CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022272Orig1s027

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 022272 S-027, SDN322, SDN325,	Submission Date(s): 12/10/2014, 5/11/2015, 5/14/2015
Brand Name	Oxycontin
Generic Name	Oxycodone Extended Release Tablets
Clinical Pharmacology Reviewer	Srikanth C. Nallani, Ph.D.
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OCP Division	Division of Clinical Pharmacology II
OND Division	Anesthesia, Analgesia and Addiction Products
Sponsor	Purdue Pharma LP
Submission Type	Pediatric Efficacy Supplement
Formulation; Strength(s)	Extended Release Tablet; 10 -80 mg
Indication	Chronic Pain Management
Proposed Dosage Regimen	Twice daily dosing based on efficacy and tolerability.

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1 Executive Summary

1.1 Recommendation

The submission is acceptable provided that a mutually acceptable agreement is arrived on the product label.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

Purdue Pharma LP submitted a response to the Pediatric Written Request issued by the Agency. In addition, the sponsor has also submitted Oxycontin product label with changes to the Dosage and Administration (Section 2), Specific Populations, Pediatrics (Section 8); Clinical Pharmacology, Pharmacokinetics, Special Populations (Section 12.3). Data from five multiple dose and one single dose pediatric pharmacokinetic studies, and two single dose BA/BE studies in adults were submitted (listed below in the table) to support meeting the exclusivity requirements and the labeling changes proposed. The sponsor also refers to a previously completed safety, PK study (OC96-0602 from 1998) that evaluated relative bioavailability of Oxycontin (original formulation) compared to oral immediate release tablet in pediatric patients on other opioid medications. Additional reference is made to relative bioavailability study of Oxycontin (old and new formulations) with IR oxycodone solution/tablet for bridging PK information (OTR1001 (previously reviewed in 2010), OC94-0101 in attached synopsis, OTR1005, and OTR1502 in table below).

Table: Studies Submitted to support pediatric population PK analysis.

Study (Country)	Study Objective(s)	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID],	No. of Dosed Subjects. (M/F) Type Age: mean (range)
		PEDIATRIC		
OTR1020 (United States and Australia)	To characterize the single and multiple dose PK and safety of reformulated OxyContin tablets (OTR) of various strengths in pediatric patients	Multicenter, multinational, open-label, single- and multiple dose	OTR 10, 15 and 20 mg tablets, po [10 mg: CB-2010-03], [15 mg: CB-2010-04], [20 mg: CB-2009-15]	30 (13M/17F) Pediatric patients 13.5 y (9-16y)
OTR3001 (Multinational) WR Study 3	To evaluate safety, efficacy and pharmacokinetics of OTR in opioid tolerant pediatric patients	Multicenter, multi-national, open-labeled, multiple-dose	OTR 10, 15, 20, 30, or 40 tablets, po [*]	155 (66M/89F) Pediatric patients 13.7 (6 to 16y)
OXP1005 (Multinational) WR Study 1	To characterize the PK and safety of oxycodone in pediatric patients following administration of IR oxycodone hydrochloride solution	Multicenter, multinational, open-label, multiple-dose, dose-ranging	Oxycodone HCl oral solution, 0.05 mg/kg, 0.1 mg/kg and 0.2 mg/kg, po [0.05 mg/kg:CB-2002-11], [0.1 mg/kg:CB-2002-11], [0.2 mg/kg:CB-2002-11]	60 (29M/31F) Pediatric patients 1.14y (birth to 4y)
OXP3003 (Multinational) WR Study 2	To characterize the PK and safety of oxycodone in pediatric patients following administration of IR oxycodone hydrochloride solution 0.1 to 0.2 mg/kg q6h	Multicenter, multinational, randomized, double-blind, multiple-dose, dose-ranging	Oxycodone HCl oral solution, 0.1 and 0.2 mg/kg, po [Oral solution: CB-2002-11],	65 (24M/41F) Pediatric patients 11.4y (5 to 16y)
OXP3004 (Multinational)	To evaluate safety and pharmacokinetics of the approved adult conversion ratio (1:1) from immediate release (IR) oxycodone q6h to OC q12h in pediatric patients	Multicenter, multinational, multiple-dose, dose-ranging	Immediate Release 5 mg capsule, po [CB41, DH61] OC 10 mg tablet , po [DR61, EB3N1]	7 (5M/2F) Pediatric patients 12.6y (7 to 16y)

OC96-0602 (United States)	To compare the relative bioavailabilities following single doses of IR oxycodone and OC in children	Single-center, randomized, open-label, two-way crossover, single-dose	OC 10 mg tablet, po [OC C25] Immediate Release 5 mg, po [IR Oxycodone 962438]	13 (7M/6F) Pediatric patients 9.6y (6 to 12y)
		ADULTS		
OTR1005 (United States)	To characterize the single-dose PK of oxycodone in healthy subjects and assess bioequivalence of OTR relative to OC	Single-center, randomized, open-label, single-dose, two-way crossover study	OTR 40 mg tablets, po [CB-2006-18] OC 40 mg tablets, po [W66G1]	92 (61M/31F) Healthy adult subjects under fasting and under naltrexone blockade, 31y (18-49y)
OTR1502 (United Kingdom)	To determine the bioequivalence of OTR (UK) and OTR (US) tablets; and bioequivalence of OTR(UK) and OC tablets	Single-center, open-label, multiple-dose, three-treatment, three-period, crossover	OTR (UK), OTR (US) and OC 80 mg tablets, po [OTR (UK) 80 mg: PN3369], [OTR (US) 80 mg: PN3374], [OC 80 mg: PN3350]	24 M Healthy adult subjects under naltrexone blockade, 31y (19-45y)

F=female; IR=immediate-release; M=male; OC= original OxyContin Tablets; OTR=reformulated OxyContin Tablets with abuse-deterrent properties; PK=pharmacokinetic(s); po=per os (by mouth); q12h=every 12 hours; WR=written request; y=years.
* Numerous lots were used in Study OTR3001,which was conducted over a 4-year period. For Product IDs please consult CSR OTR3001.

Clinical pharmacology of OxyContin: Pharmacokinetic properties of oxycodone following single and multiple dose administration (10 – 80 mg) of OxyContin (reformulated product approved in 2010) have been fairly well investigated in adults. Dose proportionality has been established for OxyContin 10 mg – 80 mg tablet strengths for both peak plasma concentrations (Cmax) and extent of absorption (AUC). Given the short elimination t½ of oxycodone (~5 hours), steady-state plasma concentrations of oxycodone are achieved within 24-36 hours of initiation of dosing with OxyContin. Oxycodone is extensively metabolized by multiple metabolic pathways to produce noroxycodone, oxymorphone and noroxymorphone, which are subsequently glucuronidated. Noroxycodone and noroxymorphone are the major circulating metabolites. CYP3A mediated N-demethylation to noroxycodone is the primary metabolic pathway of oxycodone with a lower contribution from CYP2D6 mediated O-demethylation to oxymorphone.

Pediatric Studies with OxyContin and Immediate release Oxycodone formulations:

It is important to note most of the pediatric OxyContin studies (in the table above) conducted in support of this supplement recruited pediatric patients with moderate to severe pain who were already receiving oxycodone or other opiates for pain management and could be considered opioid tolerant. These patients were administered OxyContin only if they required at least 10 mg twice daily. Patients requiring less than 10 mg twice daily were not included in the study.

Pharmacokinetics and safety of an age-appropriate oral formulation of immediate release oxycodone solution in opioid-naïve hospitalized patients from birth up to < 4 years of age were evaluated in Study OXP1005 and PK of oxycodone in opioid-naïve hospitalized pediatric patients 6 – 16 yrs. of age in Study OXP3003. (b) (4) . Therefore, this review is focused on the use of OxyContin in pediatric patients and is not intended to provide dosing recommendations of this immediate release formulation in the pediatric population.

Pediatric Bioavailability Study OC96-0602:

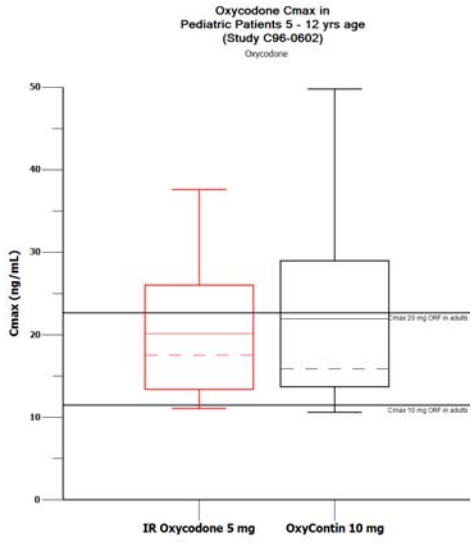
In Study OC96-0602, pharmacokinetics of oxycodone following crossover administration of OxyContin (10 mg original formulation) was compared with IR oxycodone (5 mg tablet). Pediatric patients (N=13) were previously receiving opiates other than

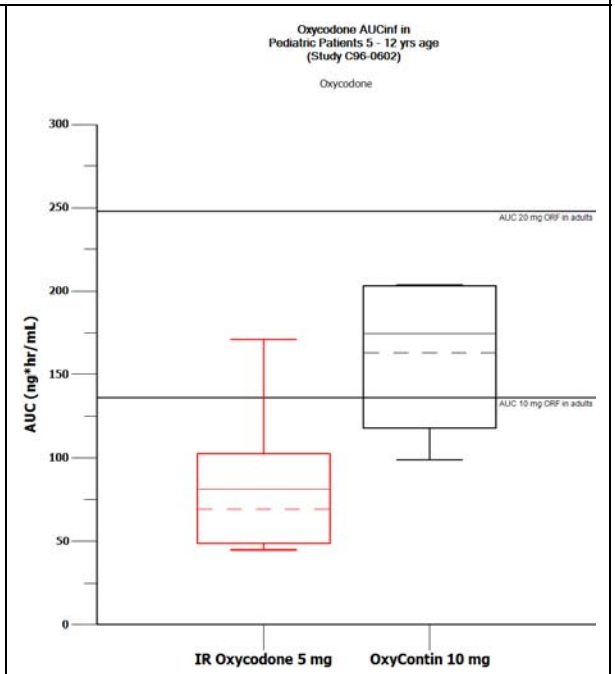
oxycodone to qualify for this study. In this study, pediatric patients in the 6-12 yrs. age group receiving 10 mg OxyContin had a Cmax or peak plasma concentration of oxycodone ~22 ng/mL; where as adults receiving the same dose would have a Cmax of ~ 11 ng/mL. OxyContin label indicates that a single 10 mg dose produces oxycodone AUC of about 136 ng.hr/mL.

Table: Summary of PK Parameters from Study OC96-0602

	Arithmetic Mean (SD)	
PK Metric	**IR Oxycodone (5 mg)**	**OxyContin® (10 mg)**
AUC_t (ng·h/mL)	83.2 (43.0)	201.0 (143.0)
AUC_∞ (ng·h/mL)	81.3 (39.1)[b]	174.6 (91.1)[c]
C_{max} (ng/mL)	20.2 (8.3)	22.0 (13.0)
t_{max} (h)	2.1 (0.9)	3.3 (1.7)
$t_{½}$(elim) (h)	2.6 (1.0)[c]	5.2 (1.8)[c]
MRT (h)	4.2 (1.2)	8.7 (1.9)

Figure: Box-Plot comparing Cmax (left figure) and AUC (right figure) of oxycodone in pediatric patients of 6 -12 yrs. age following administration of OxyContin 10 mg or IR oxycodone 5 mg (tablet) doses. Horizontal reference lines are label indicated mean Cmax (left figure) and mean AUC (right figure) of 10 mg OxyContin (bottom) and 20 mg OxyContin (top) in adults.



