2 SYNOPSIS

Name of Sponsor/Company: Purdue Pharma L.P.	**Protocol No.** OTR3001
Name of Finished Product: Twice-Daily Oxycodone Hydrochloride Controlled-release Tablets	**Name of Active Ingredient**: Oxycodone hydrochloride
IND No.: 29,038	**EudraCT No.:** 2010-020471-23
Indication: Moderate to Severe Malignant and/or Nonmalignant Pain.	
Title of the Study: An Open-label, Multicenter Study of the Safety of Twice Daily Oxycodone Hydrochloride Controlled-release Tablets in Opioid Experienced Children from Ages 6 to 16 Years Old, Inclusive, with Moderate to Severe Malignant and/or Nonmalignant Pain Requiring Opioid Analgesics	
Investigator(s), Site(s): This is a multicenter, multinational trial at 101 sites (United States of America [USA], Spain [ESP], United Kingdom [GBR], Greece [GRC], Guatemala [GTM], Hungary [HUN], Israel [ISR], and New Zealand [NZL]. The list of investigators is provided in Appendix 16.1.4.	
Publication (Reference): None	

Study Period (Dates):	**Study Status:**	**Phase of Development:**
28-Feb-2011 (FPFV) to 29-Jul-2014 (LPLV)	Completed.	Phase 3

Objectives:

Primary

- To characterize the safety of oxycodone hydrochloride controlled-release (HCl CR) tablets in opioid-tolerant pediatric patients aged 6 to 16 years, inclusive, with moderate to severe malignant and/or nonmalignant pain requiring opioid therapy.

Secondary

- To characterize the efficacy and provide additional pharmacokinetics (PK) data for a population PK model of oxycodone HCl CR tablets in opioid-tolerant pediatric patients aged 6 to 16 years, inclusive, with moderate to severe malignant and /or nonmalignant pain requiring opioid therapy.

Note: In the preceding text, “opioid-tolerant” was changed from “opioid-experienced” and “and provide additional PK data for a population PK model” was added per Amendment, 27-Jan-2011.

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Methodology: This was a phase 3, multicenter, open-label clinical trial in 155 opioid-tolerant pediatric patients at 101 study centers worldwide. The study consisted of a 0 to 72 hour screening, followed by an open label treatment for up to 4 weeks and 7 to 10 days follow-up period. Eligible patients could be treated as outpatient or inpatient, and they were required to have been treated with opioids for at least the 5 consecutive days prior to dosing and with at least 20 mg daily and no more than 240 mg daily of oxycodone or the equivalent for at least 48 hours before beginning the study. Patients' current opioid analgesic daily dose was converted to an appropriate daily dose of oxycodone HCl CR tablets and patients were treated for a minimum of 2 weeks and up to 4 weeks (including titration to a safe and effective dose between 20 and 240 mg/day, inclusive). Dose adjustments (up- or down-titrations) of oxycodone HCl CR tablets could be made by the investigator, as necessary, during treatment. The study included a total of 3 clinic visits and additional telephone interviews. Study visits could have been conducted at a patient's home if the principal investigator deemed this to be appropriate based on the patient's medical status. Supplemental opioid and nonopioid pain medication was permitted during the study as deemed appropriate by the investigator. All patients were contacted 7 to 10 days after the last dose of study drug for a safety follow-up assessment.

An independent Data Monitoring Committee (DMC) was established to review the accumulating safety data from the trial. The DMC met periodically 6 times, 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.

Note: The preceding text, "eligible" and "they were required to have been treated with opioids for at least the 5 consecutive days prior to dosing and" was added per Amendment, 27-Jan-2011. The screening period was increased from ≤48 hours to ≤72 hours per Amendment, 24 Jan-2012. Study visits could have been conducted at a patient's home if the principal investigator deemed this to be appropriate based on the patient's medical status per Amendment, 11-Jun-2012. The text "with the exception of OxyContin® or other oxycodone products", was added per Amendment, 27-Jan-2011 and removed per Amendment, 23-Jan-2014. Details of the PK sample collection were added per Amendment, 27-Jan-2011 and were removed as per Amendment, 23-Jan-2014 and Amendment, 12-Feb-2014).

