Study Number: EN3202-019	
Title of Study: A Randomized, Double-Blind, Two-Period Crossover Study Comparing the Efficacy, Safety and Tolerability of Numorphan® CR (Oxymorphone HCl, Controlled Release) and OxyContin® (Oxycodone HCl, Controlled Release) in Cancer Patients Who Require Chronic Opioid Treatments	
Investigators: Thirteen investigators treated at least one subject.	
Study Center(s): Investigators treated subjects at 13 study centers.	
Publications (reference): None	
Studied period (years): 5 March 2001 – 15 March 2002	**Phase of development:** Phase III
Objectives: The primary objective of this study was to compare the analgesic efficacy of oxymorphone ER (extended release) and oxycodone ER (OxyContin), in subjects with moderate to severe pain because of cancer, by using an equivalence (non-inferiority) model. The secondary objectives were to compare safety and tolerability profiles of oxymorphone ER and OxyContin; to compare the relative incidence of typical opioid-related side effects in subjects receiving oxymorphone ER and OxyContin; to describe the relative effect of oxymorphone ER and OxyContin on the quality of life sub-scales in the Brief Pain Inventory (BPI); and to determine the approximate dosage ratio for conversion of subjects to oxymorphone ER from either pre-study opioid analgesics (before Amendment 3) or OxyContin (after Amendment 3).	
Methodology: This was a Phase III, randomized, double-blind, multiple-dose, positive-controlled, two-period, crossover, multicenter study. Each subject completed an initial titration/stabilization period to establish an effective and tolerable dose of opioid analgesic. Amendment 3 to the protocol, which resulted in significant changes to the study design, was instituted after approximately one-third of the randomized subjects had been enrolled (14/45). Before Amendment 3, subjects completed five visits: at screening, at the beginning of titration, after 7 to 10 days of dosage titration on immediate-release oxymorphone (oxymorphone IR), after the first comparison phase of the Double-Blind Treatment Period, and after the second comparison phase of the Double-Blind Treatment Period. After Amendment 3, subjects completed four visits: at screening, after 3 to 10 days of dosage stabilization on OxyContin, after the first comparison phase of the Double-Blind Treatment Period, and after the second comparison phase of the Double-Blind Treatment Period. After screening, all subjects completed either a dose Titration Period on immediate-release (IR) oxymorphone (before Amendment 3) or a Screening/Stabilization Period on OxyContin (after Amendment 3). After a stable dose of opioid analgesic was established, subjects were randomized and entered the Double-Blind Treatment Period. During the first comparison period of 7 to 10 days, subjects received either double-blind oxymorphone ER or double-blind OxyContin. During the second comparison period of 7 to 10 days, subjects crossed over to the other double-blind treatment. During the Double-Blind Treatment Period, subjects were allowed oral morphine sulfate every 4 to 6 hours as needed for breakthrough pain. Subjects used a diary to record all study drug taken, any supplemental pain medication taken, and the intensity of pain just before rescue. An electrocardiogram (ECG) was obtained at the first visit or within 30 days before the first visit, physical examinations with vital signs were done at the first and final visits, clinical laboratory tests were performed at each visit, and adverse events were monitored throughout the study.	
Number of subjects (planned and analyzed) and analysis populations: Planned: 72 subjects were to be randomized in an effort to obtain 50 evaluable subjects. Actual: 45 were randomized. Analyzed for safety: 44 (safety population, all randomized subjects who received at least one dose of double-blind study medication, oxymorphone ER or OxyContin). Analyzed for efficacy: 42 (intent-to-treat [ITT] population, all randomized subjects who received at least one dose of double-blind study medication and	

had one or more pain intensity evaluations after treatment) and 37 (efficacy-evaluable population, all randomized subjects who completed the first comparison phase of the Double-Blind Treatment Period, completed at least 5 days of the second comparison phase, and had no major protocol violations).

Diagnosis and main criteria for inclusion: Subjects were male or female, 18 years of age or older and in generally stable health, with a diagnosis of cancer accompanied by moderate to severe pain that required chronic treatment with opioid analgesics.

Test product, dose and mode of administration: Over-encapsulated, extended-release oxymorphone (oxymorphone ER), 10 mg to 110 mg, administered orally every 12 hours. Batch numbers: 05215.07 (oxymorphone ER 10 mg), 05215.08 (oxymorphone ER 20 mg), 05215.09 (oxymorphone ER 40 mg).

Duration of treatment: About 7 to 10 days on test product and about 7 to 10 days on reference therapy, in randomly determined order.

Reference therapy, dose and mode of administration: Over-encapsulated, controlled-release oxycodone (OxyContin, Purdue Pharma), 20 mg to 220 mg, administered orally every 12 hours. Batch numbers: 05215.13 (OxyContin 20 mg), 05215.14 (OxyContin 40 mg), 05215.15 (OxyContin 80 mg).

