Study Number: EN3202-022

Title of Study: An Open-Label Assessment of the Long-Term Safety and Utility of Numorphan® CR for the Relief of Moderate to Severe Pain in Patients with Cancer

Investigators: (Site #) Principal Investigator

(001) Mahmoud Afifi, M.D.; (005) G. Dastgir Qureshi, M.D.; (006) Daniel Walsh, M.D.; (008) Ferdinand Addo, M.D.; (011) Timothy P. Rearden, M.D.; (014) Arthur J. Matzkowitz, M.D.; (018) Alan Grosset, M.D.; (022) Jerome Provenzano, M.D.; (023) Nashat Y. Gabrail, M.D.; (025) Haresh Jhangiani, M.D.; and (029) Phatama Padavanija, M.D.

Study Center(s): (Site #) Study Center

(001) Trinity Cancer Care Center; (005) West End Hematology and Medical Oncology Group, Inc.; (006) Altru Health Systems; (008) Medcenter One Health Systems; (011) Hematology Oncology Consultants, Inc.; (014) New Hope Cancer Center; (018) North Idaho Cancer Center; (022) Optioncare of Southeastern Virginia; (023) 4184 Holiday Street, NW; (025) Pacific Coast Hematology/Oncology Group; and (029) Cancer Care Center of Montgomery

Publications (reference): None

Studied period (years): Planned: 12 months; actual: 22 months, 18 days (686 days)	**Phase of development:** Phase III

Objectives: The primary objective of this study was to monitor the long-term analgesic effectiveness, safety, and utility of oxymorphone ER for the relief of moderate to severe pain due to cancer.

Methodology: This was an open-label, long-term safety trial. Eligible study participants received open-label treatment with oxymorphone ER following completion of their participation in Study EN3202-018. The initial oxymorphone ER dosage was the dosage established in Study EN3202-018 (patients receiving MS Contin at the end of Study EN3202-018 were converted to oxymorphone ER based on a 3:1 ratio). This dosage was adjusted as necessary to achieve desired pain relief. Subjects were followed at monthly intervals for a total of 12 months.

Number of subjects (planned and analyzed): Up to 75 subjects was permitted; 24 subjects enrolled in the study; 24 were analyzed for safety and 14 were analyzed for efficacy.

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 (i.e., strong opioids) were eligible to enter the study after their participation in Study EN3202-018.

Test product, dose and mode of administration, batch number: EN3202 (oxymorphone ER) 10, 20, and 40 mg tablets (over-encapsulated), oral administration

Lot Numbers: 10 mg: 0002236-C
20 mg: 0002830-C
40 mg: 9905924-A and 310183

Duration of treatment: The planned treatment period was 12 months; however, 7 subjects received treatment beyond 12 months. Actual treatment duration ranged from 3 to 686 days.

Reference therapy, dose and mode of administration, batch number: Reference therapy was not administered in this open-label study. Rescue therapy for breakthrough pain was provided with EN3203, oxymorphone HCl immediate release (oxymorphone IR) 5 and 10 mg tablets, oral administration.

Lot Numbers: 5 mg: 2831 and 2832
10 mg: 9906335 and 2837

Criteria for evaluation:

Efficacy: The effectiveness of the analgesic regimen was assessed periodically throughout the study. Subjects completed the Brief Pain Inventory Short Form (BPI) to measure both pain and its impact on activities and quality of life. Question #1, Question #7, and item #2 of the BPI were not completed.

Safety: Safety was assessed through the recording and monitoring of adverse events (AEs) and clinical laboratory values. In addition, opioid side effects were measured by assessing the presence or absence of seven opioid symptoms using a checklist. The severity of each symptom and the action taken with study medication were also recorded.

Statistical methods:

Efficacy: This was an uncontrolled, open-label study, and hypothesis testing was not conducted. The results of the individual items in the BPI were displayed using appropriate descriptive statistics and were summarized by month. Change from baseline computations used the last value obtained in the previous study (EN3202-018) as the baseline measurement.

Safety: Adverse events, new-onset AEs, and treatment-related new-onset AEs were tabulated by MedDRA® term and body system. The incidence of AEs was summarized using appropriate descriptive statistics. Changes in incidence and new onset AEs were examined over time. All clinical laboratory measurements were summarized by mean values and changes from baseline using the last result from study EN3202-018 as the baseline value. The number of subjects with out-of-normal-range clinical laboratory parameters was tabulated. In addition, clinical laboratory abnormalities were summarized by worst toxicity grade (according to the NCI Common Toxicity Criteria).

SUMMARY:

Efficacy Results: Of the 24 subjects entered into the study, 14 had at least one post-baseline efficacy assessment and were analyzed for efficacy. Only small improvements were observed for any of the BPI parameters evaluated because the patients achieved relatively adequate pain relief in Study EN3202-018 prior to entering this long-term study. In addition, the small sample size and high degree of inter-subject variability precluded a clinically meaningful interpretation of these results.

Safety Results: Among all 24 subjects enrolled, study duration ranged from 3 days to 686 days. However, without a daily dosing diary, specific treatment duration and exposure information cannot be discerned. A total of 22 subjects (91.7%) experienced at least one new-onset AE. Nineteen subjects (79.2%) had treatment-related AEs; 10 (41.7%) had a serious AE, including 4 subjects who died of disease progression; and 8 subjects (33.3%) had an AE that led to study discontinuation. Consistent with the study population and the known effects of opioid treatment, the most commonly reported AEs were gastrointestinal disorders (18/24, 75%), nervous system disorders (15/24, 62.5%), and general disorders and administration site conditions (10/24, 41.7%).

The majority of the opioid side effects were mild or moderate in severity. Among the severe opioid side effects reported, nausea was the most common (4 subjects), followed by vomiting (3 subjects), constipation and sedation (2 subjects each), and dizziness and sweating (1 subject each). None of the opioid side effects was considered to be life-threatening. Few opioid side effects led to an interruption or change in study drug dosage or study discontinuation. Of those that did result in study discontinuation, nausea was the most common (3 subjects), followed by sweating (2 subjects), and dizziness, sedation, and pruritus (1 subject each). Although some subjects did experience a worsening severity of opioid side effects over time, the severity of opioid side effects was unchanged from baseline for the majority of subjects, suggesting a favorable long-term tolerability profile for oxymorphone ER.

Of the 22 subjects who had at least one abnormal laboratory value, 6 had a Grade 3 laboratory abnormality. For 4 subjects, the abnormalities occurred at baseline, defined as the last visit in Study EN3202-018. Consistent with the study population, the most commonly observed Grade 3 laboratory abnormalities involved decreased hematology values, specifically white blood cells (WBC), neutrophils,

lymphocytes, and platelets. No Grade 4 laboratory abnormalities were reported during the study, and no apparent treatment-related increases in the incidence of laboratory abnormalities were observed over time.