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Number of Patients:

Planned: 154 patients

Screened: 173

Screen failures: 18

Enrolled: 173

Treated: 155

Discontinued early: 33

Completed: 122

Note: The number of patients was changed from 100 to 135 patients per Amendmen, 27-Jan-2011 and to 154 per Amendment, 24-Jan-2012).

Indication and Main Criteria for Inclusion/Exclusion:

Male and female opioid-tolerant pediatric patients aged 6 to 16 years (inclusive) were eligible if they were expected to require ongoing around-the-clock opioid treatment equivalent to 20 to 240 mg daily of oxycodone for at least 2 weeks for management of moderate to severe malignant or nonmalignant pain, had tolerated opioid therapy and had been exposed to or treated with opioids for at least 5 consecutive days prior to dosing, and with at least 20 mg daily and no more than 240 mg daily of oxycodone or the equivalent for at least 48 hours before dosing (start of study drug). Patients who had a contraindication to the use of opioids or did not meet screening laboratory and clinical evaluation requirements were not eligible. Eligible postoperative patients who met the definition of opioid tolerant were not to be dosed with oxycodone HCl CR until at least 5 days after surgery.

Note: The preceding text “opioid tolerant” was changed from “opioid experienced”, and the preceding text “and been treated with opioids for at least the 5 consecutive days prior to dosing and with at least 20 mg daily and no more than 240 mg daily of oxycodone or the equivalent for at least 48 hours before dosing (start of study drug).” was changed from “and had been exposed to or treated with the equivalent of at least 20 mg of oxycodone daily” per Amendment, 27-Jan-2011. The text “eligible postoperative patients who met the definition of opioid tolerant were not to be dosed with oxycodone HCl CR until at least 5 days after surgery” was added per Amendment, 27-Jan-2011 and Amendment, 24-Jan-2012.

Test Treatment, Dose, and Mode of Administration: Oxycodone HCl controlled-release (CR) twice daily tablets, at strengths of 10, 15, 20, 30, or 40 mg (20 to 240 mg daily), every 12 hours taken orally with water. The batch/ lot numbers for the tablets are presented below.

Test Treatment	Strength	Batch/Lot Number
Oxycodone HCl CR	10 mg	CB-2010-03, WFK70, WKM40 & WMS20
Oxycodone HCl CR	15 mg	CB-2010-04, WFL20, WKL70 & WPE60
Oxycodone HCl CR	20 mg	CB-2009-15, WFM10, WKL80 & WPF90
Oxycodone HCl CR	30 mg	CB-2009-16, WFL10, WFK90, WKY00 & WMP80
Oxycodone HCl CR	40 mg	CB-2010-05, WFK60, WKY40 & WPF10

Reference Treatment, Dose, Mode of Administration, and Batch Number: Not applicable

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Supplemental Analgesia: Supplemental opioid and nonopioid pain medication was permitted during the study as deemed appropriate by the investigator.

Note: The text "with the exception of OxyContin® or other oxycodone products" was added to the previous sentence per Amendment, 27-Jan-2011 and removed as per Amendment, 23-Jan-2014.

Duration of Treatment:

Screening phase – up to 72 hours.

Treatment phase – total of 4 weeks (minimum of 2 weeks and up to 4 weeks)

Follow-up period – 7 to 10 days

Total study duration – 5 weeks

Note: The text "screening and treatment phase – total of 6 weeks (screening period is up to 14 days and treatment period is a minimum of 2 weeks and up to 4 weeks)" was replaced per Amendment, 27-Jan-2011. The screening phase increased from 48 to 72 hours per Amendment, 24-Jan-2012.

