Clinical Trial Results Summary
Study EN3202-018

Study Number: EN3202-018

Title of Study: A Randomized, Double-Blind, Two-Period Crossover Trial Comparing the Safety and Effectiveness of Numorphan® CR (oxymorphone controlled-release tablets) and MS Contin® (morphine sulfate controlled-release tablets) for the Relief of Moderate to Severe Pain in Patients with Cancer

Investigators: Multicenter study conducted at 25 centers

Study Centers: Twenty-five (25) study centers in the United States

Publication (reference): None

Study Period (years): March 2001 – March 2002 | **Phase of Development**: III

Objectives: The primary objective of this study was to compare the analgesic efficacy of EN3202 (oxymorphone extended-release [ER] tablets) and MS Contin® (morphine extended-release [ER] tablets) in subjects with moderate to severe pain due to cancer.

The secondary objectives of this study were to:

- Determine the approximate dosage ratio for conversion of subjects from pre-study analgesic regimens to oral oxymorphone ER
- Examine the relative effect of oxymorphone ER and morphine ER on the quality of life sub-scales in the Brief Pain Inventory (BPI) (Short Form)
- Compare the relative incidence of typical opioid adverse experiences (AEs) in subjects receiving oxymorphone ER and morphine ER
- Compare the relative safety and tolerance of oxymorphone ER and morphine ER

Methodology: This was a multi-center, randomized, double-blind, two-period crossover study conducted in outpatients with moderate to severe cancer pain. The study had two designs–one prior to Amendment 2 and one following Amendment 2.

Prior to Amendment 2, the study had three phases: screening, open-label titration, and double-blind crossover treatment. During screening, eligibility and the effectiveness of pre-study analgesia were determined. During titration, the total daily dosage requirement of oxymorphone IR needed to achieve stable and effective analgesia was determined. During double-blind treatment, subjects were randomly assigned to 1 of 2 treatment sequences: Sequence 1 (oxymorphone ER→morphine ER) or Sequence 2 (morphine ER→ oxymorphone ER). Each subject's oxymorphone ER dosage requirement was based on the oxymorphone IR dose required during titration. Subjects received one-half of the total daily oxymorphone IR dosage requirement every 12 hours (q12h) (eg, a subject who required 60 mg of oxymorphone IR during titration received 30 mg of oxymorphone ER q12h during double-blind treatment). Each subject's morphine ER dose was based on a 3:1 fixed ratio of morphine to oxymorphone (eg, the subject who received 30 mg of oxymorphone ER q12h received 90 mg of morphine ER q12h).

With Amendment 2, the study design was changed to two phases: screening/stabilization and double-blind treatment. During screening/stabilization, eligibility and the total daily dosage requirement of morphine ER needed to achieve stable and effective analgesia were determined. During double-blind treatment, subjects were randomly assigned to one of two treatment sequences as described above. During double-blind treatment, subjects received the same dose of morphine ER as that determined from stabilization and one-third as much oxymorphone ER.

Number of Subjects Planned and Analyzed: Fifty (50) subjects were planned (25 per randomized treatment group); 40 enrolled and were included in the safety population; 38 had titration/stabilization dosing data (20 received oxymorphone IR and 18 received morphine ER); 36 were randomized (20 to Sequence 1 and 16 to Sequence 2); 34 (32 in each treatment group) were included in the intent-to-treat (ITT) population; and 20 (20 in each treatment group) were in included in the efficacy evaluable population.

Diagnosis and Main Criteria for Inclusion: Adult (≥18 years of age) subjects with moderate to severe chronic cancer pain who required the use of World Health Organization (WHO) Step 3 analgesics (ie, strong opioids) were eligible to enter the study.

Test Product, Dose and Mode of Administration; Batch Number(s):
EN3202 (oxymorphone HCl extended-release) 10-, 20-, and 40-mg tablets (over-encapsulated), oral administration,
Lot Numbers: 10 mg: 0002236-A and 310176 (resupply)
20 mg: 0002830-A and 310180 (resupply)
40 mg: 9905924-C and 310183 (resupply)

Reference Therapy, Dose and Mode of Administration; Batch Number(s):
MS Contin® (morphine extended-release) 30- , 60-, and 2×60-mg tablets (over-encapsulated), oral administration,
Lot Numbers: 30 mg: 5H01 and BK11 (resupply)
60 mg: 5D25 and BK21 (resupply)
120 mg: 5D25 and BK21 (resupply) 2×60 mg (the two tablets were over-encapsulated into one capsule to maintain blinding)

Open-Label Drug Therapy, Dose and Mode of Administration; Batch Number(s):
EN3203 (oxymorphone immediate-release) 5- and 10-mg tablets, oral administration,
Lot Numbers: 5 mg: 0002832 and 9903522
10 mg: 0002837
Percolone® (oxycodone HCl immediate-release) 5-mg tablets, oral administration,
Lot Number: 5 mg: PD287A

Duration of Treatment: Subjects entered a 7-day titration/stabilization phase followed by two 7-day treatment periods with no washout. The titration/stabilization phase could be extended to allow a stable and effective dose of analgesia to be attained, and to allow for scheduling, subjects could extend double-blind treatment up to 2 days in each period.

