had one or more SAEs during the study, four during titration and two during treatment; three of these subjects received oxymorphone ER, two received OxyContin, and one received placebo. The four titration subjects discontinued study medication because of their SAEs. All of these subjects' SAEs resolved without sequelae. An additional 38 subjects withdrew because of non-serious AEs; the majority, 32, discontinued during titration and the remaining 6 during treatment. There was no statistically significant difference among treatment groups in the overall number of subjects withdrawing or in the number of subjects withdrawing because of an AE within a specific body system (all $p\geq0.2117$).

The frequency and intensity of AEs, laboratory abnormalities, and opioid side effects observed during this study were within acceptable limits, were consistent with the demographic and medical status of this subject population, and in most cases, did not differ significantly among the titration/treatment groups. No abnormalities of concern were observed in these measures or in the physical exam and vital signs findings. Typical opioid side effects were common, and the titration groups were similar in the frequency and severity of the side effect that they reported. Few opioid side effects were severe or resulted in dosing changes, interruption of study drug, or withdrawal from the study.
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