Criteria for Evaluation:

Efficacy

Efficacy assessments consisted of pain scores, Functional Disability Inventory (FDI), Parent/ Caregiver-assessed Global Impression of Change (PGIC), and supplemental opioid analgesic use. To assess pain, patients aged 6 to <12 years completed the Faces Pain Scale-Revised (FPS-R) and patients aged ≥ 12 to ≤ 16 years completed the visual analogue scale (100-mm VAS).

Pharmacokinetics

Note: This section was added per Amendment, 27-Jan-2011, and removed per Amendment, 23-Jan-2014 and Amendment, 12-Feb-2014.

Safety

Safety assessments consisted of reports of adverse events (AEs), physical examinations, vital signs, weight, pulse oximetry (SpO2), clinical laboratory assessments, and somnolence (University of Michigan Sedation Scale [UMSS]) evaluations.

Statistical Methods:

Analysis Populations

- Enrolled population: Patients for whom informed consent/assent was provided.
- Safety population: Patients who received at least 1 dose of study drug.
- Full analysis population (FAP) for pharmacokinetics (PK): Patients who received at least 1 dose of study drug and had at least 1 valid PK concentration.

Note: The word "oral" was deleted from "oral study drug" per Amendment, 22-Jul-2010, and the text was changed to "patients who received at least 1 dose of study drug and had at least 1 valid PK concentration" per Amendment, 27-Jan-2011.

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Sample Size Rationale

There was no formal sample size justification based on statistical power considerations. The sample size for this study was planned to be 154 patients.

The incidence rate of observed AEs would depend on the true (but unknown) underlying rates in the population. With a sample size of n = 154 if the true rate (θ) of a specific AE in the population for the duration of the study was 0.01, there would be 78.7% probability that at least 1 patient would have the event during the study; if θ = 0.02, the corresponding probability was 95.5%, and if θ = 0.05, the probability was 99.96%.

Note: The planned sample size was changed from 100 to 135 patients per Amendment, 27-Jan-2011 and to 154 per Amendment, 24-Jan-2012. The probability that at least 1 patient would have the event during the study was changed from "63.4%" to "74.3%" per Amendment, 27-Jan-2011 and from "74.3%" to "78.7%" per Amendment, 24-Jan-2012. The corresponding θ = 0.02 probability was changed from "86.7%" to "93.5%", per Amendment, 27-Jan-2011, and from "93.5%" to "95.5%" per Amendment, 24-Jan-2012, and the corresponding θ = 0.05 probability was changed from "99.4%" to "99.9%" per Amendment, 27-Jan-2011, and from "99.9%" to "99.96%" per Amendment, 24-Jan-2012.

Efficacy Analyses

All efficacy variables (pain scores [FPS-R and 100-mm VAS], FDI, PGIC, and supplemental opioid analgesic use) were listed for patients in the safety population. Data were summarized by age group (6 to <12 years and ≥ 12 to ≤ 16 years), assessor (self or parent/caregiver), and by time point as appropriate. Summaries included descriptive statistics along with the associated 95% confidence intervals if deemed appropriate.

Note: The population was changed from the FAP to the safety population per Amendment, 27-Jan-2011.

Population PK Analyses

All concentration data were listed for patients in the FAP for PK. Methodology and results of the population PK analyses are contained in a separate report.

Note: This section was added per Amendment, 27-Jan-2011.

Safety Analyses

Safety variables were summarized descriptively within age group for the safety population. Safety assessments to be summarized consisted of reports of AEs, physical examinations, clinical laboratory test results, vital signs measurements, SpO2, and somnolence assessments.