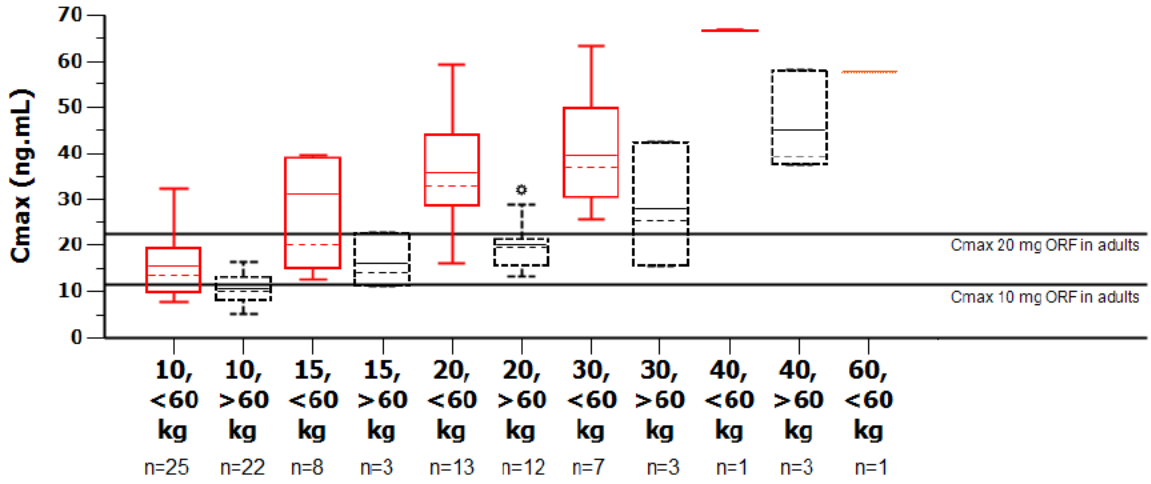


The observed increase in exposure of oxycodone following OxyContin administration in the 6 -12 year age group is possibly due to decreased metabolic clearance in these patients with lower body weight.

In another pediatric safety study (OTR3001) where OxyContin safety and PK was evaluated in 6 -16 year old patients, it was observed that for any given dose of OxyContin (10 – 30 mg) patients in 6 – 12 yr. age group had higher Cmax compared to 13 -16 yr. old patients (See appended results for OTR3001). The higher Cmax appeared to be a more consistent observation in pediatric patients < 60 kg bodyweight compared to >60 kg bodyweight (See figure below). Very limited number of subjects received doses ≥40 mg OxyContin; hence a comparison could not be made. These findings are consistent with the population pharmacokinetic analysis which demonstrated that body weight is an important covariate for the volume of distribution and clearance of oxycodone. A dose-proportional increase in Cmax and AUC was noted in pediatric patients in each age group or body weight group.

It is important to note most of the pediatric studies conducted in support of this supplement (including study OTR3001) recruited pediatric patients who were already receiving oxycodone or other opiates for pain management and could be considered opioid tolerant. Hence, the observed difference in Cmax in pediatric patients with lower age/bodyweight becomes clinically relevant when considering 10 mg OxyContin for opioid naïve patients. In fact, pediatric patients in the age range of 6 – 12 yrs., especially those with lower body weight, might benefit from a 5 mg OxyContin formulation. (b) (4) . It is noteworthy that pediatric patients 12 – 17 yrs. Old have similar exposure to oxycodone compared to adults receiving similar dose of OxyContin.

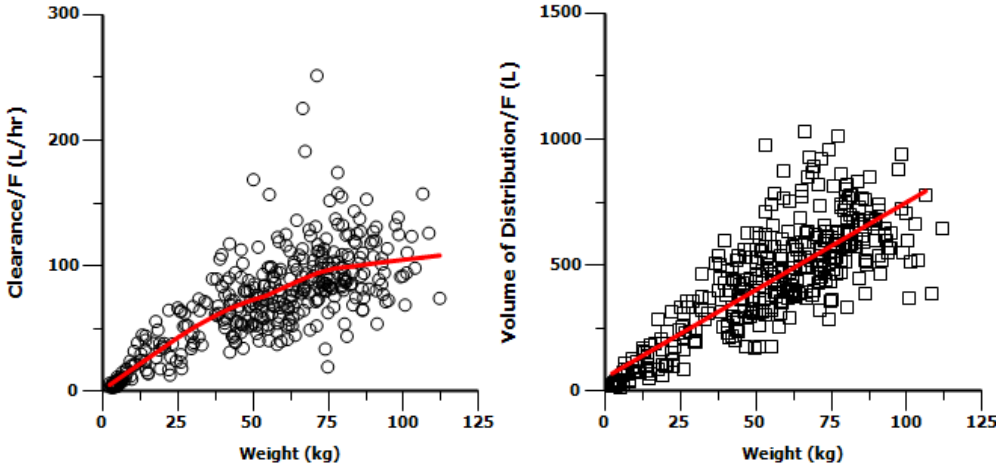
Figure: Box-Plot comparing Cmax (first dose) of oxycodone in pediatric patients (Study OTR3001) of bodyweight <60 kg vs. >60 kg bodyweight following administration of different OxyContin doses. Horizontal reference lines are label indicated mean Cmax of 10 mg OxyContin (bottom) and 20 mg OxyContin (top) in adults.



Note: Limited number of patients received doses ≥40 mg of OxyContin; hence a comparison could not be made.

Data from several adult and pediatric studies (as indicated above) were combined in a population PK analysis to characterize the population pharmacokinetics of oxycodone in adult and pediatric subjects and to estimate the effects of individual-specific covariate factors, in particular, age and weight on the variability in pharmacokinetics. Full review of the population PK analysis is appended to this memo. The main conclusions of the analysis are discussed below. The final model identified weight as a predictor of variability in clearance (CL/F) and volume of distribution (V/F) and age as a predictor of variability in CL/F in patients less than one year of age. No other covariates investigated demonstrated any relationship in the graphical evaluation of unexplained variability in oxycodone PK.

Figure: A plot of oxycodone clearance against bodyweight of pediatric patients and healthy subjects (Based on final model).



The table below describes clearance and volume of distribution for oxycodone in different bodyweight groups.

Table: Summary statistics of clearance and volume of distribution of oxycodone based on bodyweight groups from all studies.

Weight Group	Variable	N	Mean	SD	Median	Variable	N	Mean	SD	Median
<10 kg	CL/F	43	8.4	4.8	7.2	V/F	43	45.8	26.4	37.6
11-20 kg	CL/F	23	31.2	11.4	31.9	V/F	23	127.4	55.6	117.9
21-60 kg	CL/F	138	66.8	25.2	64.8	V/F	138	388.9	156.6	369.6
>60 kg	CL/F	168	96.7	31.5	91.8	V/F	168	590.4	151.5	584.1

These results provide further support that a 10 mg dose in lighter patients (i.e., less than 10 years of age) would result in higher exposure than the same dose in the adult population. Therefore, pediatric patients would benefit from a 5 mg OxyContin formulation.

We also note that the Sponsor's pharmacokinetic model has adequately characterized the pharmacokinetics of oxycodone throughout the entire pediatric population. Therefore, this model could potentially be used to derive pediatric dosing regimens of immediate release oxycodone formulation that would match the exposure in adults at dosing regimen of FDA-approved oxycodone products.

1.4 General Biopharmaceutics

OxyContin (reformulated) product 10 – 80 mg strengths were used in pediatric patients and adult PK studies. For Studies OXP1005 and OXP3003 an oral (20 mg/ml) solution was diluted to the appropriate strength with cherry syrup. This diluted solution was administered to patients orally using a 1 cc syringe.

Table: Composition of the pediatric oxycodone IR solution used in the clinical studies OXP1005 and OXP3003.

Ingredients	Percentage (% W/V)
Oxycodone HCl USP, Ph. Eur	0.1
	(b) (4)

(b) (4)

Drug Name	Oxy Pediatric Liquid (oxycodone hydrochloride oral solution)
Strength	1 mg/mL
Lot Number	CB2002-11
Storage	Ambient (not to exceed 25°C)
DEA Registration No.	(b) (4)
Amount Supplied	120 mL
Manufacturer	Purdue Pharmaceuticals L.P., distributed by Purdue Pharma, LP, 444 Saw Mill River Rd, Ardsley NY 10502

Pediatric study OC96-0602, which was conducted in 1998, employed original formulation of OxyContin and an immediate release 5 mg tablet of oxycodone.

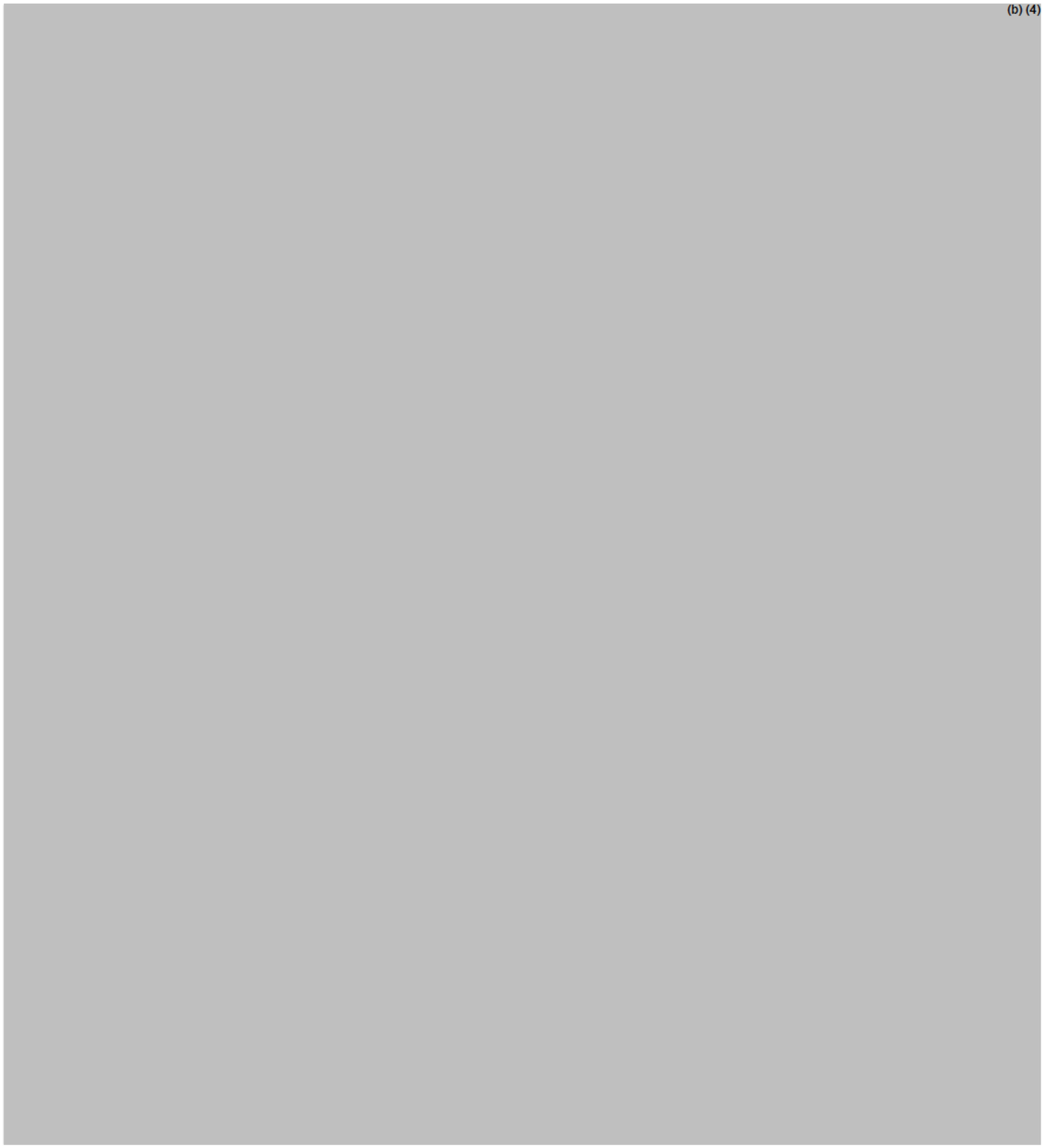
Relative bioavailability study OC94-0101 compared original formulation of OxyContin with 2 X 5 mg tablets of oxycodone by Boots Labs (Endone, lot AV4522), and immediate release solution of oxycodone by Roxane laboratories (Lot 940729).

Bioavailability Study OC94-0101

A variety of different formulations were evaluated in pediatric patients over a period of 15 years by Purdue Pharma. Results of study OC94-0101, originally conducted in support of the original NDA 20553 for Oxycontin, were resubmitted to support bridging of bioavailability of different formulations used. In this study bioavailability of old OxyContin formulation 10 mg of Purdue Pharma L.P. was compared with immediate-release oxycodone tablets (IR Oxy 2 X 5mg tablet, Endone, The Boots Company) and immediate-release oxycodone (Roxicodone, 10 mg oral solution, Roxane Laboratories). Following oral administration in the fasted state, the OC 10 mg tablet was equally bioavailable to IR oxycodone 2x5 tablets and to IR oxycodone 10 mL oral solution with respect to the extent (AUC) but not the rate of absorption (neither Cmax or Tmax were similar). The Cmax of the controlled-release tablet was approximately one-third of that observed with the IR products. Minor differences were noted in the two IR products (See appended results of Study OC94-0101).