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint was the 24-hour average pain intensity (Question 5 on the Brief Pain Inventory Short Form [BPI]) score at the end of each double-blind treatment period for the efficacy evaluable population. Other efficacy endpoints included: self-rated pain intensity and pain relief as measured on an 11-point numeric rating scale at the end of each double-blind treatment period just prior to dosing (trough) and 3 hours after dosing (peak); average daily dose of rescue analgesic taken; individual BPI scales at the end of each double-blind treatment period; subjects' daily assessment of average pain based on diary scores; subject and investigator global pain relief assessments at the end of each double-blind treatment period; Karnofsky performance status scores at the end of each double-blind treatment period; determination of the oxymorphone ER equivalent dose; and correlation of oxymorphone ER plasma levels and pain intensity.

Safety: Safety was assessed by recording and monitoring AEs, clinical laboratory values, vital signs, and abnormal findings upon physical examination. In addition, opioid side effects were measured by assessing presence or absence of seven opioid symptoms using a checklist. The severity of each symptom, the severity compared with the prior week, and the action taken with study medication were also recorded.

Statistical Methods:

Efficacy: The primary efficacy analysis was a comparison between treatment groups of the 24-hour average pain intensity score for the efficacy evaluable population using a mixed effects model with treatment, sequence, and period as fixed effects and subject as a random effect; the 2 treatments were considered comparable if the 95% confidence interval around treatment included zero. Carryover was evaluated a significance level of 0.10. Secondary efficacy endpoints were analyzed using the mixed effects model described above or were summarized using descriptive statistics; plasma levels of oxymorphone ER and pain intensity were summarized at peak and trough and analyzed using Spearman's correlation coefficient.

Safety: AEs were summarized by treatment group for the titration/stabilization phase (oxymorphone IR, morphine ER) and for the double-blind treatment phase (oxymorphone ER, morphine ER) using MedDRA® system organ class and preferred term. Clinical laboratory parameters and vital signs were summarized using descriptive summary statistics and change from baseline. Additional tabulations of safety data were also provided.

SUMMARY:

EFFICACY RESULTS: For the efficacy evaluable population, oxymorphone ER and morphine ER were not statistically comparable with respect to the primary endpoint (average pain intensity score over the last 24 hours [Question 5 from the BPI]) (95% CI: –2.0, –0.8; $p<0.001$). In addition, there were statistically significant sequence ($p=0.025$) and period ($p=0.019$) effects. Similar results were obtained for the ITT population; however, there was not a statistically significant sequence effect in this population. Descriptive summary statistics by period for the efficacy evaluable population showed that the average pain score in Period 1 was lower for subjects who received morphine ER (mean±SD=1.1±0.93) compared with subjects who received oxymorphone ER (mean±SD=4.1±1.70); however, the scores were similar between treatment groups for Period 2 (3.2±1.64 oxymorphone ER vs. 3.5±1.86 morphine ER).

Oxymorphone ER and morphine ER were comparable for pain intensity at peak ($p=0.725$) and trough ($p=0.087$) for the efficacy evaluable population and at peak ($p=0.859$) and trough ($p=0.304$) for the ITT population; however, there were statistically significant ($p<0.10$) sequence effects at trough for the efficacy evaluable population and at peak for the ITT population. Oxymorphone ER and morphine ER were comparable for pain relief at peak ($p=0.627$) for the efficacy evaluable population and at peak ($p=0.868$) and trough ($p=0.055$) for the ITT population. There were no statistically significant sequence or period effects for pain relief for either analysis population.

