Study Number: EN3202-020	
Title of Study: A Multicenter, Open Label Extension Study to Evaluate the Long-term Safety and Effectiveness of Numorphan® CR in Patients with Chronic Pain	
Investigators: 32 Investigators	
Study Center(s): 32 study centers located in the United States	
Publications (reference): None	
Studied period (years): Date of First Enrollment: 1 December 1999 Date of Study Completion: 11 July 2002	**Phase of development:** Phase III
Objectives: The primary objective of the study was to assess the long-term safety of oxymorphone ER in patients with chronic cancer pain or chronic non-malignant pain. The secondary objective was to assess the long-term effectiveness of oxymorphone ER in patients with chronic cancer pain or chronic non-malignant pain.	
Methodology: This was a 104-week, open-label, non-comparative, multicenter study. Patients who had previously completed EN3202-015 (a study in chronic osteoarthritis pain patients) or EN3202-017 (a study in chronic cancer pain patients) and who met all inclusion and exclusion criteria were eligible to participate. Patients received oxymorphone ER in the dosage determined in their previous study. For patients who did not receive oxymorphone ER in their previous study, the initial dosage used was equal to the lowest oxymorphone ER dose used in the previous study. Oxymorphone ER was to be taken twice daily in equally divided doses. Patients with inadequate pain control or unacceptable side effects had their dose of oxymorphone ER reassessed. For cancer pain patients, rescue medication in the form of immediate-release oxymorphone (oxymorphone IR) was dispensed at the time of enrollment, and was to be taken as needed for breakthrough pain. Patients with significant rescue medication use were assessed for a possible increase in oxymorphone ER dose. Patients with pain unresponsive to dosage adjustments or with unacceptable side effects were to be discontinued from the study. During the first year, patients returned to the clinic for efficacy and safety assessments, collection of remaining study and rescue medications from the previous visit, and dispensing of additional study and rescue medications at the completion of Weeks 1, 2, 6, 10, 16, and at 6-week intervals thereafter through Week 52. During the second year, patients returned to the clinic at 4-week intervals beginning at Week 56 for the assessment of adverse events and concomitant medications, for collection of remaining study and rescue medications from the previous visit, and for dispensing of additional study and rescue medications. Efficacy and additional safety assessments were conducted at 12-week intervals beginning at Week 64. Effectiveness assessments included ratings of current pain intensity using a five-point categorical scale, where 0 = “no pain” and 4 = “excruciating pain”, and a 100 mm visual analog scale (VAS) bounded on the left by “no pain” and on the right by “excruciating pain.” Similar VAS assessments were provided for the least pain, the worst pain, and average pain experienced during the preceding week. A global assessment of the study medication using a five-point scale (where 1 = “poor” and 5 = “excellent”) was also obtained. Quality of life assessments included evaluations of current nausea and current drowsiness using two separate 100 mm VASs. Safety was assessed using non-directed adverse event questionnaires, clinical laboratory tests, vital signs, electrocardiograms (EKGs) and physical examinations.	
Number of patients (planned and analyzed): Determined by the numbers of patients who completed EN3202-015 and EN3202-017 and agreed to continue into the study. A total of 197 patients (153 with non-malignant pain and 44 with cancer pain) were included in the analysis.	
Diagnosis and main criteria for inclusion: Patients were to have completed either EN3202-015 or EN3202-017 according to the protocol, were to be age 18 or older with chronic non-malignant or cancer pain, and with no evidence of intractable nausea or vomiting, clinically significant gastrointestinal	

disorders, unstable renal function, chronic respiratory insufficiency, or history of intolerance to oxymorphone.

Test product, dose and mode of administration, batch number: Extended-release oxymorphone 20-mg and 40-mg tablets (second year only) administered orally every 12 hours. Lot numbers for oxymorphone ER 20 mg: 9906368, 310181 and 9902090. Lot numbers of oxymorphone ER 40 mg: 310183. Lot numbers for oxymorphone IR 5 mg (rescue medication for chronic cancer pain patients): 9903522 and 310028.

Duration of treatment: Up to 2 years

Reference therapy, dose and mode of administration, batch number: None

Criteria for evaluation: The assessment of long-term safety was the primary objective of this study; effectiveness assessments addressed the secondary objective.