Results:

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Disposition of Patients

Of the 155 patients included in the safety population, 122 patients (78.7%) completed the study, 68 patients (43.9%) completed in ≥ 2 to <4 weeks and 54 patients (34.8%) completed in ≥ 4 weeks. Of the 155 patients in the overall safety population, 21 (13.5%) patients discontinued from the study with <2 weeks of study drug treatment and 12 (7.7%) patients discontinued from the study with ≥ 2 to <4 weeks of study drug treatment. Reasons for discontinuation reported for ≥ 2% of patients were administrative reasons (5.8%), AEs (4.5%), and subjects choice (2.6 %) in patients discontinuing in <2 weeks, and lack of therapeutic effect (2.6%) in patients discontinuing in ≥ 2 to <4 weeks. For a small number of patients, some sites requested an extension of treatment beyond the 4 weeks permitted by protocol for OTR3001 in order to allow these patients who had achieved adequate analgesia with the study drug to continue their therapy. This need was related to the disease state of individual patients: a subset of those with cancer and chronic diseases needed >4 weeks of treatment, whereas many postsurgical patients did not require the entire 4 weeks allowed in OTR3001. Patients who completed this study with good pain control and who needed to continue receiving treatment with the study drug, oxycodone HCL CR tablets, as determined by their investigator, were eligible for enrollment in the extension study, OTR3002.

Patient disposition varied between the 27 patients that were 6 to <12 years of age at screening, referred to here as the younger age group, and the 128 patients that were ≥ 12 to ≤ 16 years of age at screening, referred to here as the older age group. Patients in the younger age group discontinued more often than the older age group in <2 weeks (33.3% and 9.4%, respectively). Reasons for discontinuation in <2 weeks reported for ≥ 2% of patients were AEs (11.1%), administrative (11.1%), and subjects choice (11.1%) in the younger age group, and administrative (4.7%) and AEs (3.1%) in the older age group. Reasons for discontinuation in ≥ 2 to <4 weeks reported for ≥ 2% of patients were administrative (3.7%) in the younger age group and lack of therapeutic effect (3.1%), AEs (2.3%), and subjects choice (2.3%) in the older age group.

Concomitant Medications

In the total safety population and in both the younger and older age groups, hydrocodone (34.8%, 33.3%, and 35.2%, respectively), oxycodone (31.0%, 25.9%, and 32.0%, respectively), hydromorphone (20.6%, 14.8%, and 21.9%, respectively), and morphine (17.4%, 25.9%, and 15.6%, respectively) were the most frequently reported opioid supplemental pain medications, and ibuprofen (36.8%, 29.6%, and 38.3%, respectively) and gabapentin (21.9%, 33.3%, and 19.5%, respectively) were the most frequently reported nonopioid supplemental pain medications.

Demographic and Baseline Characteristics

In the total population, 57.4% of patients were female, 69.7% were white, and 88.4% wer not Hispanic or Latino, with a mean age of 13.7 years (range: 6 to 16 years). The younger and older age groups had similar demographic characteristics with the exception of mean ages 9.6 years (range: 6 to 11 years) and 14.5 years (range: 12 to 16 years), respectively.

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Efficacy:

Based on the results, treatment with oxycodone HCl CR provided well maintained pain control in patients between 6 and ≤16 years. The magnitude of improvement was greater for patients between ≥ 12 and ≤ 16 years.

Overall, based on changes from baseline in pain right now scores, supplemental analgesic usage (opioid and nonopioid), and changes from baseline in FDI and PGIC ratings in these opioid-tolerant, pediatric patients:

