2. SYNOPSIS

Name of Sponsor/Company: Purdue Pharma L.P.	**Protocol No.** **OTR3002**
Name of Finished Product: Oxycodone Hydrochloride Twice Daily Controlled-release Tablets	**Name of Active Ingredient**: Oxycodone
IND No.: 29,038	**EudraCT No.**: 2011-002235-26

Title of the Study: An Open-label, Extension Study to Assess the Long-Term Safety of Twice Daily Oxycodone Hydrochloride Controlled-release Tablets in Opioid Experienced Children Who Completed the OTR3001 Study

Investigator(s), Site(s):
All study centers from the OTR3001 study were eligible to participate in OTR3002; it was not mandatory for the sites participating in OTR 3001 to participate in this study. A total of 14 sites enrolled patients in this study.

Publication (Reference):
None to date.

Study period (Dates):	**Study Status:**	**Phase of Development:**
05-Jan-2012 to 01-Jan-2014	Completed	3B

Objective: The primary objective was to characterize the long-term safety of oxycodone hydrochloride (HCl) controlled release (CR) tablets in opioid experienced pediatric patients aged 6 to < 17 years, inclusive, with moderate to severe malignant and/or nonmalignant pain requiring opioid therapy who completed the 4-week treatment period in study OTR3001.

Methodology:
This was an open-label, extension study for OTR3001 to characterize the long-term safety of oxycodone HCl CR tablets in pediatric patients 6 to 17 years of age (inclusive). The duration of study drug treatment was up to 6 months. Only patients who completed the 4-week treatment period in OTR3001 study were eligible for this study. Upon entry into this study, patients could continue with the oxycodone HCl CR dose they received at the end of OTR3001 treatment period, or, if necessary, have their doses adjusted by the investigator. Unlimited number of dose adjustments between oxycodone HCl CR 20 mg/day and oxycodone HCl CR 240 mg/day, inclusive, were permitted during the study until pain control was achieved. Supplemental opioid and nonopioid analgesics, including any oxycodone-containing products, were permitted at the discretion of the investigator. Following the last dose of study drug, all patients were contacted within 7 to 10 days for a safety follow-up assessment.
An independent Data Monitoring Committee (DMC) established for OTR3001 also reviewed the accumulating safety data from this trial. The DMC met periodically during the course of the study to review safety data and make recommendations to Purdue Pharma L.P. regarding early stopping of the study, continuation of the study, or modification of the study protocol, as needed.

Number of Subjects (Planned and Analyzed):
Planned: All patients who completed the 4- week treatment period in OTR3001 at the time when OTR3002 was open for enrollment were eligible. Study OTR3002 was closed by PPLP due to administrative reasons not related to safety after 23 patients had been enrolled.
Enrolled: A total of 23 patients were enrolled and treated.

Diagnosis and Main Criteria for Inclusion/Exclusion:
Patients were eligible if they completed the 4-week treatment period in OTR3001 and, in the opinion of the investigator, were appropriate for continuing treatment with around-the-clock opioid therapy equivalent to 20 to 240 mg (inclusive) daily of oxycodone for management of moderate to severe malignant or nonmalignant pain. Patients who did not meet laboratory and clinical evaluation requirements at visit 1 were not eligible.

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Test Product, Dose, Mode of Administration, and Batch Number:
Oxycodone HCl CR tablets, at strengths of 10, 15, 20, 30, or 40 mg (total of 20 to 240 mg daily), every 12 hours taken orally with water.

Test Treatment	Dose	Dosage Form	Lot Number
Oxycodone HCl CR tablets	10 mg	Tablets	WFK70 and WKM40
Oxycodone HCl CR tablets	15 mg	Tablets	WFL20 and WKL70
Oxycodone HCl CR tablets	20 mg	Tablets	WFM10 and WKL80
Oxycodone HCl CR tablets	30 mg	Tablets	WFK90 and WKY00
Oxycodone HCl CR tablets	40 mg	Tablets	WFK60 and WKY40

Reference Treatment, Dose, Mode of Administration, and Batch Number:

Not applicable

Rescue Medication:

Supplemental opioid and non-opioid analgesic medication, including any oxycodone-containing products, were permitted at the investigator's discretion.