(b) (4)


(b) (4)


(b) (4)


(b) (4)

[redacted] (b) (4)

[redacted] (b) (4)

The sponsor did not specifically provide any information bridging pediatric oxycodone solution product used in clinical trials and marketed oxycodone products. However, the sponsor generally indicates that alternative sources of a formulation suitable for younger children are commercially available in the US. Glenmark Pharma, Lannett Holdings Inc, Lehigh Valley Tech, Mallinckrodt, Roxane, Midlothian Labs, and Vistapharm market a 20 mg/mL oral solution of oxycodone HCl. Glenmark Pharma, Lehigh Valley Tech, Mallinckrodt, Roxane, and Vistapharm also market a 5 mg/5mL oral solution. All these are available by prescription.

1.5 Analytical

During routine investigation of one clinical site for OXP1005 and OXP3003, OSI investigators noted "The temperature log for the freezer did not include temperature records for the first nine of the total 15 months of PK blood sample storage." The bioanalytical method of oxycodone and its metabolites had been reviewed several times over the past decades for this NDA. However, the reason for inclusion of PK data from the pediatric studies is documented in the Bioanalytical methodology report (see attached Appendix 3.2.1), with specific emphasis on long-term stability of oxycodone & metabolite samples in human plasma for an extended period of time. In conclusion, the stability data showed that oxycodone and its metabolites, noroxycodone and oxymorphone, were stable in human plasma for up to 22 months. The stability data also showed that oxycodone and its metabolites, noroxycodone and oxymorphone, were stable in 1:1 MeOH/H2O stock and spiking solutions for up to 4 months.

2 Labeling

Discussion is still ongoing regarding what specific pediatric PK information should be included in the final product label. Refer to the approved label for details.

Pediatric PK information for 6 to 11 yrs. age group may imply established safety or efficacy and hence such may not be included.

Section 12.3 Pharmacokinetics

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Pediatrics

In the pediatric age group of 11 years and older systemic exposure of oxycodone is expected to be similar to adults at any given dose of OxyContin.

29 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

3.2 Individual Study Reviews

3.2.1 Bioanalytical Method (Long term stability, Fifteen Freeze Thaw cycle stability) & OXNSR06-022-1 report synopsis.

In Study OXP3003, The first set of samples was collected January 31, 2003 and was received on March 11, 2003. The last batch of samples was analyzed on June 29, 2004 for Oxycodone, Noroxycodone, and Oxymorphone; the last batch of samples was analyzed on May 6, 2005 for Morphine. The maximum storage duration for the study samples from collection to extraction was 348 days for Oxycodone, Noroxycodone, and Oxymorphone, and 700 days for Morphine.

In Study OXP1005, the first set of samples was collected March 31, 2003, and was received on May 1, 2003. The last batch of samples was analyzed on February 27, 2004. The maximum storage duration for the study samples from collection to extraction was 234 days.

Frozen storage stability of oxycodone and its metabolites, noroxycodone and oxymorphone, in human plasma stored at approximately -20°C was demonstrated for up to 22 months. Stability of stock solutions of oxycodone and its metabolites, noroxycodone and oxymorphone stored at 5ºC was demonstrated for up to 4 months.

Frozen storage stability of morphine in human plasma stored at approximately -20°C was demonstrated for up to five and a half months. Stability of stock solutions of morphine stored at 1-8ºC was demonstrated for up to 26 days.This report describes the results of the long-term stability of oxycodone and its metabolites, noroxycodone and oxymorphone, in human plasma based on method OXYMR00-004:1, "Quantitation of Oxycodone and Metabolites in Human Plasma by Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)." The full validation results were also reported in the validation report OXYVR00-017:1.

Long-Term Stability in Human Plasma

The long-term storage stability of oxycodone and its metabolites, noroxycodone and oxymorphone, in human plasma stored at approximately –20 °C was assessed at 2, 3, 7 and 22 months. The results are shown in Tables 6.1 A-C.

Long-Term Stability in Stock and Spike Solution

The long-term storage stability of oxycodone and its metabolites, noroxycodone and oxymorphone, in the specific solvent defined in the method OXYMR00-004:1(draft) was assessed using the highest concentration stock solution and two spiking solutions (high and low) stored at 5 °C for 4 months. The results are shown in Tables 6.2 A-C.

TABLE 6.1A. Oxycodone Long-Term Stability in Human Plasma

	Calculated Concentration (ng/mL)				
Nominal Concentration	Day 0	2 months	3 months	7 months	22 months
QC Low-QC A 0.300 ng/mL	0.294	0.353	0.327	0.264	0.299
	0.329	0.318	0.309	0.268	0.298
	0.277	0.287	0.306	0.292	0.271
	0.256	0.286	0.320	0.296	0.282
	0.316	0.316	0.310	0.273	0.267
	0.306	0.318	0.310	0.293	0.271
n	6	6	6	6	6
mean	0.296	0.313	0.314	0.281	0.281
SD	0.0265	0.0245	0.00812	0.0141	0.0142
CV (%)	8.95	7.81	2.59	5.01	5.06
%Diff	N/A	**5.58**	**5.78**	**-5.27**	**-5.14**
QC High-QC C 40.0	36.6	35.3	35.0	33.9	37.9
	36.6	35.3	36.0	33.7	34.5
	36.7	36.6	33.1	35.6	31.4
	39.1	38.5	36.5	36.1	35.7
	35.8	34.4	33.9	34.8	36.0
	36.8	38.9	35.8	34.2	35.6
n	6	6	6	6	6
mean	36.9	36.5	35.1	34.7	35.2
SD	1.11	1.84	1.30	0.973	2.16
CV (%)	3.00	5.04	3.72	2.80	6.15
%Diff	N/A	**-1.24**	**-5.13**	**-5.99**	**-4.73**

TABLE 6.1B. Noroxycodone Long-Term Stability in Human Plasma

	Calculated Concentration (ng/mL)				
Nominal Concentration	Day 0	2 months	3 months	7 months	22 months
QC Low-QC A 0.303 ng/mL	0.265	0.326	0.296	0.289	0.283
	0.287	0.320	0.304	0.281	0.258
	0.243	0.330	0.309	0.290	0.265
	0.230	0.296	0.300	0.288	0.253
	0.283	0.297	0.282	0.286	0.265
	0.259	0.305	0.304	0.286	0.264
n	6	6	6	6	6
mean	0.261	0.312	0.299	0.287	0.265
SD	0.0221	0.0148	0.00944	0.0033	0.0100
CV (%)	8.46	4.74	3.15	1.15	3.79
%Diff	N/A	**19.7**	**14.6**	**9.77**	**1.38**
QC High-QC C 40.4 ng/mL	38.5	40.1	40.6	37.9	36.1
	37.9	39.9	40.8	36.0	36.8
	38.8	39.6	37.3	38.0	34.7
	39.2	40.2	42.5	38.9	36.7
	40.3	40.2	40.0	36.8	36.5
	37.6	40.5	38.9	37.8	35.0
n	6	6	6	6	6
mean	38.7	40.1	40.0	37.6	36.0
SD	0.946	0.306	1.77	1.02	0.887
CV (%)	2.44	0.764	4.43	2.71	2.47
%Diff	N/A	**3.55**	**3.35**	**-3.00**	**-7.15**

TABLE 6.1C. Oxymorphone Long-Term Stability in Human Plasma

	Calculated Concentration (ng/mL)				
Nominal Concentration	Day 0	2 months	3 months	7 months	22 months
QC Low-QC A 0.300 ng/mL	0.270	0.266	0.313	0.298	0.270
	0.274	0.285	0.308	0.271	0.227
	0.250	0.251	0.332	0.260	0.254
	0.231	0.276	0.300	0.280	0.245
	0.266	0.252	0.252	0.266	0.274
	0.261	0.232	0.288	0.282	0.247
n	6	6	6	6	6
mean	0.259	0.260	0.299	0.276	0.253
SD	0.0162	0.0193	0.02734	0.0135	0.0174
CV (%)	6.27	7.43	9.15	4.88	6.90
%Diff	N/A	**0.584**	**15.5**	**6.69**	**-2.38**
QC High-QC C 3.80	4.11	3.60	3.90	3.74	3.17
	3.98	3.65	4.00	3.63	3.07
	4.00	3.38	3.90	3.51	3.21
	4.05	3.37	3.84	3.48	3.60
	3.76	3.62	3.73	3.71	3.54
	3.88	3.53	3.47	3.24	3.01
n	6	6	6	6	6
mean	3.96	3.53	3.81	3.55	3.27
SD	0.126	0.124	0.186	0.184	0.246
CV (%)	3.18	3.51	4.90	5.17	7.53
%Diff	N/A	**-11.1**	**-3.97**	**-10.4**	**-17.5**

Excerpt from bioanalytical report TM-543 indicating stability of oxycodone in plasma or solutions following different storage conditions (with focus on 15 cycles of Freeze/Thaw).

STABILITY

The following stability data for Oxycodone, Noroxycodone, Oxymorphone, Noroxymorphone and the internal standards Oxycodone-d_3, Noroxycodone-d_3, Oxymorphone-d_3, and Noroxymorphone-d_9 were established during the validation.

Solution Type	***Storage***	***Container***	***Interval***
Solutions	*See Sect 3.3	*	*
Freezer Storage	-20°C	Polypropylene tubes	603 days
Bench (in Matrix)	Ambient Temp	Polypropylene tubes	24 hours
Freeze/Thaw	-20°C	Polypropylene tubes	15 cycles
Extract Stability	Ambient Temp	Polypropylene autosampler vials	99 hours**
Extract Stability	~ 4 °C	Polypropylene autosampler vials	137 hours**

*** Reinjection of an entire batch of samples must be initiated within this timeframe.*

Note: Stability information is correct as of the effective date of this Test Method version. Stability evaluation is ongoing and the intervals listed are understood to be minimum stability intervals, but may not represent the most current information.

TABLE 6.2A. Oxycodone Long-Term Stability in Solution - 4months

Solution	Area	IS Area	PAR	Area	IS Area	PAR
	8/4/00 - Old			12/4/00- New		
Std Spk 1F - Low	1879	N/A	N/A	1511	N/A	N/A
	1588	N/A	N/A	1401	N/A	N/A
	1561	N/A	N/A	1422	N/A	N/A
	1542	N/A	N/A	1457	N/A	N/A
	1585	N/A	N/A	1388	N/A	N/A
	1510	N/A	N/A	1407	N/A	N/A
Mean	1611	N/A	N/A	1431	N/A	N/A
SD	135	N/A	N/A	45.6	N/A	N/A
CV (%)	8.36	N/A	N/A	3.19	N/A	N/A
Final Concentration (ng/mL)	1.00	N/A	N/A	1.00	N/A	N/A
Adjusted Mean PA	1611	N/A	N/A	1431	N/A	N/A
%Diff	**12.6**	N/A	N/A	N/A	N/A	N/A
Std Spk 1D - High	133060	N/A	N/A	131534	N/A	N/A
	138863	N/A	N/A	135323	N/A	N/A
	136510	N/A	N/A	133956	N/A	N/A
	134684	N/A	N/A	133545	N/A	N/A
	133195	N/A	N/A	133316	N/A	N/A
	133702	N/A	N/A	131491	N/A	N/A
Mean	135002	N/A	N/A	133194	N/A	N/A
SD	2281	N/A	N/A	1477	N/A	N/A
CV (%)	1.69	N/A	N/A	1.11	N/A	N/A
Final Concentration (ng/mL)	100	N/A	N/A	100	N/A	N/A
Adjusted Mean PAR	1350	N/A	N/A	1332	N/A	N/A
%Diff	**1.36**	N/A	N/A	N/A	N/A	N/A
Stock Solution - Std 1A	2493023	N/A	N/A	2559840	N/A	N/A
	2595994	N/A	N/A	2635478	N/A	N/A
	2619788	N/A	N/A	2648216	N/A	N/A
	2637286	N/A	N/A	2635625	N/A	N/A
	2647361	N/A	N/A	2701425	N/A	N/A
	2670406	N/A	N/A	2730491	N/A	N/A
Mean	2610656	N/A	N/A	2651846	N/A	N/A
SD	62884	N/A	N/A	59418	N/A	N/A
CV (%)	2.41	N/A	N/A	2.24	N/A	N/A
Final Concentration (ug/mL)	1.00	N/A	N/A	1.00	N/A	N/A
Adjusted Mean PA	2610656	N/A	N/A	2649197	N/A	N/A
%Diff	**-1.45**	N/A	N/A	N/A	N/A	N/A