- The study drug alone or in combination with supplemental analgesics maintained the reduction in mean average pain right now scores from week 1 to 4 or further reduced these scores. The control of pain as indicated by the reduction in pain scores was clinically meaningful. These results are applicable for the overall safety population and both age groups. The reduction or improvement in pain right now scores were slightly greater in the morning than in the evening.
- The study drug alone or in combination with supplemental analgesics resulted in a clinically meaningful reduction in maximum pain right now scores from week 1 to 4. There was no difference between maximum scores in the morning and evening. This improvement is clinically meaningful for both age groups.
- The use of opioid supplemental pain medication was somewhat higher in the younger age group compared with the older age group (77.8% vs 72.7%, respectively). The most frequently used opioid supplemental medications in both age groups were hydrocodone, oxycodone, hydromorphone, and morphine. These data are consistent with those observed in medical practice.
- For the overall safety population and the 2 age groups, including patients that remained in the study ≤ 2 weeks or >2 weeks, mean daily and cumulative daily doses of opioid supplemental pain medication decreased. These results are consistent with those observed from week 1 to week 4 for mean average and mean maximum pain right now scores; the decreases were greater in the older age group compared with the younger age group.
- The incidence of patients using nonopioid supplemental pain medication was similar between the 2 age groups, and was less than that for the use of opioid supplemental pain medication. The most frequently used nonopioid supplemental medications in both age groups were ibuprofen and gabapentin.
- For the overall safety population and both age groups, the mean total FDI scores at week 4/ early study discontinuation decreased from those at baseline, indicating less functional disability. Patients in the younger age group had higher mean total FDI scores at all timepoints than did patients in the older age group. The mean total FDI scores for the older age group were less variable from baseline to week 4/ early discontinuation compared with the younger age group, most likely due to differences in the baseline medical pain-related conditions.
- There was little difference in the PGIC scores between the overall safety population and both age groups at week 4/early discontinuation. In the overall safety population, the younger age population, and the older age population, 72%, 67%, and 73%, respectively, had PGIC scores indicating very much or much improved.

Pharmacokinetics

Population PK results will be presented in a separate report.

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Safety:	
Dosing and Extent of Exposure The mean weekly dose mean (33.30 mg/day), minimum (17.56 mg/day), and maximum (40.32 mg/day), and the extent of exposure (20.7 days) for the total population were similar to those in both age groups.	
Adverse Events • Overall, the exposure (mean number of days on study drug therapy and weekly duration of treatment) to study drug from week 1 to week 4 was relatively stable and consistent between the age groups and the overall safety population. • In the total safety population, TEAEs were reported by similar proportions of patients in each study drug exposure category (<2 weeks; ≥ 2 weeks). • The most frequently reported treatment-related TEAEs in the younger and older age groups and in the total population were vomiting, nausea, and headache. • Twenty-four (24) SAEs (including the deaths) were severe in severity; 18 SAEs were moderate in severity; and 7 SAEs were mild in severity. • The percentage of patients with down-titration of study drug was higher than that for up-titration. • Seventy-nine (79) percent of the study data were obtained while patients were not hospitalized (outpatients) and 21% while patients were hospitalized (inpatients). • The most frequently reported TEAEs were vomiting, nausea, constipation, diarrhea, pyrexia, headache, pruritus, and dizziness. • No severe TEAEs were reported for more than 2 patients in the overall safety population except neutropenia. • The incidence of TEAEs did not increase with the mean daily dose of study drug. • There were 3 treatment-emergent deaths and 1 nontreatment-emergent death in the overall safety population; none were related to the study drug. All 4 of these patients had a malignant neoplasm. Two of the patients were younger (7 years old and 10 years old), and 2 were older (15 years old and 16 years old). • A total of 24 patients experienced treatment-emergent SAEs; the last dose prior to the event was between 20 mg and 100 mg. The onset of all of the SAEs in relation to study drug dosing was more than 4 hours after the last dose prior to the onset of the SAE. • The number of patients in the overall safety population experiencing TEAEs leading to study drug discontinuation or dose reduction was modest. Only 1 patient (in the older age group) experienced TEAEs leading to study drug interruption.	

Summary of Incidence of Deaths, Serious AEs (SAEs) and Other Significant AEs – Safety Population

Category	Age Group		Total (N=155) n (%)
	6 to <12 Years (N=27) n (%)	≥12 to ≤16 Year (N=128) n (%)	
Deaths	2 (7.4)	2 (1.6)	4 (2.6)
Serious TEAEs	5 (18.5)	19 (14.8)	24 (15.5)
TEAEs leading to study drug discontinuation	3 (11.1)	7 (5.5)	10 (6.5)
TEAEs leading to dose reduction	1 (3.7)	4 (3.1)	5 (3.2)
TEAEs leading to dose interruption	0	1 (0.8)	1 (0.6)

Abbreviations: TEAE = treatment-emergent adverse event; N = number of patients in population groups and total; n = number of patients with data.
Cross-reference: Table 14.3.2.1

Note: Death includes both TEAEs and non-TEAEs. Patients who experienced 2 or more AEs within the same category are counted only once. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 13.0 dictionary. Percentages are based on N.