Duration of Treatment:
Treatment phase – up to 6 months
Follow-up period – 7 to 10 days

Treatment Schedule (Procedure):
Visit 1 occurred immediately following the completion of visit 3 in OTR3001 for all eligible patients. At visit 1, after written informed consent was obtained, patients who completed the 4-week treatment period in OTR3001 were evaluated for study eligibility for OTR3002. Patients who met all inclusion criteria and none of the exclusion criteria (excluding laboratory results) began treatment at visit 1 with the same dose oxycodone HCl CR they received at the end of OTR3001, or had their oxycodone HCl CR doses adjusted if deemed necessary by the investigator. Laboratory results from visit 3 in OTR3001 were used to establish patient eligibility for OTR3002. If the clinical laboratory results did not meet the entry criteria for this study and the patients had already begun study drug treatment, the patients were instructed to discontinue study drug treatment and to return to the study site to complete all early discontinuation procedures.
Clinic visits occurred at weeks 4, 8, 12, 16, 20, and 24 (visit 2 to 7) of the study. Safety assessments were performed at the scheduled visits. The patients could return to the study site at any time, if necessary, for safety or tolerability assessments, for dose adjustments, or for study drug resupply. Study visits could be conducted at a patient's home if the investigator deemed this to be appropriate based on the patient's medical status.

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Patients were allowed an unlimited number of dose adjustments (between 20 mg and 240 mg of oxycodone HCl CR), as deemed appropriate by the investigator during the study. Dose down-titration could occur anytime for safety or tolerability reasons. In order to decrease the likelihood of developing opioid withdrawal in patients who required down-titration of study drug, amendment 1 of OTR3002 required a single dose down-titration. Dose up-titration for efficacy reasons could occur only after the patient had been treated for ≥ 48 hours with the same dose. The maximum dose for a single up-titration was not to exceed 25% of the patient's current dose. Dose adjustments could take place at the study site or while patients were away from the study site per investigator judgment.
In order to decrease the likelihood of developing opioid withdrawal in patients who required study drug down-titration, amendment 1of the OTR3002 study required the total daily dose of oxycodone HCl CR tablets and any supplemental opioid medications to be reduced by no more than 20% of the patient's current dose, unless there were concerns related to safety (eg, respiratory depression). Additionally, an immediate-release opioid medication was provided to the patient should symptoms of opioid withdrawal manifest.
All patients had a follow-up phone call or study visit 7 to 10 days after their last dose of oxycodone HCl CR tablets for a follow-up evaluation.

Bioanalytical Methods:

Not applicable for this study.

Criteria for Evaluation:

Safety:
Safety assessments included monitoring and recording all adverse events (AEs) and serious AEs (SAEs; obtained through spontaneous reports and/or patient interview or observed during physical examinations or other safety assessments); concomitant medications; vital signs; and clinical laboratory tests (hematology, blood chemistry, urinalysis values, pregnancy tests for female patients of childbearing potential), and somnolence (University of Michigan Sedation Scale [UMSS]).

Suspected or confirmed diversion was reported via a clinical supply product complaint (CSPC) report form. Abuse of study drug or other drug was to be reported as an SAE if no prior history of abuse was reported.

Statistical Methods:

Summary results described in this report were for the extension safety population. Some summaries used only the data from OTR3002, while other summaries used the combined data from the core (OTR3001) and extension (OTR3002) studies, as indicated in amendment 2.

Analysis Populations:
The enrolled population was the group of patients for whom informed consent/assent was provided

The safety population was the group of patients who received at least 1 dose of study drug in the core or extension study.

The extension safety population was the group of patients who received at least 1 dose of study drug during the extension study.

Safety Analysis:
Safety variables were summarized descriptively within age group (ages 6 to < 12 and ages ≥12 to ≤ 16 years) for the extension safety population (amendment 2). Safety assessments to be summarized included reports of AEs, clinical laboratory test results, vital signs measurements, and somnolence.

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Sample Size:
There was no formal sample size justification. A total of 23 patients was enrolled in the extension study.