TABLE 6.2B. Noroxycodone Long-Term Stability in Solution - 4 months

Solution	Area	IS Area	PAR	Area	IS Area	PAR
	8/4/00 - Old			12/4/00 - New		
	1186	N/A	N/A	819	N/A	N/A
Std Spk 2F - Low	796	N/A	N/A	759	N/A	N/A
	802	N/A	N/A	755	N/A	N/A
	820	N/A	N/A	763	N/A	N/A
	818	N/A	N/A	776	N/A	N/A
	788	N/A	N/A	784	N/A	N/A
Mean	868	N/A	N/A	776	N/A	N/A
SD	156	N/A	N/A	23.6	N/A	N/A
CV (%)	18.0	N/A	N/A	3.04	N/A	N/A
Final Concentration (ng/mL)	1.00	N/A	N/A	1.00	N/A	N/A
Adjusted Mean PAR	868	N/A	N/A	776	N/A	N/A
%Diff	**11.9**	N/A	N/A	N/A	N/A	N/A
Std Spk 2D - High	71834	N/A	N/A	70869	N/A	N/A
	72605	N/A	N/A	70657	N/A	N/A
	70323	N/A	N/A	69419	N/A	N/A
	69224	N/A	N/A	68844	N/A	N/A
	69628	N/A	N/A	68449	N/A	N/A
	69358	N/A	N/A	69100	N/A	N/A
Mean	70495	N/A	N/A	69557	N/A	N/A
SD	1410	N/A	N/A	989	N/A	N/A
CV (%)	2.00	N/A	N/A	1.42	N/A	N/A
Final Concentration (ng/mL)	100	N/A	N/A	100	N/A	N/A
Adjusted Mean PA	705	N/A	N/A	696	N/A	N/A
%Diff	**1.35**	N/A	N/A	N/A	N/A	N/A
Stock Solution - Std 2A	2626726	N/A	N/A	2627386	N/A	N/A
	2649903	N/A	N/A	2699278	N/A	N/A
	2700838	N/A	N/A	2788092	N/A	N/A
	2753835	N/A	N/A	2772082	N/A	N/A
	2737825	N/A	N/A	2816021	N/A	N/A
	2782393	N/A	N/A	2805479	N/A	N/A
Mean	2708587	N/A	N/A	2751390	N/A	N/A
SD	60918	N/A	N/A	73445	N/A	N/A
CV (%)	2.25	N/A	N/A	2.67	N/A	N/A
Final Concentration (ug/mL)	1.00	N/A	N/A	1.00	N/A	N/A
Adjusted Mean PA	2708587	N/A	N/A	2748641	N/A	N/A
%Diff	**-1.46**	N/A	N/A	N/A	N/A	N/A

TABLE 6.2C. Oxymorphone Long-Term Stability in Solution - 4 months

Solution	Area	IS Area	PAR	Area	IS Area	PAR
	8/4/00 - Old			12/4/00 - New		
Std Spk 3F - Low	2164	N/A	N/A	1619	N/A	N/A
	1780	N/A	N/A	1559	N/A	N/A
	1789	N/A	N/A	1582	N/A	N/A
	1816	N/A	N/A	1592	N/A	N/A
	1815	N/A	N/A	1524	N/A	N/A
	1740	N/A	N/A	1512	N/A	N/A
Mean	1851	N/A	N/A	1565	N/A	N/A
SD	156	N/A	N/A	41.2	N/A	N/A
CV (%)	8.43	N/A	N/A	2.63	N/A	N/A
Final Concentration (ng/mL)	1.00	N/A	N/A	1.00	N/A	N/A
Adjusted Mean PA	1847	N/A	N/A	1561	N/A	N/A
%Diff	**18.3**	N/A	N/A	N/A	N/A	N/A
Std Spk 3D - High	141249	N/A	N/A	129944	N/A	N/A
	139764	N/A	N/A	130808	N/A	N/A
	139373	N/A	N/A	129921	N/A	N/A
	139352	N/A	N/A	129542	N/A	N/A
	137332	N/A	N/A	129882	N/A	N/A
	135557	N/A	N/A	127474	N/A	N/A
Mean	138771	N/A	N/A	129595	N/A	N/A
SD	2011	N/A	N/A	1121	N/A	N/A
CV (%)	1.45	N/A	N/A	0.865	N/A	N/A
Final Concentration (ng/mL)	100	N/A	N/A	100	N/A	N/A
Adjusted Mean PA	1385	N/A	N/A	1293	N/A	N/A
%Diff	**7.08**	N/A	N/A	N/A	N/A	N/A
Stock Solution - Std 3A	2640503	N/A	N/A	2661134	N/A	N/A
	2723660	N/A	N/A	2734738	N/A	N/A
	2753098	N/A	N/A	2752353	N/A	N/A
	2803758	N/A	N/A	2742413	N/A	N/A
	2793673	N/A	N/A	2828773	N/A	N/A
	2810508	N/A	N/A	2839453	N/A	N/A
Mean	2754200	N/A	N/A	2759811	N/A	N/A
SD	64878	N/A	N/A	66065	N/A	N/A
CV (%)	2.36	N/A	N/A	2.39	N/A	N/A
Final Concentration (ug/mL)	1.00	N/A	N/A	1.00	N/A	N/A
Adjusted Mean PA	2754200	N/A	N/A	2759811	N/A	N/A
%Diff	**-0.203**	N/A	N/A	N/A	N/A	N/A

CONCLUSION

The stability data showed that oxycodone and its metabolites, noroxycodone and oxymorphone, were stable in human plasma for up to 22 months. The stability data also showed that oxycodone and its metabolites, noroxycodone and oxymorphone, were stable in 1:1 MeOH/H2O stock and spiking solutions for up to 4 months.

3.2.2 Population PK Analysis of OxyContin and Immediate Release Oxycodone.

Population Pharmacokinetics in Pediatric Patients and Healthy Adult Subjects:

The sponsor conducted a rather comprehensive pharmacokinetic data analysis strategy involving population pharmacokinetics modeling based on nonlinear mixed-effects modeling (NONMEM). The population PK analysis was conducted with a qualified installation of the nonlinear mixed effects modeling (NONMEM) software, Version 7, Level 2.0 (ICON Development Solutions, Hanover, MD). A covariate modeling approach emphasizing parameter estimation rather than stepwise hypothesis testing was implemented for this population PK analysis. Predefined covariate-parameter relationships were identified based on exploratory graphics, scientific and clinical interest, and mechanistic plausibility of prior knowledge; a full model was then constructed with care to avoid correlation or collinearity in predictors.

This involved pooling of all available plasma oxycodone concentrations (intensive and sparse) from single- and multiple-dose PK studies. The pooled data represented oxycodone concentrations across a range of formulations [oral immediate release from liquid and tablet, extended release original OxyContin (OC) and reformulated OxyContin (OTR or ORF)] in pediatric patients and representative oral OxyContin data in adult subjects for the population pharmacokinetic (POPPK) dataset. A total of 5 Phase 1 and three Phase 3 clinical studies were included in the POPPK modeling of oxycodone in pediatric patients and adult subjects.

Table: Studies included in final population pharmacokinetic analysis of oxycodone and the different formulations, doses, and demographics of patients/subjects employed.

Study Number	Formulations	Dose (mg)*	No. of Subjects	% Male	Weight	Age	No. of
					Range (kg)	Range (yr)	PK Samples
OC960602	IR solid, OC	5, 10	13	50	15-63	6-12	304
OTR1005	OC, ORF	40	92	67	51-106	18-49	3427
OTR1020	ORF	10, 15, 20, 30	30	39	28-86	9-16	180
OTR1502	ORF	80	23	100	62-98	19-45	463
OTR3001	ORF	10, 15, 20, 30, 40, 50, 60, 80	99	45	24-112	6-16	394
OXP1005	IR liquid	0.05, 0.1, 0.2 (mg/kg)	59	46	2-22	0-5	398
OXP3003	IR liquid	0.1, 0.2 (mg/kg)	44	41	14-101	5-16	299
OXP3004	IR solid, OC	5, 10, 15, 20, 30	10	54	26-73	7-16	102

*Studies OXP1005 and OXP3003 used mg/kg dosing; IR= immediate release; OC=original OxyContin Tablets; ORF=reformulated OxyContin Tablets

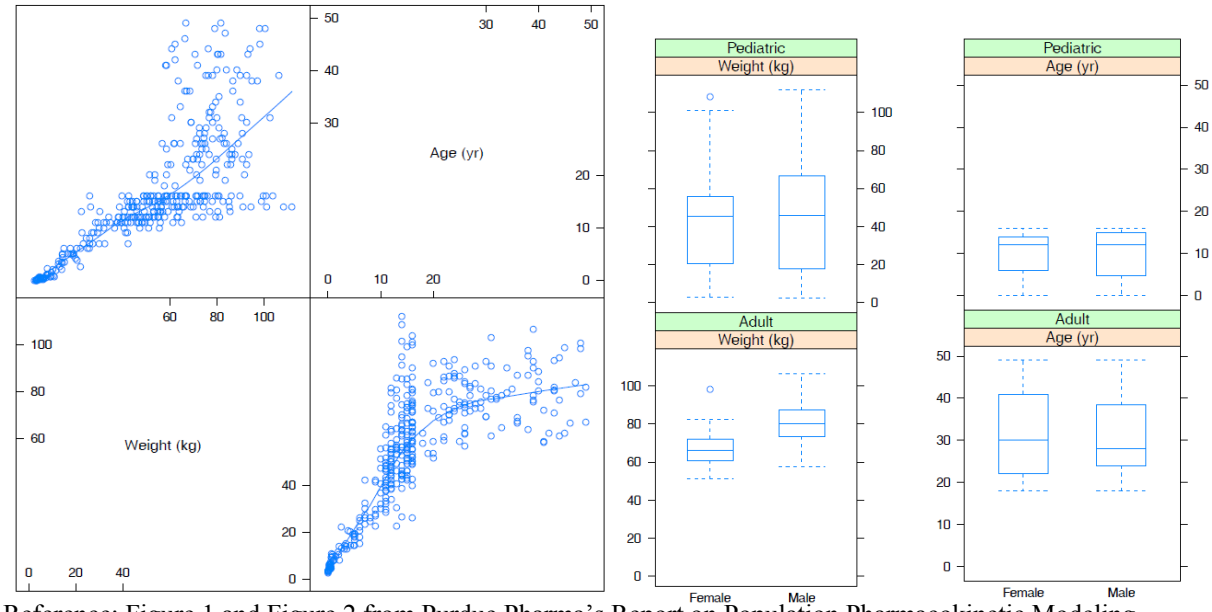
Reference: Table 1 from Purdue Pharma's Report on Population Pharmacokinetic Modeling of Oxycodone in Pediatric and Adult subjects.

The final oxycodone POP PK dataset consisted of 5567 oxycodone concentrations from 370 subjects from 8 studies (see Table below). There were 255 pediatric patients (< 18 years), with weights ranging from 2.4 to 112 kg. The final dataset contained 184 pediatric

patients between the ages of 6 and 16 years, of which 43 (23%) were > 6 to < 12 years old and 141 (77%) were ≥ 12 to ≤ 16 years old. Clinical PK experience with IR oxycodone formulations accounted for the rest of the pediatric patients.

Weight and age were positively correlated with a correlation coefficient of 0.76 and an obvious trend evident in scatter plots (bottom left).

Scatter plot matrix of continuous covariates. Circles represent data points and lines represent loess smoothing trend lines. (source: ../figure/ScatterContCov.pdf)



Reference: Figure 1 and Figure 2 from Purdue Pharma's Report on Population Pharmacokinetic Modeling of Oxycodone in Pediatric and Adult subjects.

Distributions of continuous covariates (top right) were similar for pediatric subjects in both sexes. In adult subjects, age was similar across sexes but weight demonstrated the typical dependency on sex, with males having a higher median weight and overall range than females. Weight, age and sex were considered as potential covariates in the model (table below)

Covariate	Model component	Rationale
Weight	CL/F, V/F	Clearance and volume parameters are known to have an allometric relationship with body size. Determination is of clinical interest (was included in base model).
Age	CL/F	Maturational development of cytochrome P450 enzymes will impact the clearance of oxycodone. Determination is of clinical interest (was included in base model).
Sex	CL/F, V/F	Differences in pharmacokinetic parameters between males and females was explored graphically after inclusion of other covariates.

Reference: Table 2 from Purdue Pharma's Report on Population Pharmacokinetic Modeling of Oxycodone in Pediatric and Adult subjects.

The population PK of oxycodone in pediatric patients and adult subjects was described by a one-compartment model with first-order absorption and elimination. The model was parameterized in terms of apparent (oral) clearance (CL/F), apparent (oral) volume of distribution (V/F), relative bioavailability (F) and first-order absorption rate constant (Ka). Separate relative F terms and absorption models were included to model each oral oxycodone formulation. A single first-order absorption model described the absorption of the IR liquid, IR solid, and ORF, while a parallel first-order absorption model described the absorption of the OC formulation.