Clinical Laboratory Evaluations

- The majority of patients stayed within the normal range for hematologic and blood chemistry parameter values during the study.
- Laboratory values with toxicity grades ≥ grade 3 occurred in 24 patients; these included low hemoglobin and platelets, and elevated blood glucose, bilirubin, ALT, and AST. The most frequent laboratory abnormality was low hemoglobin in 13 of these 24 patients. Eight of these 13 patients had a medical history of sickle cell disease or thalassemia, 1 of these 13 patients had a medical history of aplastic anemia, and 4 of these 13 patients had a medical history of neoplasm.

Vital Signs and Other Observations Related to Safety

- There were no clinically significant changes in systolic and diastolic blood pressure or pulse rate from baseline to the end of the study.
- There were no patients with treatment-emergent clinically significant respiratory depression or somnolence in either age group or in the total safety population during the study.
- Two patients had a treatment-emergent, clinically significant pulse oximetry finding that did not result in study drug discontinuation or reduction.
- No unexpected safety concerns were observed in the study.
- There were no cases of abuse or diversion by patients.

Conclusions:

This was a phase 3, multicenter, open-label clinical trial to evaluate the safety and efficacy of oxycodone HCl CR tablets in opioid-tolerant children from ages 6 to 16 years old, inclusive, with moderate to severe malignant and/or nonmalignant pain requiring opioid analgesics. The most frequent medical conditions of

patients enrolled in this study were postsurgical pain (scoliosis, pectum excavatum), cancer pain, sickle cell disease, and pain due to other causes.

Patients enrolled in the study were opioid tolerant and required to have been taking around-the-clock opioid medication for at least 5 consecutive days prior to taking the study drug. Thus, because pain was already being treated with opioid medication, the pain right now scores were low at baseline. Of the 155 patients who enrolled in the study, approximately 35% were treated with study drug for at least 4 weeks, 85% were treated with study drug for at least 2 weeks, and only 10% were treated with study drug for less than 2 weeks. The majority of the data were obtained in the outpatient setting. The distribution of patients between the 2 age groups (≥ 6 to <12 years old and ≥ 12 to ≤ 16 years old) was consistent with that observed in the population of pediatric patients who need opioid treatment for pain.

After switching to the study drug, patients' pain right now scores were maintained near the low baseline levels or improved throughout the 4 weeks of the study, showing that oxycodone HCl CR was effective, used alone or in combination with supplemental pain medications, in maintaining pain control in this pediatric patient population. The majority of patients took supplemental pain medication during study drug treatment. The requirement for opioid supplemental pain medication was higher in the younger age group, but similar proportions of younger and older patients took nonopioid supplemental pain medication. The FDI scores showed less functional disability, and the PGIC scores showed very much or much improvement in both age groups.

The safety of oxycodone HCl CR tablets was characterized in the opioid-tolerant pediatric patients enrolled in the study. Adverse events were as expected for opioid treatment, with vomiting, nausea, and headache as the most frequently reported treatment-related TEAEs and headache as the most frequently reported individual TEAE that led to study discontinuation. The 4 deaths and the majority of nonfatal SAEs that occurred during the study were considered unrelated to the study drug. Clinical laboratory tests and vital sign assessments did not reveal any apparent safety concerns. There were no significant changes from baseline in mean respiratory rate, the degree of hemoglobin-oxygen saturation or desaturation, or somnolence scores between the age groups.

Under the conditions of this study, oxycodone HCl CR tablets were safe and effective when administered to opioid-tolerant pediatric patients aged 6 to 16 years, inclusive, with moderate to severe malignant and/or nonmalignant pain requiring opioid therapy.

Date of the Report: 18-Nov-2014