Criteria for evaluation:

Efficacy: The primary efficacy measure, analgesic efficacy, was evaluated by using the 24-hour average pain intensity rating, BPI Question 5, from the final visit of each comparison phase of the Double-Blind Treatment Period in the efficacy-evaluable population of subjects.

The secondary efficacy measures were the 24-hour average pain intensity rating (BPI Question 5), from the final visit of each comparison phase of the Double-Blind Treatment Period in the ITT population; trough and peak pain intensity, obtained just before and 3 hours after the administration of study medication on the last day of each comparison phase of the Double-Blind Treatment Period; trough and peak pain relief, obtained just before and 3 hours after the administration of study medication on the last day of each comparison phase of the Double-Blind Treatment Period; amount of rescue analgesic required, computed from the subject diary records for each comparison phase of the Double-Blind Treatment Period; BPI scales, with separate analyses conducted for each item on the BPI obtained at the end of each comparison phase of the Double-Blind Treatment Period; subject and physician global evaluations; Karnofsky Performance Status scores, obtained at the end of each comparison phase of the Double-Blind Treatment Period; daily pain intensity during each comparison phase of the Double-Blind Treatment Period, and oxymorphone equivalent dose, the amount of reference opioid (OxyContin) that was equivalent in analgesic effect to a stated dose of oxymorphone ER.

Also analyzed were the correlation between pain ratings and plasma concentrations of oxymorphone ER.

Safety: Safety assessments were adverse events (AEs), ECGs, physical examinations, vital signs, and clinical laboratory tests. The incidence of common opioid side effects was summarized for each treatment.

Statistical methods:

Efficacy: Mixed-effects model, with Kolmogornov-Smirnov test for normality; Spearman's Correlation Coefficient. Safety: Summary statistics, change from baseline, and shift summaries.

All statistical tests were 2-sided at a significance level of 0.05 unless otherwise specified. SAS® Version 8.2 was used in all statistical analysis.

SUMMARY:

Efficacy Results: The results of the primary and secondary efficacy analyses consistently supported the equivalence of oxymorphone ER with OxyContin in the relief of chronic pain in subjects with cancer. The primary efficacy analysis, comparing patients' ratings of average 24-hour pain intensity, demonstrated a significant treatment effect favoring oxymorphone ER ($p = 0.0344$) and a significant

difference in least-squares (LS) means for the treatments (95% confidence interval of -0.72 to -0.03), indicating a significantly lower 24-hour average pain rating in subjects receiving oxymorphone ER. All the secondary efficacy analyses demonstrated statistical equivalence between oxymorphone ER and OxyContin: trough and peak pain intensity, trough and peak pain relief, amount of rescue analgesic taken, pain and quality of life ratings from the BPI, subjects' and physicians' global assessments, Karnofsky performance status, and average daily pain intensity from diary records. The evaluations of efficacy demonstrated that oxymorphone ER had a statistically equivalent efficacy to OxyContin in a wide range of measures, and calculation of the ratio between the average daily dose of OxyContin and oxymorphone ER by the subjects gave a value of 1.99 OxyContin/oxymorphone, very close to the predicted value of 2.

Safety Results: The incidence and severity of AEs did not differ notably between subjects taking double-blind oxymorphone ER and OxyContin. At least one AE was reported for 21% (9/43) subjects receiving oxymorphone ER and for 42% (18/43) of subjects receiving OxyContin. The AEs reported most frequently during double-blind treatment were in the body systems cardiac disorders (5% on oxymorphone ER versus 7% on OxyContin), gastrointestinal disorders (2% on oxymorphone ER versus 9% on OxyContin), and general disorders (5% on oxymorphone ER versus 16% on OxyContin). The majority of AEs were of mild or moderate severity, 100% (19/19) during treatment with oxymorphone ER and 83% (29/35) during treatment with OxyContin. Few AEs had either a possible or probable relationship to treatment, only 11% (2/17) during treatment with oxymorphone ER and 20% (7/35) during treatment with OxyContin. AEs during titration/stabilization on open label oxymorphone IR or OxyContin showed a similar pattern.

Four subjects had SAEs during the study, one receiving open-label oxymorphone IR during the Titration Period and three receiving double-blind OxyContin. One of the patients receiving OxyContin died. All of these adverse events were judged by the investigators to be unrelated to treatment with study medication. Three additional subjects discontinued study treatment because of AEs: two subjects receiving oxymorphone IR discontinued during titration, and one subject receiving oxymorphone ER discontinued during double-blind treatment. The frequency and intensity of AEs, laboratory abnormalities, and opioid side effects observed during this study were within acceptable limits and were consistent with the medical status of the subject population. No abnormalities of concern were observed in these measures or in the physical exam and vital signs findings. Both study medications were well tolerated by the subjects; neither treatment was associated with dose changes or discontinuations because of opioid side efects.