The model was implemented in NONMEM using ADVAN7 TRANS1, which accounts for multiple dosing or steady-state conditions. CL/F and V/F were allometrically scaled by weight using a power model. CL/F was also modeled as a function of age using a power model with three age categories (<1 month, ≥1 month to <1 year, and ≥1 year) as described in the equations below. An attempt was made to model the age covariate effect as a continuous function using both Emax and sigmoid Emax models, however, these models were not stable and resulted in inadequate estimates for CL/F and the maturation half-life. Interindividual random effect terms for CL/F, V/F, Ka,OC fast , Ka,OC slow, and Ka,ORF were modeled using exponential variance models, with a covariance term between CL/F and V/F. Residual random effects were described with a combined additive and proportional error model. The residual error model was allowed to vary by oral formulation type.

The typical estimates of the PK model parameters for the reference covariates (70 kg, age ≥ 1year, ORF formulation) were 88.2 L/hr and 554 L for CL/F and V/F, respectively. Estimates for the different oral formulation Ka terms (hr^{-1}) were 0.972, 1.54, 0.954, 0.156, and 0.358 for Ka,IR liquid, Ka,IR solid, Ka,OC fast, Ka,OC slow, and Ka,ORF , respectively. Estimates for the different oral formulation relative F terms were 0.863, 1.08, 1.08, and 1 (FIXED; reference formulation) for FIR liquid, FIR solid, FOC, and FORF , respectively. The FastOC was estimated to be 0.595, so approximately 60% of the available OC dose was absorbed via the fast absorption phase and 40% via the slow absorption phase (Final parameter list is in the summary of the clinical pharmacology findings).

Variability in CL/F and V/F were partially described by allometrically scaled weight. An additional effect of age on CL/F was also described for subjects under one year of age that may partially represent maturational changes in CL/F. Final estimates of unexplained variability in CL/F and V/F were 38.1 %CV and 38.7 %CV, respectively.

The base model is described by the equations below.

$$CL/F_i = \theta_1 \cdot \left(\frac{WT_i\,(\text{kg})}{70\,(\text{kg})}\right)^{0.75} \cdot \theta_{13}^{CAGE_1} \cdot \theta_{14}^{CAGE_2} \cdot \exp\left(\eta_{CL/F_i}\right)$$

$$V/F_i = \theta_2 \cdot \left(\frac{WT_i\,(\text{kg})}{70\,(\text{kg})}\right)^{1.0} \cdot \exp\left(\eta_{V/F_i}\right)$$

$$K_{a,IR\,liquid} = \theta_3$$

$$K_{a,IR\,solid} = \theta_4$$

$$K_{a,OC\,fast,i} = \theta_5 \cdot \exp\left(\eta_{K_{a,OC\,fast,i}}\right)$$

$$K_{a,OC\,slow,i} = \theta_6 \cdot \exp\left(\eta_{K_{a,OC\,slow,i}}\right)$$

$$K_{a,ORF,i} = \theta_7 \cdot \exp\left(\eta_{K_{a,ORF,i}}\right)$$

$$F_{IR\,liquid} = \theta_8$$

$$F_{IR\,solid} = \theta_9 \qquad (10)$$

$$F_{OC\,fast} = \theta_{10} \cdot \theta_{11}$$

$$F_{OC\,slow} = \theta_{10} \cdot (1 - \theta_{11})$$

where $F_{OC} = \theta_{10}$ and $Fast_{OC} = \theta_{11}$

$F_{ORF} = \theta_{12}$ (FIXED to 1 for reference formulation)

IF (IR liquid formulation) $C_{ij} = \hat{C}_{ij}(1 + \varepsilon 1_{pij}) + \varepsilon 2_{aij}$

IF (IR solid formulation) $C_{ij} = \hat{C}_{ij}(1 + \varepsilon 3_{pij}) + \varepsilon 4_{aij}$

IF (OC formulation) $C_{ij} = \hat{C}_{ij}(1 + \varepsilon 5_{pij}) + \varepsilon 6_{aij}$

IF (ORF formulation) $C_{ij} = \hat{C}_{ij}(1 + \varepsilon 7_{pij}) + \varepsilon 8_{aij}$

Where:

- All parameters are as defined in the text and individual PK parameters are denoted by the subscript i.
- $CAGE_1 = 1$ if age <1 month, else equals 0; $CAGE_2 = 1$ if age ≥1 month to <1 year, else equals 0.

Reference: Equation 10 from Purdue Pharma's Report on Population Pharmacokinetic Modeling of Oxycodone in Pediatric and Adult subjects.

A table of the parameter estimates is provided below.

Parameter	Model	Estimate	%RSE	Bootstrap 95% CI
$CL/F\ (\theta_1)$	$CL/F \sim \theta_1 \cdot (\mathrm{WT}/70)^{0.75} \cdot \theta_{13}^{CAGE_1} \cdot \theta_{14}^{CAGE_2}$	88.2 L/hr	2.65	(84.2, 92.8)
$V/F\ (\theta_2)$	$V/F \sim \theta_2 \cdot (\mathrm{WT}/70)^{1.0}$	554 L	3.91	(521, 590)
$K_{a,IR\,liquid}\ (\theta_3)$		0.972 hr^{-1}	6.11	(0.627, 1.74)
$K_{a,IR\,solid}\ (\theta_4)$		1.54 hr^{-1}	9.83	(0.854, 2.63)
$K_{a,OC\,fast}\ (\theta_5)$		0.954 hr^{-1}	12.4	(0.797, 1.14)
$K_{a,OC\,slow}\ (\theta_6)$		0.156 hr^{-1}	5.39	(0.143, 0.173)
$K_{a,ORF}\ (\theta_7)$		0.358 hr^{-1}	5	(0.328, 0.399)
$F_{IR\,liquid}\ (\theta_8)$		0.863	5.13	(0.768, 0.988)
$F_{IR\,solid}\ (\theta_9)$		1.08	4.76	(0.944, 1.24)
$F_{OC}\ (\theta_{10})$		1.08	0.679	(1.04, 1.12)
$Fast_{OC}\ (\theta_{11})$		0.595	2.41	(0.554, 0.642)
$F_{ORF}\ (\theta_{12})$		1 FIXED		
$AGE_{<1\,month}\ (\theta_{13})$		0.493	17.3	(0.383, 0.721)
$AGE_{1\,month-1\,year}\ (\theta_{14})$		0.612	7.89	(0.493, 0.77)
$\Omega^{1,1}\,CL/F$		0.145 (%CV=38.1)	6.04	(0.107, 0.187)
$\Omega^{2,1}\,COV_{CL/F-V/F}$		0.0654 ($corr$=0.44)	17.4	(0.0388, 0.0899)
$\Omega^{2,2}\,V/F$		0.15 (%CV=38.7)	11.7	(0.0818, 0.211)
$\Omega^{3,3}\,K_{a,OC\,fast}$		0.671 (%CV=81.9)	17.6	(0.444, 0.935)
$\Omega^{4,4}\,K_{a,OC\,slow}$		0.119 (%CV=34.5)	19.8	(0.0686, 0.176)
$\Omega^{5,5}\,K_{a,ORF}$		0.14 (%CV=37.4)	16	(0.0361, 0.288)
σ^2_{prop} *IR liquid*		0.147 (%CV=38.3)	6.81	(0.109, 0.201)
σ^2_{add} *IR liquid*		0.848 (SD=0.92 (ng/mL))	33.3	(7.91e-05, 1.75)
σ^2_{prop} *IR solid*		0.301 (%CV=54.9)	15.6	(0.195, 0.369)
σ^2_{add} *IR solid*		0.851 (SD=0.92 (ng/mL))	48.3	(9.8e-05, 2.5)
σ^2_{prop} *OC*		0.0522 (%CV=22.8)	2.43	(0.0447, 0.0594)
σ^2_{add} *OC*		0.00828 (SD=0.09 (ng/mL))	16.4	(0.00457, 0.0124)
σ^2_{prop} *ORF*		0.0822 (%CV=28.7)	1.47	(0.069, 0.0986)
σ^2_{add} *ORF*		0.0287 (SD=0.17 (ng/mL))	2.63	(0.00672, 0.0608)

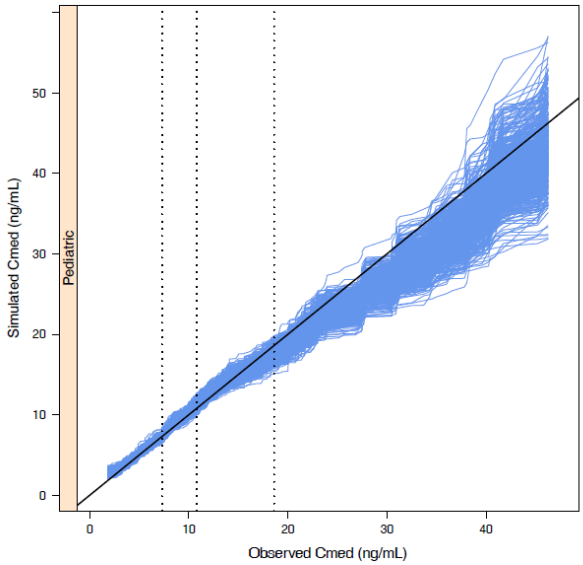
$AGE_{<1\,month}$ = age effect on CL/F for <1 month; $AGE_{1\,month-1\,year}$ = age effect on CL/F for ≥1 month to <1 year; $CAGE_1$ = flag equals 1 if age <1 month else equals 0; $CAGE_2$ = flag equals 1 if age ≥1 month to <1 year else equals 0; CI = confidence interval; CL/F = apparent (oral) clearance; $corr$ = correlation coefficient; CV = coefficient of variation; F = relative bioavailability (ORF as reference formulation); $Fast_{OC}$ = fraction of OC dose absorbed via fast absorption phase; IR liquid = immediate-release liquid; IR solid = immediate-release solid (tablet or capsule); K_a = absorption rate constant; OC = OxyContin original formulation; OC_{fast} = OC fast absorption phase; OC_{slow} = OC slow absorption phase; ORF = reformulated OxyContin; RSE = relative standard error; SD = standard deviation; V/F = apparent (oral) volume of distribution; WT = body weight (kg); Ω = interindividual covariance matrix; σ^2_{add} = additive residual error variance; σ^2_{prop} = proportional residual error variance; θ = fixed effect parameter; source: ../table/FinalParTab.tex, ReportTable.R

Reference: Table 10 from Purdue Pharma's Report on Population Pharmacokinetic Modeling of Oxycodone in Pediatric and Adult subjects.

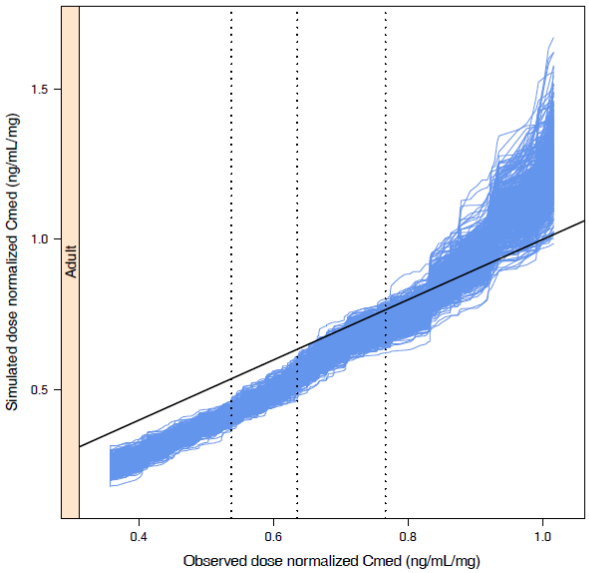
Model Evaluation

The adequacy of the final model and parameter estimates was investigated with a predictive check method. The precision of model parameters was investigated by performing a stratified non-parametric bootstrap procedure. One thousand (1000) replicate datasets were generated by random sampling with replacement and were stratified by clinical study, using the individual as the sampling unit. Population parameters for each dataset were subsequently estimated using NONMEM. This resulted in a distribution of 1000 estimates for each population model parameter. Empirical 95% CIs were constructed by observing the 2.5th and 97.5th quantiles of the resulting parameter distributions for all bootstrap runs.