Efficacy Results:
No efficacy data were collected for this extension study.

Safety Results:

Dosing and Extent of Exposure

- The median duration of exposure (core and extension studies combined) was 198 days overall, and the median daily dose was 25.2 mg. Thirteen patients (56.5%) received supplemental opioid analgesic during the extension study.

Adverse Events and Other Observations Related to Safety:

- In general, the TEAEs observed in the core and extension studies were similar to those expected with systemic use mu-opioid agonist analgesics. The most common TEAEs during the extension study occurred in the SOCs of gastrointestinal disorders (including vomiting, 4 patients, 17.4%), and general disorders and administration site conditions (including pyrexia, 5 patients, 21.7%). Most of these events were considered by the investigator to be mild or moderate in intensity; 3 patients (13.0%) experienced severe TEAEs during the extension study, and 1 of these 3 patients (4.3%) experienced a TEAE of fatigue that was considered by the investigator to be severe and related to treatment .
- There was no evidence of any new TEAE or increase in the incidence of any TEAE in the extension study compared with the core and extension studies combined.
- There were no deaths or study drug discontinuations due to TEAEs during the extension study.
- Four patients (17.4%) experienced treatment-emergent SAEs in the extension study: 2 (8.7%) patients experienced sickle cell anemia with crisis (1 in the younger age group and 1 in the older age group), 1 (4.3%) patient in the younger age group experienced pyrexia, 1 (4.3%) patient in the in the older age group experience vomiting, back pain, and headache. All treatment-emergent SAEs were considered by the investigator to be not related or unlikely related to treatment, and all patients recovered from the SAEs.
- A total of 4 patients (17.4%; 2 patients in the younger age group and 2 patients in the older age group) experienced TEAEs that led to dose reduction and/or interruption during the core and extension studies.
- There were no cases of suspected or confirmed abuse or diversion.

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Synopsis Table 1

Category	Age Group: 6 to < 12 Years (N=9) n (%)	Age Group: ≥ 12 to ≤ 16 Years (N=14) n (%)	Total (N=23) n (%)
Deaths	0	0	0
Serious TEAEs	2 (22.2)	2 (14.3)	4 (17.4)
TEAEs Leading to Study Drug Discontinuation	0	0	0
TEAEs Leading to Dose Reduction [a]	2 (22.2)	2 (14.3)	4 (17.4)
TEAEs Leading to Dose Interruption	1 (11.1)	2 (14.3)	3 (13.0)

Cross-reference: Table 14.3.2.1, Table 14.3.2.2, Table 14.3.2.3.1 , Table 14.3.2.4.1, Appendix 16.2.7.1

All adverse events were coded using the MedDRA version 13.0 dictionary.

[a] Includes 2 patients who had dose reductions due to TEAEs only during the core study (Table 14.3.2.4.1)

- For both hematology and blood chemistry parameter values, mean changes from baseline were generally small and not clinically notable, with the exception of neutrophils, neutrophil bands, lymphocytes, and monocytes, which had notable mean changes over the course of treatment (but less notable median changes). No laboratory test had a notable trend of an increase or decrease over the full duration of treatment. The notable changes in neutrophils, neutrophil bands, lymphocytes, and monocytes values may have been due to the concurrent diseases and/or concomitant treatments received by patients in this study population. These results do not appear to raise any safety concerns for oxycodone HCl CR.
- There was no evidence of clinically significant mean changes from baseline in any vital sign measurement during the core and extension studies. Five patients had shifts from normal at baseline to high at the end of the extension study for respiratory rate. No patients had shifts from normal at baseline to low at the end of the extension study for respiratory rate; 2 patients had TEAEs of respiratory depression reported, and 1 patient had a TEAE of respiratory rate (< 12) reported. All of these TEAEs were considered by the investigator to be mild in intensity and not related to treatment.
- There was no evidence of clinically significant somnolence scores during the extension study.

Conclusions:

Though interpretation is limited by the small number of patients in this study population (N = 23), oxycodone HCl CR was generally safe and well tolerated when used for a period of up to 28 weeks in this pediatric population. No new or unexpected risks were identified.

Date of the Report: 04 September 2014