Study Number: EN3202-021

Title of Study: An Open-Label Extension Study to Evaluate the Long-Term Safety, Tolerability and Analgesic Efficacy of Numorphan® CR (oxymorphone HCl controlled release) in Subjects With Cancer Pain or Chronic Lower Back Pain

Investigators: 44 investigators

Publications (reference): None

Studied period (years):	**Phase of development:** Phase III
Date of First Enrollment: March 14, 2001 Date of Study Completion: July 2, 2003	

Objectives:

Primary: To evaluate the long-term safety and tolerability of oxymorphone ER as an analgesic in cancer and lower back pain subjects having chronic moderate to severe pain.

Secondary: To evaluate long-term efficacy of oxymorphone ER as an analgesic in cancer and lower back pain subjects having chronic moderate to severe pain.

Methodology: This was an open-label, non-controlled, 1-year clinical evaluation of the safety and tolerability of oxymorphone ER used as an analgesic for treatment of chronic, moderate to severe pain in subjects with cancer or lower back pain. Subjects who were randomized, had entered the double-blind treatment phase, and had completed the exit visit in the lower back pain study EN3202-016 or cancer study EN3202-019 were eligible for consideration for enrollment for this study. Subjects who withdrew from these previous studies due to lack of efficacy were eligible if they completed the exit evaluations, but subjects who withdrew for other reasons were not eligible. Subjects must not have experienced any form of serious drug-related adverse event (AE) in these previous studies to be eligible for this study.

Consenting subjects who met the inclusion/exclusion criteria at the exit visit of the back pain or cancer pain studies began dosing with oxymorphone ER at their next scheduled dose after completing the exit evaluations of the above studies. Subjects were converted to oxymorphone ER based on their dose in the previous studies. Because both previous studies were double blinded and randomized, the investigator and subject did not have knowledge of the subject's prior exposure to oxymorphone ER or optimal dose. Thus, the optimal dose of oxymorphone ER for each subject was established during the first week of dosing in this study. Subjects received oxymorphone ER for 12 months. Subjects were given oxymorphone IR as a supplemental analgesic for breakthrough pain.

Safety and efficacy of oxymorphone ER were assessed at monthly study visits.

Number of subjects (planned and analyzed):
Planned: maximum of 150
Enrolled: 239
Treated: 239
Analyzed for efficacy: 226 (Modified Intent-to-Treat population)
Analyzed for safety: 239 (Safety population)

Diagnosis and main criteria for inclusion: Eligible subjects from studies EN3202-016 and EN3202-019 with chronic moderate to severe pain secondary to cancer or with chronic moderate to severe lower back pain.

Test product, dose and mode of administration, batch number: EN3202 (oxymorphone ER) 10, 20, and 40 mg tablets administered orally every 12 hours. Each subject was converted to a starting dose of oxymorphone ER based on his or her dose in the previous study unless the investigator considered it necessary to initiate dosing at a different dose. Each subject was to titrate to a dose of oxymorphone ER that produced adequate analgesia, tolerable side effects, and minimal rescue medication usage in 1 week

or less. Lot numbers were 2236-B, 2236-C, 310176 for the 10 mg tablets; 2830-A, 2830-B, 2830-C, 31079, 310180 for the 20 mg tablets; and 9905924-A, 9905924-B, 9905924-C, 310182 for the 40 mg tablets.

Duration of treatment: 12 months

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

Rescue medication, dose and mode of administration, batch number: Numorphan IR (oxymorphone hydrochloride immediate-release), alternately referred to as oxymorphone IR, 5 and 10 mg tablets administered orally every 4-6 hours as needed as supplemental rescue medication for breakthrough pain. Lot numbers: 2832 and 310604 for the 5 mg tablets and 310030 and 900335 for the 10 mg tablets.

Criteria for evaluation:

Efficacy: Monthly assessments of pain with the Brief Pain Inventory (BPI) questionnaire, recall of average pain relief, total rescue medication usage, and subject's and physician's global assessment of oxymorphone ER.

Safety: AEs, opioid side effects, physical examination; vital signs; clinical laboratory tests.

Statistical methods:

Efficacy: The results of the BPI, subject's and physician's global assessment of oxymorphone ER, and rescue medication usage were summarized by visit. The significance of the mean change from baseline, assessed by paired-t-tests, was the only formal statistical analysis performed. Subjects had to have both baseline and post-baseline values to be included in this analysis.

Safety: AEs, treatment-emergent AEs (TEAEs), and treatment-related TEAEs were tabulated by Medical Dictionary for Regulatory Activities (MedDRA) term and body system. The incidence of AEs was summarized using appropriate descriptive statistics. The incidence of opioid side effects was summarized by study visit and by severity, change in severity from baseline, change in severity from previous week, and action taken. Clinical laboratory test results were summarized by mean values and changes from baseline. The number of subjects with clinical laboratory test results outside the normal range was tabulated. Changes from baseline in vital signs and physical examination findings were summarized.

SUMMARY:

Efficacy Results:

Analgesic efficacy, as measured by pain intensity and pain relief indices of BPI, improved over the first month of treatment and then remained stable throughout the study. The improvement from baseline to Month 1 was due to a higher pain score of placebo subjects who entered this study from the short-term double-blind study EN3202-016.

Only 7.9% of enrolled subjects discontinued due to lack of efficacy, most of whom discontinued during the first 6 months of treatment.

The mean average daily dose of the study medication was 110 mg across the duration of the study, with average daily doses of 92 mg during the first month of treatment and approximately 128 mg at the end of the study. The mean average daily dose of oxymorphone IR, as rescue medication, was 17.3 mg (range 0 to 59 mg) across the duration of the study.

The majority of subjects rated their overall satisfaction with oxymorphone ER as good to excellent. The physicians' global assessment of the study medication was consistent with the subjects' assessment.

Safety Results: Overall, 180/239 (75.3%) treated subjects experienced at least one TEAE, most of which were considered unrelated to study medication. TEAEs that occurred in ≥5.0% of subjects were influenza, back pain aggravated, headache NOS, arthralgia, insomnia NEC, upper respiratory tract infection NOS, edema lower limb, back pain, fatigue, edema lower limb, nausea, sinusitis NOS, urinary traction infection NOS, hypoaesthesia, and diarrhea NOS.

Twelve (5.0%) subjects died during the study. All of these subjects were cancer patients, and 11 of them had concomitant disease progression as the cause of death.

Serious adverse events (SAEs) occurred in 28 (11.7%) subjects. The most frequent SAE was concomitant disease progression in cancer patients.

Overall, 42 (17.6%) subjects discontinued due to AEs, with concomitant disease progression (not study medication related) in cancer subjects as the single most prevalent AE causing discontinuation.

At each visit, most subjects reported having no opioid side effects.

Changes from baseline in laboratory tests, vital signs, and physical examinations were minor and not clinically meaningful.