Distributions of simulated median oxycodone concentrations within each individual (Cmed) are compared to the actual observed distribution of Cmed values from the population PK dataset for pediatrics. Simulations were performed using the final population PK model. Quantile-quantile (QQ) plots for each of the 500 simulation replicates are depicted by a solid blue line and are overlaid on the plot. The solid black line represents a reference line of identity. Dotted vertical lines represent the 1st quartile, median, and 3rd quartile of the observed Cmed values. (source: ../figure/PredCheckPed.pdf)



Distributions of simulated dose normalized median oxycodone concentrations within each individual (Cmed) are compared to the actual observed distribution of Cmed values from the population PK dataset for adults. Simulations were performed using the final population PK model. Quantile-quantile (QQ) plots for each of the 500 simulation replicates are depicted by a solid blue line and are overlaid on the plot. The solid black line represents a reference line of identity. Dotted vertical lines represent the 1st quartile, median, and 3rd quartile of the observed Cmed values. (source: ../figure/PredCheckAdult.pdf)



Reference: Figure 21 and Figure 22 from Purdue Pharma's Report on Population Pharmacokinetic Modeling of Oxycodone in Pediatric and Adult subjects.

Visual predictive check on observed vs. predicted concentrations were made for each study utilizing Pirana software with Xpose package. Two hundred Monte Carlo simulation replicates of the original dataset were generated using the final model. Satisfactory distributions of lower 95% CI, median, and upper 95% CI of the observations were contained within the predictions.

Final model diagnostic plots suggest that the model describes the pediatric and adult data well. Simulation based model evaluation shows reasonable predictive ability for both pediatric and multiple-dose adult oxycodone PK.

Exposure Comparison: Exposures for OxyContin were compared using the dose at the time of the first dose as well as the dose at the time of last dose in the data set. The sponsor provided graphical comparison of oxycodone exposure in pediatric patients in 6 – 12 yrs and 13 -16 yrs groups. However, an approach to provide descriptive statistics of oxycodone systemic exposure parameters were found suitable for this submission and described in the summary of clinical pharmacology findings.

The population pharmacokinetic model can be used, however, to derive dosing regimens in pediatric patients that will match adult exposures at the doses of FDA-approved oxycodone products. In this submission, empirical Bayes estimates from final model were used to calculate individual pharmacokinetic parameters for patients in studies OXP1005, OXP3003, and OTR3001. For each individual, PK parameters (Cmax, AUC, Cmax & Cmin at Steady-state were calculated and reported for that individual's first and last dose appearing in the data set with at least one observation record following that dosing record.

To calculate maximum concentration in the dosing interval (Cmax) and minimum concentration in the dosing interval (Cmin) using the final model, first dose concentrations were simulated every 0.25 hours over the dosing interval (tau). Cmax was taken as the maximum simulated oxycodone concentration over the dosing interval and Cmin was the simulated oxycodone concentration when time was equal to Tau (dosing interval 6 hours for IR, 12 hours for OxyContin Reformulation (ORF)).

Table: Descriptive Statistics of oxycodone following pediatric IR oxycodone liquid administration by weight normalized dosing. AR = accumulation ratio.

Variable	Dose/ Wt (mg/kg)	Dosing (First/ Last)	FORM	N	Mean	SD	Median	Min	Max
AR	0.05	First	IR liq	26	1.60	0.26	1.58	1.18	2.13
AR	0.1	First	IR liq	37	1.60	0.30	1.64	1.07	2.21
AR	0.2	First	IR liq	40	1.55	0.40	1.49	1.04	2.58
AUCss	0.05	First	IR liq	26	33.57	11.99	32.15	12.5	55.3
AUCss	0.1	First	IR liq	37	65.19	30.82	57.60	27	190
AUCss	0 2	First	IR liq	40	120.94	54.55	104.00	51.4	300
AUCtau	0.05	First	IR liq	26	20.60	5.77	20.40	10.4	32.8
AUCtau	0.1	First	IR liq	37	40.82	16.51	37.70	19.1	96.1
AUCtau	0.2	First	IR liq	40	78.37	28.76	71.45	41.4	164
CAVGss	0.05	First	IR liq	26	5.60	2.00	5.35	2.09	9.22
CAVGss	0.1	First	IR liq	37	10.86	5.13	9.60	4.51	31.6
CAVGss	0.2	First	IR liq	40	20.16	9.09	17.35	8.57	50
CL_F	0.05	First	IR liq	26	13.28	16.26	6.88	2.9	75.8
CL_F	0.1	First	IR liq	37	37.96	24.24	38.40	3.73	82.1
CL_F	0.2	First	IR liq	40	39.95	26.31	37.95	6.65	94.3
CMAX	0.05	First	IR liq	26	3.80	1.01	3.88	2.06	6.27
CMAX	0.1	First	IR liq	37	7.73	3.22	6.93	3.61	16.7
CMAX	0.2	First	IR liq	40	15.43	6.06	13.10	7.31	29.5
CMAXss	0.05	First	IR liq	26	6.14	1.99	5.91	2.66	9.56
CMAXss	0.1	First	IR liq	37	12.13	5.30	10.90	5.2	32.9
CMAXss	0.2	First	IR liq	40	23.16	9.15	20.40	12.1	52.8
CMIN	0.05	First	IR liq	26	2.38	0.79	2.36	0.884	3.59
CMIN	0.1	First	IR liq	37	4.53	2.09	3.98	1.97	12.5
CMIN	0.2	First	IR liq	40	8.15	3.68	7.54	2.46	20.6
CMINss	0.05	First	IR liq	26	3.93	1.70	3.70	1.06	7.25
CMINss	0.1	First	IR liq	37	7.46	4.27	6.91	2.29	24.6
CMINss	0.2	First	IR liq	40	13.29	8.13	10.80	2.58	38.1
KEL	0.05	First	IR liq	26	0.18	0.05	0.17	0.106	0.312
KEL	0.1	First	IR liq	37	0.19	0.08	0.16	0.1	0.455
KEL	0.2	First	IR liq	40	0.22	0.12	0.19	0.0819	0.555
THALF	0.05	First	IR liq	26	4.21	1.16	4.15	2.22	6.56
THALF	0.1	First	IR liq	37	4.17	1.38	4.40	1.52	6.92
THALF	0.2	First	IR liq	40	3.93	1.86	3.75	1.25	8.46
TMAX	0.05	First	IR liq	26	2.19	0.24	2.25	1.75	2.5
TMAX	0.1	First	IR liq	37	2.15	0.29	2.25	1.5	2.5
TMAX	0.2	First	IR liq	40	2.08	0.39	2.13	1.25	2.75
V_F	0.05	First	IR liq	26	78.68	119.63	39.95	19.9	628

V_F	0.1	First	IR liq	37	240.63	187.32	204.00	15	570
V_F	0.2	First	IR liq	40	239.91	213.89	148.50	26.1	783
AR	0.05	Last	IR liq	23	1.59	0.26	1.55	1.18	2.13
AR	0.1	Last	IR liq	36	1.60	0.31	1.64	1.07	2.21
AR	0.2	Last	IR liq	35	1.59	0.41	1.55	1.04	2.58
AUCss	0.05	Last	IR liq	23	33.99	12.11	32.20	12.5	55.3
AUCss	0.1	Last	IR liq	36	65.73	31.34	57.75	27	190
AUCss	0 2	Last	IR liq	35	125.63	56.50	114.00	51.4	300
AUCtau	0.05	Last	IR liq	23	20.95	5.89	20.50	10.4	32.8
AUCtau	0.1	Last	IR liq	36	40.91	16.55	38.00	19.1	96.1
AUCtau	0.2	Last	IR liq	35	79.95	30.24	71.80	41.4	164
CAVGss	0.05	Last	IR liq	23	5.67	2.02	5.36	2.09	9.22
CAVGss	0.1	Last	IR liq	36	10.95	5.22	9.63	4.51	31.6
CAVGss	0.2	Last	IR liq	35	20.94	9.41	19.00	8.57	50
CL_F	0.05	Last	IR liq	23	10.07	9.52	6.71	2.9	44.8
CL_F	0.1	Last	IR liq	36	39.19	24.77	39.60	3.73	82.1
CL_F	0.2	Last	IR liq	35	40.72	26.89	38.10	6.65	94.3
CMAX	0.05	Last	IR liq	23	3.87	1.04	3.92	2.06	6.27
CMAX	0.1	Last	IR liq	36	7.75	3.22	7.15	3.61	16.7
CMAX	0.2	Last	IR liq	35	15.65	6.38	12.90	7.31	29.5
CMAXss	0.05	Last	IR liq	23	6.23	2.01	5.98	2.66	9.56
CMAXss	0.1	Last	IR liq	36	12.22	5.36	11.10	5.2	32.9
CMAXss	0.2	Last	IR liq	35	23.90	9.52	21.30	12.1	52.8
CMIN	0.05	Last	IR liq	23	2.41	0.80	2.39	0.884	3.59
CMIN	0.1	Last	IR liq	36	4.54	2.12	3.99	1.97	12.5
CMIN	0.2	Last	IR liq	35	8.42	3.82	7.67	2.46	20.6
CMINss	0.05	Last	IR liq	23	3.97	1.72	3.78	1.06	7.25
CMINss	0.1	Last	IR liq	36	7.54	4.37	6.93	2.29	24.6
CMINss	0.2	Last	IR liq	35	13.99	8.40	11.80	2.58	38.1
KEL	0.05	Last	IR liq	23	0.18	0.06	0.17	0.106	0.312
KEL	0.1	Last	IR liq	36	0.19	0.09	0.16	0.1	0.455
KEL	0.2	Last	IR liq	35	0.22	0.12	0.17	0.0819	0.555
THALF	0.05	Last	IR liq	23	4.19	1.17	4.03	2.22	6.56
THALF	0.1	Last	IR liq	36	4.20	1.44	4.41	1.52	6.92
THALF	0.2	Last	IR liq	35	4.08	1.90	4.01	1.25	8.46
TMAX	0.05	Last	IR liq	23	2.18	0.24	2.25	1.75	2.5
TMAX	0.1	Last	IR liq	36	2.15	0.30	2.25	1.5	2.5
TMAX	0.2	Last	IR liq	35	2.11	0.39	2.25	1.25	2.75
V_F	0.05	Last	IR liq	23	53.77	39.42	39.00	19.9	152
V_F	0.1	Last	IR liq	36	252.87	198.77	235.00	15	628
V_F	0.2	Last	IR liq	35	250.56	219.70	156.00	26.1	783

Table: Descriptive Statistics of oxycodone in pediatric patients receiving OxyContin ORF (by Dose). AR = accumulation ratio.

Variable	Dose First/ Last	FORM	DOSE (mg)	N	Mean	SD	Median	Min	Max
AR	First	ORF	10	47	1.18	0.21	1.14	1	2.41
AUCss	First	ORF	10	47	152.81	85.84	138	44.4	514
AUCtau	First	ORF	10	47	126.79	55.26	106	44.3	302
CAVGss	First	ORF	10	47	12.74	7.15	11.5	3.7	42.8
CL_F	First	ORF	10	47	80.62	36.63	72.6	19.4	225
CMAX	First	ORF	10	47	13.18	6.02	11.7	5.17	32.3
CMAXss	First	ORF	10	47	15.53	7.60	12.6	6.62	39.2
CMIN	First	ORF	10	47	5.33	3.07	5.08	0.128	17.2
CMINss	First	ORF	10	47	6.71	5.79	5.94	0.128	36.3
KEL	First	ORF	10	47	0.19	0.08	0.177	0.0447	0.576
THALF	First	ORF	10	47	4.26	2.10	3.91	1.2	15.5
TMAX	First	ORF	10	47	3.98	1.07	3.75	1.75	7.75
V_F	First	ORF	10	47	447.79	174.36	421	164	960
AR	Last	ORF	10	48	1.16	0.13	1.14	1	1.67
AUCss	Last	ORF	10	48	148.53	68.27	131	44.4	413
AUCtau	Last	ORF	10	48	127.02	53.71	106	44.3	302
CAVGss	Last	ORF	10	48	12.38	5.69	10.95	3.7	34.4
CL_F	Last	ORF	10	48	79.93	35.18	76.2	24.2	225
CMAX	Last	ORF	10	48	13.40	5.90	11.8	5.21	32.3
CMAXss	Last	ORF	10	48	15.42	6.68	12.7	7.05	36.6
CMIN	Last	ORF	10	48	5.19	2.84	4.66	0.128	17.2
CMINss	Last	ORF	10	48	6.23	3.99	5.53	0.128	24.6
KEL	Last	ORF	10	48	0.19	0.08	0.1765	0.0759	0.576
THALF	Last	ORF	10	48	4.08	1.49	3.92	1.2	9.14
TMAX	Last	ORF	10	48	3.89	1.07	3.75	1.75	8.25
V_F	Last	ORF	10	48	438.17	172.07	400.5	164	1030
AR	First	ORF	15	11	1.17	0.09	1.14	1.09	1.38
AUCss	First	ORF	15	11	300.00	200.78	230	131	826
AUCtau	First	ORF	15	11	260.91	187.55	203	120	759
CAVGss	First	ORF	15	11	25.00	16.75	19.2	10.9	68.9
CL_F	First	ORF	15	11	65.06	28.78	65.1	18.2	115
CMAX	First	ORF	15	11	27.22	23.17	20.1	11.2	90.9
CMAXss	First	ORF	15	11	31.15	24.84	23.1	13.5	98.8
CMIN	First	ORF	15	11	10.68	5.65	8.61	4.64	24
CMINss	First	ORF	15	11	12.41	6.12	10.5	5.06	26.1
KEL	First	ORF	15	11	0.17	0.03	0.173	0.108	0.21
THALF	First	ORF	15	11	4.27	0.96	4	3.31	6.44
TMAX	First	ORF	15	11	4.02	0.55	4	3	5.25
V_F	First	ORF	15	11	404.69	193.16	401	86.6	757
AR	Last	ORF	15	13	1.26	0.36	1.14	1.09	2.41
AUCss	Last	ORF	15	13	324.54	232.22	210	131	826
AUCtau	Last	ORF	15	13	257.92	177.96	192	120	759
CAVGss	Last	ORF	15	13	27.05	19.38	17.5	10.9	68.9
CL_F	Last	ORF	15	13	64.28	30.47	71.4	18.2	115