Subjects receiving oxymorphone ER took significantly more rescue medication on Days 4 through 10 for both the efficacy evaluable ($p=0.020$) and ITT ($p=0.003$) populations; there were no statistically significant sequence or period effects. Of the BPI assessments of worst, least, and current pain and percent pain relief, oxymorphone ER and morphine ER were comparable only for worst pain ($p=0.152$) in the efficacy evaluable population; treatment groups were comparable for worst ($p=0.266$) and current pain ($p=0.140$) for the ITT population. There was a statistically significant sequence effect for least pain for the efficacy evaluable population. In the efficacy evaluable population, oxymorphone ER and morphine ER were comparable ($p>0.05$) for five of the seven quality of life endpoints; "pain interference with general activity in the last 24 hours" and "pain interference with sleep in the last 24 hours" were statistically higher for subjects who received oxymorphone ER than those who received morphine ER ($p<0.01$). One(1) additional quality of life endpoint, "pain interference with enjoyment of life in the last 24 hours," approaced statistical significance ($p=0.054$). There were no significant sequence or period effects for any quality of life endpoint for the efficacy evaluable population.

The average daily pain intensity scores (diary) were comparable between treatment groups for the efficacy evaluable population on Day 1 and Days 4 through 10 and there were no significant sequence or period effects on these days. Trends toward significance (>0.05 $p \leq 0.10$) were observed on Days 9 and 10, and a significant sequence effect was observed on Day 3. Results from the ITT population were similar, with treatment reaching statistical significance on Days 2 and 3 and a significant sequence effect on occurring on Day 3.

Equianalgesia between oxymorphone ER and morphine ER was not attained, ie, oxymorphone ER and morphine ER were not statistically comparable with respect to the primary efficacy analysis. In addition, this crossover study demonstrated a statistically significant sequence effect, thus, a valid dose ratio cannot be calculated from the data.

SAFETY RESULTS: Two (2) subjects died from progression of disease state (one in each treatment group). Serious AEs not resulting in death were reported by six subjects (5 morphine ER and 1 oxymorphone ER); each of these AEs was considered of unlikely relationship to study medication. Five (5) subjects prematurely discontinued study medication because of an AE; one subject received titration/stabilization medication, but had no dosing data provided on the case report form (CRF); 2 subjects discontinued in Period 1 (morphine ER), but had no dosing data provided on the CRF; and two additional subjects received morphine ER in Period 1 prior to discontinuation and had dosing data.

The majority of all AEs occurring during double-blind treatment were mild or moderate in severity and there were no apparent trends in severity. The most commonly observed (≥10% of subjects) AEs occurring during the double-blind treatment period were those events listed on the opioid symptom checklist. Because these events were elicited, they were automatically assigned a relationship to study medication of "probable." Thus, these same events (with the same incidence) were also the most commonly observed treatment-related AEs. In order of incidence in the oxymorphone ER treatment group, these AEs were: constipation (50% oxymorphone ER vs. 59% morphine ER), nausea (38% vs. 34%), sedation (31% vs. 31%), increased sweating (31% vs. 28%), pruritus NOS (22% vs. 34%), dizziness exc. vertigo (22% vs. 31%), and vomiting NOS (19% vs. 25%). Overall, there were no apparent clinically relevant differences in the incidence or severity of these AEs between treatment groups. In general, the proportion of subjects whose opioid symptom was unchanged, better, or worse compared with the previous week (ie, the other treatment) was similar between treatment groups. No subjects in either treatment group had an interruption in study medication because of an opioid event, and the incidence of subjects requiring a change in medication or dose adjustment was similar between treatment groups.

Report Date: 24-Sep-2002

There were no clinically meaningful differences between treatment sequence (screening), between oxymorphone IR and morphine ER (titration/stabilization), or between oxymorphone ER and morphine ER (end of Period 2) for any clinical chemistry, hematology, urinalysis, or vital sign parameter. At the end of Period 2, one subject (oxymorphone ER) reported a Grade 3 clinical chemistry value (phosphorus) and six subjects (two oxymorphone ER and four morphine ER) reported one or more Grade 3 hematology values (WBC, platelet, lymphocyte, or neutrophil count); the observed laboratory abnormalities were consistent with a cancer population receiving concurrent chemotherapy. No subject reported a Grade 4 value for any laboratory parameter, and no subject reported a Grade 3 value for any urinalysis parameter. In general, the number of subjects with abnormal physical examination findings at the end of Period 2 was less than the number at screening. In addition, the number of subjects with abnormal findings in each system organ class was similar between treatment sequences. The findings for which there was a shift from normal at baseline to abnormal at the end of Period 2 were: general appearance (1 subject, morphine ER), abdomen (3 subjects, morphine ER), extremities (2 subjects, oxymorphone ER), skin (2 subjects, oxymorphone ER), and lymph nodes (1 subject, oxymorphone ER).

Report Date: 24-Sep-2002