Clinical Trial Results Summary
Study EN3202-012

Study Number: EN3202-012	
Title of Study: Double-Blind, Placebo-Controlled, Parallel-Group Comparison of the Efficacy, Opioid Dose Sparing Effects and Safety of Controlled Release Oxymorphone and Placebo in Patients with Postsurgical Pain Following Knee Arthroplasty	
Investigators: 14 investigators	
Study Centers: 14 investigational centers, in the USA	
Publication (reference): None	
Study Period (years): 28 September 1999 - 30 November 2000	**Phase of Development**: III
Objectives: The primary objective of this study was to compare the analgesic efficacy of controlled release oxymorphone 20 mg (oxymorphone-20) to placebo in patients with moderate to severe postoperative pain. The secondary objective of this study was to evaluate the safety and tolerability of oxymorphone-20 compared to placebo in patients with moderate to severe postoperative pain.	
Methodology: This was a multicenter, double-blind, parallel-group, placebo-controlled, multiple dose study incorporating 2 measures of analgesic efficacy (1) a standard analgesic evaluation and (2) a patient-controlled analgesia (PCA)-opioid dose sparing analgesic evaluation. Patients who had undergone knee arthroplasty received intermittent bolus doses of opioids (such as hydromorphone, morphine, meperidine, or fentanyl) followed by a standardized dose range of open label IV opioid by PCA until the morning of the day after surgery (Day 1). PCA was to be discontinued between 5:00 AM and 8:00 AM. Patients who developed both at least moderate pain intensity (on a categorical scale) and a visual analog scale (VAS) ≥ 45 mm within six hours of PCA discontinuation received study medication (oxymorphone-20 or placebo) between 5:00 AM and 11:00 AM on Day 1, followed by a second dose in 12 hours. Patients recorded the following pain assessments at the indicated time points after the first dose of study medication, or immediately prior to the first dose of rescue medication or study termination. For the **Standard Analgesic Evaluation**: pain intensity (VAS and categorical), pain relief (categorical), whether pain was half-gone, and a global evaluation of study medication at 12 hours. Time to onset of perceptible and meaningful pain relief were measured using stopwatches. For the **PCA Opioid Dose Sparing Analgesic Evaluation**: average (usual) pain intensity (VAS) since the previous assessment, average (usual) pain intensity since the first dose of study medication (pain recall), and a second global evaluation at 24 hours. Safety was assessed by adverse events, routine laboratory analyses, physical examinations and vital signs. The use of any concomitant medication was recorded.	
Number of Subjects (Planned and Analyzed): **Planned**: Approximately 125 enrolled patients to achieve 100 evaluable patients (approximately 50 patients each oxymorphone-20 or placebo). **Actual**: Safety Analyses: 126 (all who received study medication: 65 oxymorphone-20, 61 placebo). Efficacy Analyses: Standard Analgesic Evaluation: 104 (Intent-to-Treat [ITT], all randomized patients who took first dose, completed 1-hour efficacy evaluation, and did not receive rescue medication or withdraw prior to 1 hour); 88 (Efficacy evaluable, all ITT patients without significant protocol violations). PCA-Opioid Dose Sparing Evaluation: 116 (ITT, all randomized patients who took first dose and completed 12-hour efficacy evaluation); 94 (Efficacy evaluable, all ITT patients without significant protocol violations). One additional patient received oxymorphone-60 (prior to Protocol Amendment 1, see Section 9.8) and was excluded from all analyses.	
Diagnosis and Main Criteria for Inclusion: Patients were 18-80 years of age, in generally good health, which had undergone unilateral knee arthroplasty (under general or regional anesthesia). Patients were PS-1 to PS-3 in the American Society of Anesthesiologists (ASA) Physical Status Classification System.	
Test Product, Dose and Mode of Administration, Batch Numbers: Oxymorphone CR 20 mg tablets, Lots: 9906368 and 9902090	
Duration of Treatment: Patients received a dose of study medication at 0 hour and a second dose at 12 hours.	
Reference Therapy, Dose and Mode of Administration, Batch Number: placebo tablets matching oxymorphone 20 mg tablets, Lot number: 9902984	

Criteria for Evaluation:
Efficacy: **Standard Acute Pain Analgesic Evaluation** - Primary efficacy variable was total pain relief (TOTPAR) 0-8 hours. Secondary efficacy variables were TOTPAR 0-4, 0-6, and 0-12 hours; sum of pain intensity difference (SPID) (categorical and VAS) 0-4, 0-6, 0-8, and 0-12 hours; time to rescue medication; time to meaningful pain relief; patient's global evaluation at 12 hours; pain intensity difference (PID) VAS and categorical scale; pain relief (PR); sum of pain relief and pain intensity difference on the categorical scale (PRID); peak pain intensity difference (PPID); peak pain relief (PPR); summed PRID scores (SPRID) 0-4, 0-6, 0-8, and 0-12 hours; time to perceptible pain relief; time to onset of analgesia (defined as the time of change in PID categorical from previous assessment ≥ 1); time to first experienced 50% pain relief; and number of patients experiencing 50% pain relief.