CMAX	Last	ORF	15	13	26.70	21.88	20.2	11.2	90.9
CMAXss	Last	ORF	15	13	32.62	24.76	22	13.5	98.8
CMIN	Last	ORF	15	13	10.95	6.35	8.01	4.64	24
CMINss	Last	ORF	15	13	14.75	13.20	9.87	5.06	54.4
KEL	Last	ORF	15	13	0.16	0.05	0.173	0.0447	0.21
THALF	Last	ORF	15	13	5.01	3.28	4	3.31	15.5
TMAX	Last	ORF	15	13	4.19	1.20	3.75	3	7.75
V_F	Last	ORF	15	13	416.89	201.00	435	86.6	757
AR	First	ORF	20	25	1.13	0.07	1.12	1	1.27
AUCss	First	ORF	20	25	297.54	121.71	278	79.5	583
AUCtau	First	ORF	20	25	262.57	105.04	256	79.2	525
CAVGss	First	ORF	20	25	24.80	10.14	23.2	6.63	48.6
CL_F	First	ORF	20	25	81.52	44.82	72	34.3	251
CMAX	First	ORF	20	25	28.29	11.73	28	13.3	59.3
CMAXss	First	ORF	20	25	31.84	12.95	29.6	14.4	65.8
CMIN	First	ORF	20	25	10.18	4.80	9.23	0.614	21.2
CMINss	First	ORF	20	25	11.68	5.87	10.6	0.617	26.5
KEL	First	ORF	20	25	0.20	0.06	0.189	0.129	0.445
THALF	First	ORF	20	25	3.75	0.91	3.66	1.56	5.39
TMAX	First	ORF	20	25	3.66	0.70	3.75	2	5.25
V_F	First	ORF	20	25	412.60	156.67	364	178	718
AR	Last	ORF	20	18	1.18	0.13	1.15	1	1.57
AUCss	Last	ORF	20	18	282.47	127.31	262.5	79.5	516
AUCtau	Last	ORF	20	18	236.96	99.24	209	79.2	438
CAVGss	Last	ORF	20	18	23.54	10.61	21.85	6.63	43
CL_F	Last	ORF	20	18	88.55	50.59	76.3	38.8	251
CMAX	Last	ORF	20	18	24.32	10.62	20.5	13.3	46.3
CMAXss	Last	ORF	20	18	28.54	12.12	24.85	14.4	53.1
CMIN	Last	ORF	20	18	10.18	5.37	10.08	0.614	21.2
CMINss	Last	ORF	20	18	12.45	7.60	12.25	0.617	30.9
KEL	Last	ORF	20	18	0.19	0.08	0.1695	0.0844	0.445
THALF	Last	ORF	20	18	4.25	1.49	4.09	1.56	8.21
TMAX	Last	ORF	20	18	3.97	0.95	4	2	6
V_F	Last	ORF	20	18	481.78	154.62	518.5	213	718
AR	First	ORF	30	10	1.23	0.22	1.135	1.04	1.67
AUCss	First	ORF	30	10	431.90	153.53	383.5	295	745
AUCtau	First	ORF	30	10	352.70	111.54	308.5	230	566
CAVGss	First	ORF	30	10	35.98	12.82	31.95	24.6	62.1
CL_F	First	ORF	30	10	76.41	22.43	78.3	40.3	102
CMAX	First	ORF	30	10	36.04	13.55	35.05	15.6	63.1
CMAXss	First	ORF	30	10	43.00	14.40	41.05	26.1	70.6
CMIN	First	ORF	30	10	15.16	6.67	14.3	5.28	29.5
CMINss	First	ORF	30	10	19.40	11.25	16.1	5.47	46.4
KEL	First	ORF	30	10	0.17	0.07	0.178	0.0759	0.281
THALF	First	ORF	30	10	4.76	2.27	3.9	2.47	9.14
TMAX	First	ORF	30	10	4.33	1.65	4	2.5	8.25
V_F	First	ORF	30	10	498.50	228.57	460	253	1030
AR	Last	ORF	30	6	1.10	0.07	1.07	1.04	1.24

AUCss	Last	ORF	30	6	456.17	134.59	476.5	296	633
AUCtau	Last	ORF	30	6	414.83	118.24	418	281	566
CAVGss	Last	ORF	30	6	38.00	11.26	39.7	24.6	52.8
CL_F	Last	ORF	30	6	71.28	23.06	62.95	47.4	101
CMAX	Last	ORF	30	6	47.75	13.76	46.25	30.3	63.7
CMAXss	Last	ORF	30	6	52.23	14.61	49.35	32.6	70.6
CMIN	Last	ORF	30	6	14.10	5.73	14.65	5.28	20.7
CMINss	Last	ORF	30	6	15.73	7.07	15.5	5.47	23.9
KEL	Last	ORF	30	6	0.22	0.05	0.229	0.135	0.281
THALF	Last	ORF	30	6	3.35	0.96	3.03	2.47	5.12
TMAX	Last	ORF	30	6	3.33	0.58	3.375	2.5	4.25
V_F	Last	ORF	30	6	334.00	103.10	308.5	228	455
AR	First	ORF	40	4	1.27	0.12	1.27	1.14	1.4
AUCss	First	ORF	40	4	682.75	266.18	589.5	482	1070
AUCtau	First	ORF	40	4	533.00	172.68	483	400	766
CAVGss	First	ORF	40	4	56.90	22.27	49.1	40.1	89.3
CL_F	First	ORF	40	4	64.23	19.80	68.3	37.3	83
CMAX	First	ORF	40	4	50.38	14.41	48.65	37.4	66.8
CMAXss	First	ORF	40	4	64.15	21.19	58	47.2	93.4
CMIN	First	ORF	40	4	26.53	11.34	22.15	18.5	43.3
CMINss	First	ORF	40	4	34.33	17.64	27.3	22.2	60.5
KEL	First	ORF	40	4	0.14	0.03	0.1315	0.105	0.176
THALF	First	ORF	40	4	5.32	1.23	5.36	3.93	6.62
TMAX	First	ORF	40	4	4.31	0.55	4.25	3.75	5
V_F	First	ORF	40	4	479.50	146.48	459.5	355	644
AR	Last	ORF	40	3	1.21	0.10	1.2	1.12	1.31
AUCss	Last	ORF	40	3	601.00	148.92	553	482	768
AUCtau	Last	ORF	40	3	494.33	93.51	496	400	587
CAVGss	Last	ORF	40	3	50.07	12.43	46.1	40.1	64
CL_F	Last	ORF	40	3	69.13	15.69	72.3	52.1	83
CMAX	Last	ORF	40	3	49.03	8.58	52.9	39.2	55
CMAXss	Last	ORF	40	3	59.23	11.11	61.4	47.2	69.1
CMIN	Last	ORF	40	3	22.60	7.36	18.5	18.2	31.1
CMINss	Last	ORF	40	3	27.73	11.27	22.2	20.3	40.7
KEL	Last	ORF	40	3	0.15	0.03	0.148	0.121	0.189
THALF	Last	ORF	40	3	4.70	1.04	4.69	3.67	5.75
TMAX	Last	ORF	40	3	4.08	0.63	4	3.5	4.75
V_F	Last	ORF	40	3	459.00	92.50	432	383	562
AR	Last	ORF	50	1	1.14	0	1.14	1.14	1.14
AUCss	Last	ORF	50	1	798	0	798	798	798
AUCtau	Last	ORF	50	1	702	0	702	702	702
CAVGss	Last	ORF	50	1	66.5	0	66.5	66.5	66.5
CL_F	Last	ORF	50	1	62.6	0	62.6	62.6	62.6
CMAX	Last	ORF	50	1	72.6	0	72.6	72.6	72.6
CMAXss	Last	ORF	50	1	82.6	0	82.6	82.6	82.6
CMIN	Last	ORF	50	1	28.8	0	28.8	28.8	28.8
CMINss	Last	ORF	50	1	32.8	0	32.8	32.8	32.8
KEL	Last	ORF	50	1	0.176	0	0.176	0.176	0.176

THALF	Last	ORF	50	1	3.93	0	3.93	3.93	3.93
TMAX	Last	ORF	50	1	3.75	0	3.75	3.75	3.75
V_F	Last	ORF	50	1	355	0	355	355	355
AR	First	ORF	60	1	1.15	0	1.15	1.15	1.15
AUCss	First	ORF	60	1	702	0	702	702	702
AUCtau	First	ORF	60	1	608	0	608	608	608
CAVGss	First	ORF	60	1	58.5	0	58.5	58.5	58.5
CL_F	First	ORF	60	1	85.5	0	85.5	85.5	85.5
CMAX	First	ORF	60	1	57.9	0	57.9	57.9	57.9
CMAXss	First	ORF	60	1	66.8	0	66.8	66.8	66.8
CMIN	First	ORF	60	1	27.7	0	27.7	27.7	27.7
CMINss	First	ORF	60	1	32	0	32	32	32
KEL	First	ORF	60	1	0.167	0	0.167	0.167	0.167
THALF	First	ORF	60	1	4.14	0	4.14	4.14	4.14
TMAX	First	ORF	60	1	4.25	0	4.25	4.25	4.25
V_F	First	ORF	60	1	511	0	511	511	511
AR	First	ORF	80	1	1.08	0	1.08	1.08	1.08
AUCss	First	ORF	80	1	1190	0	1190	1190	1190
AUCtau	First	ORF	80	1	1100	0	1100	1100	1100
CAVGss	First	ORF	80	1	99.2	0	99.2	99.2	99.2
CL_F	First	ORF	80	1	67.2	0	67.2	67.2	67.2
CMAX	First	ORF	80	1	124	0	124	124	124
CMAXss	First	ORF	80	1	135	0	135	135	135
CMIN	First	ORF	80	1	37.3	0	37.3	37.3	37.3
CMINss	First	ORF	80	1	40.5	0	40.5	40.5	40.5
KEL	First	ORF	80	1	0.213	0	0.213	0.213	0.213
THALF	First	ORF	80	1	3.26	0	3.26	3.26	3.26
TMAX	First	ORF	80	1	3.25	0	3.25	3.25	3.25
V_F	First	ORF	80	1	316	0	316	316	316
AR	Last	ORF	80	1	1.08	0	1.08	1.08	1.08
AUCss	Last	ORF	80	1	1190	0	1190	1190	1190
AUCtau	Last	ORF	80	1	1100	0	1100	1100	1100
CAVGss	Last	ORF	80	1	99.2	0	99.2	99.2	99.2
CL_F	Last	ORF	80	1	67.2	0	67.2	67.2	67.2
CMAX	Last	ORF	80	1	124	0	124	124	124
CMAXss	Last	ORF	80	1	135	0	135	135	135
CMIN	Last	ORF	80	1	37.3	0	37.3	37.3	37.3
CMINss	Last	ORF	80	1	40.5	0	40.5	40.5	40.5
KEL	Last	ORF	80	1	0.213	0	0.213	0.213	0.213
THALF	Last	ORF	80	1	3.26	0	3.26	3.26	3.26
TMAX	Last	ORF	80	1	3.25	0	3.25	3.25	3.25
V_F	Last	ORF	80	1	316	0	316	316	316

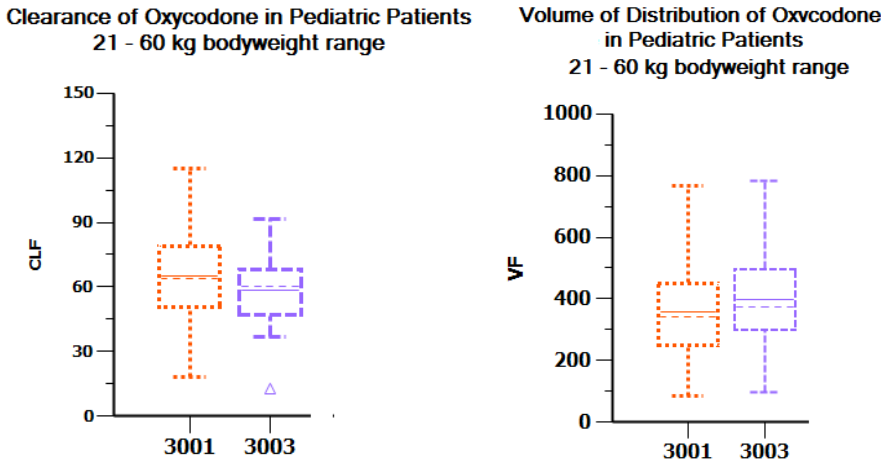
In addressing the OSI comment (See Bioanalytical Section 3.2.1) about analyte stability and possible impact on parameter estimation, we looked at clearance and volume of distribution of oxycodone from different studies. The general observation is that an age or bodyweight dependent changes in clearance are obvious.