Effectiveness: The primary effectiveness variables were the VAS ratings of the least, worst and average pain during the preceding week and the patient's global assessment of study medication. Secondary effectiveness variables were the current pain intensity assessments (VAS and categorical), the average daily dose of scheduled study medication, and the average daily dose of scheduled rescue medication (cancer pain patients only).

Quality of Life: Quality of life assessments included the VAS assessments of nausea and drowsiness.

Safety: Safety assessments included monitoring of adverse events, clinical laboratory tests, vital signs, physical examinations and EKG recordings, and pregnancy tests (in women of child-bearing potential).

Statistical methods: All analyses were conducted for the entire patient population as well as by pain type (i.e., chronic cancer pain or chronic non-malignant pain). There was no imputation of missing values. All statistical tests were two-sided, with statistical significance denoted by a p-value of 0.05 or less. Patient disposition was summarized by tabulating the number of patients who received study medication, the number and percentage of patients who completed the study, the numbers and percentages of patients who withdrew from the study and the reason for withdrawal. The time to withdrawal was depicted graphically using Kaplan-Meier methods. Descriptive statistics for demographic and baseline characteristics were tabulated for all patients who took at least one dose of study medication. Efficacy analyses were based on the intent-to-treat (ITT) population, defined as all patients who took at least one dose of study medication and who had at least one post-baseline efficacy evaluation. For pain intensity assessments (VAS and categorical), pain recall assessments (least pain, worst pain, and average pain), and quality of life assessments (VAS score for nausea and drowsiness), the following descriptive statistics were provided for each scheduled visit (including the baseline visit) and for the final visit: number of observations, mean, standard deviation, minimum, median, and maximum. These descriptive statistics were also presented for the change from baseline to each post-baseline visit and to the final visit. Paired t-tests were used to determine the statistical significance of the changes from baseline to each visit. Frequency distributions of the patients' global assessments of the study medication were tabulated for each post-baseline visit and for the final visit. The average daily dose of study medication and the average daily dose of rescue medication were summarized by exposure time using the following descriptive statistics: number of observations, mean, standard deviation, minimum, median, and maximum. Mean pain intensity scores (VAS and categorical scale), mean pain recall scores (least, worst and average) and average daily doses of study medication and rescue medication were displayed graphically. Safety analyses were based on the safety population, defined as all patients who took at least one dose of study medication. Incidence rates for adverse events were tabulated by body system and MedDRA preferred term. These incidence rates were also summarized by the intensity of the events and by their relationship to treatment. Laboratory test results at each visit and changes in laboratory test results from the baseline visit to each post-baseline visit and to the final visit were summarized using the following descriptive statistics: number of observations, mean, standard deviation, minimum, median,

and maximum. Paired t-tests were used to determine the statistical significance of the changes from baseline to each visit. For each laboratory test, a shift table of the relative change from baseline (i.e., "worsened" or "not worsened") at each scheduled post-baseline visit and at the final visit was constructed. Descriptive statistics (including the number of observations, mean, standard deviation, minimum, median, and maximum) for the change in vital sign measurements from the baseline visit to each scheduled post-baseline visit and to the final visit were tabulated. Paired t-tests were used to determine the statistical significance of the changes from baseline to each visit. For physical examination results, frequency counts and percentages by body system were provided at each scheduled visit and at the final visit. Shifts from baseline in assessment of each body system were tabulated at each scheduled visit and at the final visit. Frequency distributions for the overall assessment of the EKG (normal, abnormal and not clinically significant, or abnormal and clinically significant) were presented by visit. In addition, frequency distributions for patients who shifted from normal at baseline to abnormal during the post-baseline evaluation period were presented by visit.

SUMMARY:

Safety: In general, the most frequently occurring adverse events were those typically associated with opioid analgesic medication. Nausea and vomiting were the most frequently occurring severe adverse events. The majority of adverse events were not considered to be treatment related. Those that were considered to be treatment related were events commonly associated with opioid medications.

Eleven of the 12 deaths that occurred during the study were in cancer pain patients, and 9 of these patients died due to disease progression. None of the deaths was considered to be treatment related. Not unexpectedly, serious adverse events occurred more frequently in cancer pain patients. The most frequently occurring serious adverse events were those related to the patients' diseases (i.e., aggravation of osteoarthritis in non-malignant pain patients and disease progression in cancer pain patients). Adverse events resulting in discontinuation were typically those events related to opioid analgesic medications (nausea, vomiting, constipation and dizziness).