PCA-Opioid Dose Sparing Analgesic Evaluation - Primary efficacy variable was integrated rescue PCA and pain intensity recall score 0-12 hours. Secondary efficacy variables were integrated rescue PCA and pain intensity recall score 0-6 and 0-24 hours; PCA oxymorphone consumption 0-6, 0-12, 12-24, and 0-24 hours; patient's global evaluation at 12 and 24 hours; pain intensity recall (VAS) scores for average pain since previous assessment 0-6, 6-12, and 0-12 hours; pain intensity recall (VAS) scores for average pain since the first dose at 12 and 24 hours.

Safety: Signs and symptoms present at baseline (before administration of study medication) and adverse events throughout the course of the study; routine laboratory analyses and physical examinations performed pretreatment and 24 hours post-treatment or at early termination; and vital signs (heart rate, respiratory rate, and blood pressure) before the first dose of study medication, hourly for the first 12 hours and at 24 hours after initial dosing or at early termination.

Statistical Methods: Analysis of variance (ANOVA); Analysis of covariance (ANCOVA); Cochran-Mantel-Haenszel (CMH) test; Kaplan-Meier survival analysis methods; log-rank test; Kruskal-Wallis test; integrated assessment of pain scores and rescue medication. Two-sided tests.

SUMMARY:

EFFICACY RESULTS: In this study, the primary objectives for both efficacy evaluation approaches were achieved. In the **Standard Analgesic Evaluation**, oxymorphone-20 was superior to placebo as assessed by TOTPAR 0-8 hours, the primary endpoint.

TOTPAR Mean Score (SD)

ITT Population	0-4 Hours	0-6 Hours	0-8 Hours	0-12 Hours
Oxymorphone-20 (N=53)	5.67 (4.0)	8.47 (6.2)	**11.26 (8.4)**	19.30 (14.7)
Placebo (N=51)	4.33 (3.3)	6.12 (5.1)	**8.09 (6.9)**	13.72 (12.2)
LS Mean Difference	1.77	2.89	**4.01**	7.07
p-value	0.0110	0.0068	**0.0057**	0.0056
95% CI of Difference	(0.42, 3.12)	(0.82, 4.96)	**(1.20, 6.83)**	(2.13, 12.02)

In the **PCA-Opioid Dose Sparing Analgesic Evaluation**, oxymorphone-20 was superior to placebo as assessed by the integrated rescue PCA and pain intensity recall score at 0-12 hours, the primary endpoint.

Integrated Rescue PCA and Pain Intensity Recall Mean Score (SD)

ITT Population	0-6 Hours	0-12 Hours	0-24 Hours
Oxymorphone-20 (N=58)	-25.33 (87.7)	**-21.00 (89.2)**	-22.62 (90.2)
Placebo (N=58)	24.84 (84.2)	**19.42 (88.0)**	20.06 (84.2)
p-value	0.0004	**0.0010**	0.0024

Oxymorphone-20 was superior to placebo for most of the secondary efficacy measures, with the exception of the time-to-event measures and peak measures (Standard Analgesic Evaluation) and PCA oxymorphone consumption 0-6 hours (PCA-Opioid Dose Sparing Analgesic Evaluation).

SAFETY RESULTS: From the time of the first dose of study medication to the time of rescue or 12 hours post-dose (whichever occurred first), 31 (24.6%) of the patients experienced at least one adverse event: 17 (26.2%) of the oxymorphone-20 patients and 14 (23.0%) of the placebo patients. During this study interval, the investigator considered the relationship of 16 (59%) and 14 (64%) of the adverse events to the study medication to be suspected or probable (oxymorphone-20 and placebo, respectively), and one adverse event was determined by the investigator to be severe. Nausea and vomiting were the only adverse events occurring in more than 5% of the patients in either treatment group from the time of the first dose of study medication to the time of rescue or 12 hours post-dose. Eight patients who received oxymorphone-20 and seven patients who received placebo experienced serious adverse events. For three of these patients (each in the oxymorphone-20 group), the serious adverse events caused withdrawal from the study. The overall incidence of adverse events for oxymorphone-20 was similar to that of placebo. It must be noted, however, that 7 (10.8%) of the patients were withdrawn from the study for an adverse event in the oxymorphone-20 group (including somnolence, confusion, lethargy, CNS depression, sedation, and agitation), versus none of the patients in the placebo group and the difference was statistically significant. There were no clinically significant treatment group differences in mean change in vital sign, laboratory, or physical examination findings.

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