Clinical Trial Results Summary
Study EN 3202-017

Study Number: EN3202-017	
Title of Study: Open Label, Sequential Crossover Evaluation of the Analgesic Dose Equivalence, Efficacy and Safety of Controlled-Release Oxymorphone (Numorphan® CR) Relative to Controlled-Release Oxycodone (OxyContin®) and Controlled-Release Morphine (MS Contin®) in Patients With Cancer Pain	
Investigators: Multicenter 16 Investigators	
Study Centers: Sixteen (16) investigational centers in the USA	
Publication (reference): None	
Study Period (years): October 1999 - August 2000	**Phase of Development**: III
Objectives: The primary objectives of this study of patients with cancer pain were to compare the analgesic efficacy and tolerability of extended-release oxymorphone to both extended-release morphine (MS Contin) and to extended-release oxycodone (OxyContin). The secondary objectives of the study were to compare the analgesic dose equivalence and safety of extended-release oxymorphone to both extended-release morphine (MS Contin) to extended-release oxycodone (OxyContin).	
Methodology: This was a multi-center, open-label, sequential crossover study to compare the analgesic efficacy and safety and dose equivalence of extended-release oxymorphone (oxymorphone ER) to OxyContin and MS Contin in patients with cancer pain. Patients who were using extended-release morphine or extended-release oxycodone and who satisfied the criteria for study entry, were transferred to MS Contin or OxyContin given q12h. Patients receiving other opioids who were otherwise eligible for the study, were transferred to a presumed equianalgesic dose of MS Contin or OxyContin and had a prospective dose titration and stabilization period of at least 3 days to establish stable analgesia. Stable analgesia was defined as requiring ≤3 rescue doses of an opioid analgesic per 24 hour period, averaged over 3 consecutive days (closest to study entry). Rescue medication was administered as an immediate-release formulation of their titration medication. Patients who did not achieve stable analgesia in 2 weeks were to be terminated from the study. At the completion of the titration period, patients were to receive continued treatment for 7 days with their titration period medication (MS Contin or OxyContin) without any change in the dose. Rescue medication was administered as an immediate-release formulation of their medication. At the completion of the 7-day treatment period all patients were transferred to treatment with oxymorphone ER for 7 days at an estimated equianalgesic dose. Patients were to treat breakthrough pain with doses of immediate-release oxymorphone. Patients with inadequate pain control or unacceptable side effects could have adjustments to their daily dose of oxymorphone. At the completion of the 7-day oxymorphone ER treatment period patients returned to the center for their final visit (Visit 4), returned their diaries, and had final efficacy and safety assessments. During the titration and treatment periods, patients recorded in their study diaries efficacy assessments and use of rescue medication. Efficacy assessments included pain, nausea, and drowsiness assessments at 8:00, 12:00, 16:00, and 20:00 each day using a 100 mm visual analog scale (VAS), categorical pain assessments using a 5-point scale, and sleep assessment using a 100 mm VAS. Before starting and after completing each treatment, patients rated the pain, nausea, and drowsiness over the prior 2 days using the VAS.	
Number of Subjects (Planned and Analyzed): Planned: 30 in each treatment sequence who completed the study. Efficacy analysis: 18 MS Contin/Oxymorphone; 41 OxyContin/Oxymorphone. Safety analysis: 34 MS Contin, 52 OxyContin; 21 MS Contin/Oxymorphone; 42 OxyContin/Oxymorphone	
Diagnosis and Main Criteria for Inclusion: The study included patients who were 18 - 75 years of age, had a history of chronic cancer pain requiring treatment with daily oral doses of at least 30 mg morphine or 20 mg oxycodone, or the analgesic equivalent of at least 30 mg oral morphine per day, and had at least a 3-day history of stable analgesia.	
Test Product, Dose and Mode of Administration; Batch Number: Orally administered oxymorphone ER 20 mg tablets (lot numbers: 9902090, 9906368). Each patient's dose was the dose that was equivalent to his or her dose of MS Contin or OxyContin during the first treatment period. Orally administered immediate-release 5 mg oxymorphone tablets were used for rescue medication (lot number: 9903522).	

Reference Therapy, Dose and Mode of Administration, Batch Number: Orally administered MS Contin tablets (lot numbers: 79W1, 79X1, 79Y1, 72B1, 91V1, 0Y41, 0X42, 0X91, 0Y51) or OxyContin tablets (lot numbers: 0B01, 0B21, 0B41, 0B71, 1W51, 2J21, 2H91). Each patient's dose was his or her stabilized dose of MS Contin or OxyContin during the titration period. Orally administered immediate-release morphine tablets (lot numbers: 86E1, 80S1, 90Y1, 1L71) or oxycodone tablets (991117A, 992488A) were used for rescue medication. All reference therapies were obtained commercially.