A direct comparison of incidence rates for adverse events between the non-malignant pain patients and the cancer pain patients was problematic because of differences in prior analgesic treatments in the two populations. Cancer pain patients entered the present study after having been stabilized on a dose of oxymorphone ER that provided optimal pain relief with tolerable side effects. Among these patients, the rate of discontinuation due to non-serious adverse events was low. In contrast, non-malignant pain patients had previously been treated with fixed doses of oxymorphone, oxycodone, or placebo. Patients who previously received placebo therefore constituted an opioid-naïve subgroup, and, as expected, had higher incidence rates of adverse events, particularly opioid-related adverse events, and a higher rate of discontinuation due to non-serious adverse events. In addition, the fixed dose of oxycodone (20 mg) received by some patients in the previous trial may have been sub-optimal. Patients with non-malignant pain also had incidence rates for discontinuation due to non-serious adverse events and opioid-related adverse events that were slightly higher than those seen in cancer pain patients.

No clinically significant trends in laboratory test results, vital signs or EKGs over time were observed.

Effectiveness: Efficacy results from this study must be interpreted cautiously due to the absence of a control group. In addition, the small number of cancer pain patients in the study demands careful interpretation of data from these patients at all visits. Finally, results beyond Week 28 should be interpreted particularly cautiously due to the reduced numbers of patients upon which these findings are based. It should be borne in mind that patients who remained in the study were likely to be patients who had attained adequate analgesia with oxymorphone ER, and in whom the medication was well tolerated.

Mean baseline pain scores were generally higher in non-malignant pain patients than in cancer pain patients. This was most likely due to the fact that some portion of the non-malignant pain patients entered the present study after having received placebo or a sub-optimal fixed dose of oxycodone in their previous study (EN3202-015). In the present study, mean pain scores in non-malignant pain patients decreased initially as doses were adjusted to achieve adequate pain relief, reached stable levels after the

first few weeks, and remained stable thereafter. Analysis of the patients' global assessments of study medication, also primary effectiveness assessments, showed that the majority of non-malignant pain patients (over 80%) considered the study medication to be good, very good or excellent at relieving pain at all visits.

These findings in patients with non-malignant pain were supported by the secondary effectiveness assessments, i.e., categorical and continuous assessments of current pain intensity. The median average daily scheduled dose of oxymorphone ER remained unchanged up to Day 420, after which it was generally increased to 60–80 mg.

Unlike non-malignant pain patients, patients with cancer pain entered the present study with stable pain scores, having received oxymorphone ER titrated to adequate pain relief in their previous study (EN3202-017). Mean baseline pain scores in the present study were therefore lower than those for non-malignant pain patients. Predictably, no meaningful changes in the assessment of the least, worst or average pain intensity (all primary efficacy assessments) during the preceding week were seen at any visit. In addition, no changes in current pain intensity (secondary efficacy assessments) were seen at any visit. However, patients' global assessments of the study medication showed that the majority of cancer pain patients (over 90%) considered the study medication to be good, very good or excellent at relieving pain at each visit. Increases in the median average daily scheduled dose of oxymorphone ER were seen over time among cancer pain patients, while pain scores remained unchanged. This may have been due to progression of the disease or to increasing doses of concomitant medications or other cancer treatments received by these patients. In patients with non-malignant pain, it is possible that the apparent dose of oxymorphone ER needed to maintain pain relief was exaggerated by fact that the smallest unit dose available was 20 mg and the protocol required patients to take their study medication twice daily.

Quality of Life: Mean current nausea scores at baseline were comparable in the two patient populations. In patients with non-malignant pain, slight increases from baseline in mean nausea scores were seen at early visits (i.e., Weeks 1 through 6). From Week 10 onward, mean nausea scores were similar to the mean score at baseline. Among cancer pain patients, mean nausea scores remained relatively unchanged from baseline at all post-baseline assessments.

Mean current drowsiness scores at baseline were slightly higher in cancer pain patients than in patients with non-malignant pain. This was not unexpected, given the generally higher doses of study medication used by cancer pain patients, and the use of rescue medication (oxymorphone IR) not available to patients with non-malignant pain. Among non-malignant pain patients, slight increases from baseline in mean drowsiness scores were seen at early visits (i.e., Weeks 1 through 10). From Week 16 onward, mean drowsiness scores were similar to or slightly less than the mean drowsiness score at baseline. Among cancer pain patients, mean drowsiness scores remained essentially unchanged from baseline at all post-baseline assessments.