Study Number: EN3202-036	
Title of Study: An Open-Label Safety and Tolerability Study of Immediate-Release and Extended-Release Oxymorphone in Opioid-Tolerant Pediatric Subjects with Chronic Pain	
Investigators: Fourteen (14) investigators, of whom 5 enrolled subjects	
Study center(s): Fourteen (14) study centers in the United States, 5 of which enrolled subjects	
Publications (reference): None to date	
Studied Period (years): Date first patient enrolled: 17-Nov-2008 Date last patient completed: 22-Feb-2010	**Phase of Development**: Phase 3

Objectives:

Primary: To assess the safety and effectiveness of oxymorphone extended-release (ER) tablets in opioid-tolerant children for treatment of chronic pain of malignant or nonmalignant etiology

Secondary: To determine appropriate conversion and titration guidelines for the use of oxymorphone in opioid rotation in this subject population

Methodology: This study consisted of a screening visit followed by an open-label dose titration period of up to 4 weeks and an open-label maintenance period of up to 3 months. Prior to study entry, each subject had received a stable dose of prescribed opioid pain medication for the management of continuous pain of a well documented cause. Each subject visited the clinical site for 11 scheduled visits.

During the titration period, subjects received daily oxymorphone ER tablets by mouth (PO) every 12 hours (q12h). The Investigator initiated oxymorphone ER dosing according to a conversion chart provided in the protocol. Oxymorphone immediate-release (IR) 5 mg was provided, as needed and used as supplemental "breakthrough" pain medication (ie, rescue medication). Oxymorphone ER dosing adjustments were made under the direction of the Investigator based on a review of: the subject's pain scores; current daily dose of study medication; and evaluation of adverse events (AEs) reported by the subject and/or parent/guardian and observed by the Investigator.

Parents/guardians of the subjects were instructed to call the Investigator between scheduled study visits if their child's pain relief was unsatisfactory or if the child was experiencing intolerable side effects, so that the Investigator could evaluate the need for study medication adjustments. Subjects were to be administered an anticonstipation regimen of the Investigator's choice, which was to continue throughout the study; however, an anticonstipation regimen was not administered to subjects as planned. All study medication (including oxymorphone IR for breakthrough pain) taken by the subjects and age-appropriate pain assessments were recorded in a subject diary and reported to the Investigator on a daily basis to allow for upward titration of the study drug as required for appropriate analgesia.

The goal of the titration period was to determine each subject's fixed dose of study medication that was tolerated and achieved adequate analgesia. The titration period ended when:

- The dose of study medication was considered fixed, which was defined as the subject achieving adequate pain relief (average pain relief rated ≤4/10 on the Faces Pain Scale – Revised [FPS-R]) while receiving the same dose of study medication for 3 consecutive days and the subject tolerated the same dose of study medication for 3 consecutive days;
- The subject could not achieve an acceptable fixed dose of study medication; or
- The subject terminated early from the study.

Subjects who were unable to find an acceptable dose of study medication within 4 weeks of screening were discontinued from the study.

Eligible subjects who were able to find an acceptable dose of study medication within 4 weeks of study entry proceeded directly to the 3-month maintenance period at the fixed dose determined during the titration period. Further dose adjustments were permitted during the maintenance period, so a subject's dose may not have remained same as titration.

During the maintenance period, subjects (and/or parents/guardians) kept a daily diary record of the total oxymorphone ER and oxymorphone IR rescue medication doses. Pain assessment, performance status, evaluation of compliance, and study medication usage were completed at each visit. Safety was monitored throughout the maintenance period.

This study was terminated early by the Sponsor after 27 subjects had been enrolled. This study was being conducted under the Pediatric Research Equity Act (PREA) as a postmarketing commitment, and during the conduct of the study, the PREA commitments were updated and this study was no longer applicable. The study was not terminated due to any safety concerns. Because the study was terminated early, efficacy results are not presented in this report.

Number of Patients (Planned and Analyzed):

Planned: 60 enrolled subjects

Analyzed for Safety: 27 subjects in the titration period and 24 subjects in the maintenance period

Diagnosis and Main Criteria for Inclusion: Subjects aged 6 to 17 years with chronic pain that currently required treatment with a strong (around-the-clock) opioid (only children aged 12 to 17 were enrolled)

Test Product, Dose and Mode of Administration, Lot Number: Oxymorphone ER PO q12h; the dose was ordered based on dose conversion from the subject's current opioid therapy and titrated to a fixed dose that was tolerated and achieved adequate analgesia. Oxymorphone ER was provided by the Sponsor as commercial OPANA® ER (oxymorphone HCl) Extended-Release Tablets CII open-label stock of 5-mg tablets (lot numbers: 401069NV, 401935NV), 7.5-mg tablets (lot numbers: 401033NV, 401186NV), 10-mg tablets (lot numbers: 401091NV, 401916NV), 15-mg tablets (lot numbers: 401034NV, 401778NV), 20-mg tablets (lot numbers: 401093NV, 401939NV), 30-mg tablets (lot numbers: 401035NV, 401812NV), and 40 mg tablets (lot numbers: 401094NV, 401967NV), Oxymorphone IR 5 mg taken, as needed for breakthrough pain. Commercial OPANA® (oxymorphone HCl) Tablets CII 5-mg tablets (lot numbers: 400880NV, 401427NV) were provided by the Sponsor.

Duration of Treatment: Up to 17 weeks (up to 4 weeks during the titration period, followed by 12 weeks ± 7 days during the maintenance period)

Reference Therapy, Dose and Mode of Administration, Lot Number: None

Criteria for Evaluation:

Safety: AEs, vital signs, clinical laboratory tests, including pregnancy testing, and physical examinations

Efficacy: Pain intensity (FPS-R; daily diary assessment); performance status (Play Performance Scale; parent/guardian assessed)

DEMOGRAPHY: The mean age of the subjects was 14.8 years. Fifteen (15) female subjects (55.6%) and 12 male subjects (44.4%) entered the study. The majority of subjects were Black or African American (23 [85.2%]).

Of the 27 subjects in the study, 24 had a medical history of sickle cell anemia, 1 subject had neurofibromatosis and neuropathic pain syndrome, 1 subject had T-cell acute lymphoblastic leukemia, and 1 subject had ulcerative colitis with chronic pain.

SUMMARY

SAFETY RESULTS:

Treatment-emergent adverse events (TEAEs) were reported for 17 subjects (63.0%) overall in the study and for 15 subjects (55.6%) during the titration period and 7 subjects (29.2%) during the maintenance period. The most frequently reported TEAEs in the titration period were somnolence (6 subjects, 22.2%), headache (3 subjects, 11.1%), dizziness (3 subjects, 11.1%), and nausea (2 subjects, 7.4%). All of these TEAEs were reported more frequently in the titration period than in the maintenance period. Headache, fatigue, and dehydration (2 subjects, 8.3% each) were the most common TEAEs in the maintenance period, and of these, fatigue and dehydration were reported more frequently in the maintenance period than in the titration period.

No deaths occurred. Serious adverse events (SAEs) were reported for 3 subjects and TEAEs that led to discontinuation occurred for 2 subjects in the maintenance period; none of these events were considered by the Investigator to be related to the study drug. No SAEs or discontinuations for TEAEs occurred in the titration period.

No clinically meaningful trends were noted in laboratory test results, vital signs, or physical examination findings.