Duration of Treatment: Following dose titration, patients received MS Contin and OxyContin for 1 week followed by oxymorphone ER for 1 week.

Criteria for Evaluation:

Efficacy: The primary efficacy variable was the daily VAS pain intensity assessment. Secondary efficacy variables included daily pain intensity based on categorical scale, daily scheduled dose of study drugs, rescue analgesic use, total daily dose of study drugs (combining daily scheduled dose with rescue dose), daily quality of life assessment (patient's assessment of nausea, drowsiness, and sleep), pain recall at Visits 2, 3, and 4 (least pain, worst pain, and average pain), and patient's assessment of sleep at Visits 2, 3, and 4.

Safety: Safety was based on the incidence of adverse events, discontinuations due to adverse events, and changes over time in laboratory values, vital signs and physical examination findings.

Statistical Methods: 2-sided tests; Pearson chi-square test; paired t-test; Wilcoxon signed-rank test and McNemar's test; linear regression.

SUMMARY:

EFFICACY RESULTS:

- Equianalgesia was achieved between MS Contin/oxymorphone ER and OxyContin/ oxymorphone ER treatments as reflected by similar pain intensity VAS scores (primary efficacy variable) and supported by pain intensity categorical scores (secondary efficacy variable) during last 2 days of Week 1 treatment and last 2 days of Week 2 treatment. Likewise, there were only small changes in least and worst pain in each treatment sequence, although there was a small yet statistically significant improvement in average pain on oxymorphone in the MS Contin/oxymorphone treatment sequence.
- The percent of rescue dose with oxymorphone was the same regardless of the treatment sequence and similar to OxyContin, whereas MS Contin required substantially higher percent rescue.
- For both treatment sequences, a linear dose relationship was observed between MS Contin and oxymorphone ER (R^2= 0.6924) and OxyContin and oxymorphone ER (R^2= 0.9084). Based on this linearity, equianalgesic dose ratios were calculated. The mean ratio of MS Contin to oxymorphone ER was 1.782 to 1 and the mean ratio of the OxyContin to oxymorphone ER was 1.202 to 1. The same ratios were estimated for the total doses (scheduled ER doses plus rescue medication); the mean ratio of total morphine to total oxymorphone dose was 1.804 to 1 and the mean ratio of total oxycodone to total oxymorphone dose was 1.178 to 1. It should be noted that the estimation of dose ratios is subject to limitation imposed by the design of the study. As an open-label study, there is potential for bias, confounded by allowance for dose adjustments and rescue medication. It is very important also to point out that a further limitation imposed by the study design was the availability of only one strength of oxymorphone ER (20 mg) and IR (5 mg) in contrast to MS Contin and OxyContin. Thus there was limited flexibility in adjusting the dose of oxymorphone that may have led to an overestimatation of the dose of oxymorphone needed to provide equianalgesia to MS Contin and OxyContin. Final confirmation of the relative efficacy and potency needs to be obtained from a double-blind study specifically designed for this purpose.
- There were no clinically or statistically significant differences in the quality of life assessments (nausea, drowsiness, and sleep) between Weeks 1 and 2, in favor of oxymorphone ER.

SAFETY RESULTS:
At least one adverse event was reported for 13 (38%) patients during treatment with MS Contin, by 10 (48%) patients during treatment with oxymorphone ER after treatment with MS Contin, by 24 (46%) patients during treatment with OxyContin, and by 22 (52%) patients during treatment with oxymorphone ER after treatment with OxyContin. The highest incidence rates of AEs occurred in the gastrointestinal disorders with nausea as the most prevalent symptom. Four (4) patients died from progression of their cancers. Seven (7) patients had other serious adverse events; 1 during the screening visit and before receiving study medication, 1 during treatment with MS Contin, 4 during treatment with OxyContin, and 1 during treatment with oxymorphone ER. Twelve (12) patients, including 2 with serious adverse events discontinued treatment because of adverse events; 7 during treatment with MS Contin, 3 during treatment with OxyContin, and 2 during treatment with oxymorphone ER.

Treatment with oxymorphone ER after treatment with either MS Contin or OxyContin had no clinically meaningful effects on vital signs, physical examination findings, or any laboratory test.

Report Date: 21-Sep-2001