Table: Summary statistics of clearance and volume of distribution of oxycodone based on bodyweight groups from different studies.

Weight Group	Study Number	Variable	N	Mean	SD	Median	Variable	N	Mean	SD	Median
<10 kg	OXP1005	CL/F	43	8.4	4.8	7.2	V/F	43	45.8	26.4	37.6
11-20 kg	OXP3003	CL/F	7	37.8	13.0	38.4	V/F	7	152.0	77.6	140.6
11-20 kg	OXP1005	CL/F	15	29.2	9.3	29.7	V/F	15	112.4	39.0	103.8
21-60 kg	OC96-0602	CL/F	11	68.3	25.0	67.8	V/F	11	325.3	104.2	334.0
21-60 kg	OTR1005	CL/F	10	85.6	17.0	82.4	V/F	10	442.9	75.1	471.7
21-60 kg	OTR1020	CL/F	20	74.1	30.3	71.0	V/F	20	484.9	210.0	433.4
21-60 kg	OTR3001	CL/F	56	65.4	25.4	63.8	V/F	56	359.1	138.0	340.4
21-60 kg	OXP3003	CL/F	31	58.7	16.4	60.3	V/F	31	398.2	156.9	371.9
21-60 kg	OXP3004	CL/F	8	74.6	31.1	67.6	V/F	8	406.8	133.5	395.9
>60 kg	OTR1005	CL/F	81	99.8	25.1	94.3	V/F	81	585.4	120.0	584.1
>60 kg	OTR1020	CL/F	10	92.1	42.7	96.3	V/F	10	616.9	148.5	596.9
>60 kg	OTR1502	CL/F	23	104.7	24.2	98.3	V/F	23	726.7	155.9	684.4
>60 kg	OTR3001	CL/F	43	94.4	41.3	86.0	V/F	43	544.9	161.9	518.8
>60 kg	OXP3003	CL/F	8	65.8	20.3	64.8	V/F	8	480.5	138.3	510.2

In addition, clearance and volume of distribution from two different pediatric patient PK studies with patients in the age group of 6 – 12 yrs. (OTR3001 and OXP3003) were also compared to ensure consistency in parameter estimates. Majority of the observed bodyweights for pediatric patients in the 6 -12 yrs. old group ranged from 21 – 60 kg in these studies.

Figure: Box-Plots indicating clearance (left) and volume of distribution (right) in pediatric patients from Study OXP3003 (IR) and Study OTR3001 (ORF).



3.2.3 Synopsis of Pediatric Patient Study OC96-0602

2. SYNOPSIS

Name of Company: Purdue Pharma L.P.	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: OxyContin® (oxycodone HCl controlled-release) Tablets	Referring to Part IV of the Dossier	
Name of Active Ingredient: Oxycodone HCl	Volume: Page:	

Title of the Study: An Open-Label, Randomized, Crossover Comparison of Plasma Oxycodone Concentrations in Children After the Administration of Single Doses of Controlled-Release Oxycodone (OxyContin®) and Immediate-Release Oxycodone

Investigator: Jeffrey L. Blumer, PhD, MD

Publication (Reference): None

Study Dates:	**Study Status:**	**Phase of Development:**
11-Apr-1997 to 16-Nov-1998	Completed	Phase 1

Objectives: To compare the relative bioavailabilities following single doses of immediate-release (IR) oxycodone and controlled-release (CR) oxycodone (OxyContin®) in children.

Methodology: A single-dose, open-label, randomized, 2-period crossover pharmacokinetic (PK) study in children of both sexes aged 5 to 12 years.

Number of Subjects: Planned: 24 subjects (to complete 20). Enrolled: 13 subjects (results from the first 11 completed subjects provided sufficient study data, and so no additional subjects were enrolled). Completed: 11 subjects. All 13 subjects had valid PK data from at least 1 treatment and were considered evaluable for pharmacokinetic analysis. However, 2 subjects discontinued after completing the first period (subject 4 received only OxyContin® 10 mg, and subject 5 received only IR oxycodone 5 mg). All 13 subjects were included in the safety analysis.

Subject Demographics: Seven males and 6 females; 5 white and 8 black; all pediatric subjects, with a mean age of 9.6 (range, 6–12) years.

Diagnosis and Criteria for Inclusion: Children of both sexes aged 5 to 12 years who were hospitalized and receiving opiates other than oxycodone, who were expected to continue to need opiates for at least 4 days, and who met the inclusion/exclusion criteria specified in the protocol.

Drugs Supplied:

Product	Route	Dosage Form	Unit Strength	Lot Number
OxyContin®	Oral	Tablet	10 mg	C25
IR oxycodone	Oral	Tablet	5 mg	962438

Treatment Comparisons:

Test Treatment	Reference Treatment
OxyContin® 10 mg (CR)	IR oxycodone 5 mg (IR)

Treatment Schedule: One dose of each oxycodone formulation, separated by a washout period of at least 48 hours. Blood samples were taken for 12 hours after IR administration and for up to 36 hours after the CR (OxyContin®) administration.

Criteria for Evaluation:

Pharmacokinetic Metrics: Plasma concentrations of oxycodone, oxymorphone, and noroxycodone and the following metrics: area under the curve to the last quantifiable plasma concentration (AUC_t), area under the curve from zero to infinity (AUC_∞), maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), apparent terminal phase half-life ($t_{½}$[elim]), and mean residence time (MRT). AUC_∞ is an index of total exposure and C_{max} is an index of peak exposure to the study drug or metabolite.

Safety: Reports of adverse events, clinical laboratory tests, vital signs, and physical examinations.

Bioanalytical Method: Plasma concentrations of oxycodone, oxymorphone, and noroxycodone were quantified by gas chromatography using negative chemical ionization mass spectrometry.

Statistical Methods: Log-transformed AUC_t, AUC_∞, and C_{max} values for oxycodone for test (OxyContin® 10 mg) and reference (IR oxycodone 5 mg) treatments were analyzed using an analysis of variance (ANOVA) model with terms for sequence, subject (sequence), period, and treatment. Relative bioavailability was assessed by comparing primary metrics (AUCt, AUC∞, and C_{max} [test vs reference treatment]) using the previously mentioned ANOVA model for a 2-way crossover design. Confidence intervals (90%) were estimated around ratios (test/reference) of geometric least squares means derived from logarithmic-transformed values of AUC_t and AUC_∞. Relative bioavailability was summarized by the percent ratios of the means for AUC_t and AUC_∞ with respect to the reference treatment, and the lower and upper limits of the 90% confidence interval were examined. In addition, summary statistics for AUC_t, AUC_∞, and C_{max} were presented by treatment for the parent compound and its metabolites. Secondary metrics (t_{max}, $t_{½}$, MRT) were presented as mean and standard deviation (SD), CV, minimum and maximum. Per protocol, after the completion of the first 13 subjects (with 11 completing both treatments), pharmacokinetic analysis was performed, which confirmed that the ratio of geometric mean AUC_∞ was within the CI of 70% to 143% (or as specified in the protocol as a difference of ±30%). As a result, the decision was made to stop study enrollment. Vital signs, laboratory tests, and physical examination results were tabulated, with abnormal values listed. Descriptive shift tables for each laboratory parameter and summary tables of adverse events by body system were prepared.

Results:

Pharmacokinetic: OxyContin® (CR oxycodone) produced relatively rapid increases to initial early peak plasma concentrations for oxycodone and its metabolites, followed by measurable concentrations that were sustained beyond 24 hours. IR oxycodone produced similar early peak plasma concentrations for oxycodone and metabolites, but plasma concentrations declined more rapidly. Plasma oxymorphone concentrations were negligible. The 90% CI of the geometric mean ratio of the test treatment (OxyContin®) to the reference treatment (IR oxycodone) in terms of total exposure (AUC_∞) to the study drug was within 80% to 125%. The dose-adjusted peak exposure (C_{max}) of OxyContin® was approximately one half that of IR oxycodone. Similarly, mean values of $t_{½}$ and MRT for parent oxycodone following IR oxycodone administration were approximately half, while t_{max} was two thirds those following OxyContin® administration. See Tables 2A and 2B.

Safety: Overall, 9 (69%) out of 13 subjects experienced 1 or more adverse events during the study. Over the course of the study, 5 (42%) of 12 subjects experienced adverse events during or after receiving IR oxycodone, while 7 (58%) of 12 subjects experienced adverse events during or after receiving OxyContin® (Table 2C). The most common adverse event was fever (IR oxycodone, 25%; OxyContin®, 33%), which was expected in a postoperative population and was not regarded as drug-related (Table 2D). All other adverse events occurred in 1 or 2 subjects each. Adverse events judged by the investigator to be drug-related (seen in only 4 subjects when receiving OxyContin®) were pruritus, nausea, and vomiting. There was no apparent difference between IR oxycodone and OxyContin® in the incidence or type of adverse events reported in this 2-way crossover study. No deaths or other serious adverse events occurred during the study. One subject (subject 4, oxycodone) discontinued prematurely due to an adverse event (moderate pruritus). One subject (subject 5, IR oxycodone) discontinued prematurely due to inability to obtain IV access. No safety concerns were raised from the results of laboratory tests, vital sign measurements, or physical examinations. In conclusion, no unexpected safety concerns for oxycodone, as either the IR or the CR formulation, were suggested by the present results.

Conclusions: For the parent compound (oxycodone), the 90% confidence interval around the dose-adjusted geometric mean ratio of the test treatment (OxyContin®) to the reference treatment (IR oxycodone) in terms of total exposure (AUC_∞) to the study drug was within 80% to 125%. Due to differences in the dosage forms, for oxycodone, the dose-adjusted peak exposure (C_{max}) of OxyContin® was approximately one half that of IR oxycodone. Mean values of t_{max}, $t_{½}$, and MRT (all not dose-adjusted) for parent oxycodone following IR oxycodone administration were approximately half those following OxyContin® administration. These PK results in pediatric subjects following administration of OxyContin® and IR oxycodone are consistent with the characteristics of CR and an IR dosage forms, respectively. The PK profiles of noroxycodone and oxymorphone were similar to that of the parent compound. Noroxycodone levels were approximately one half that of the parent compound, and oxymorphone levels were negligible. As noroxycodone possesses 1/100th of the analgesic potency of oxycodone, its contribution to analgesia is not clinically meaningful. Oxymorphone, with 10 times the potency of oxycodone, contributes 10% to 15% of the analgesia of oxycodone. No unexpected safety concerns for oxycodone in pediatric subjects aged 6 to 12 years, administered as either the IR or the CR formulation, were suggested by the present results.

Date of the Report: 16-May-2001

Summary of Oxycodone Pharmacokinetic Metrics (N = 13 [a]), Not Dose-Adjusted

	Arithmetic Mean (SD)	
PK Metric	**IR Oxycodone** (5 mg)	**OxyContin®** (10mg)
AUCt (ng·h/mL)	83.2 (43.0)	201.0 (143.0)
AUC_∞ (ng·h/mL)	81.3 (39.1)[b]	174.6 (91.1)[c]
C_{max} (ng/mL)	20.2 (8.3)	22.0 (13.0)
t_{max} (h)	2.1 (0.9)	3.3 (1.7)
$t_{½}$ (h)	2.6 (1.0)[c]	5.2 (1.8)[c]
MRT (h)	4.2 (1.2)	8.7 (1.9)

[a]Thirteen subjects enrolled, with 2 subjects discontinuing after completing the first period. Subject 4 received only OxyContin®, and subject 5 only received IR oxycodone.
[b]Ten subjects.
[c]Eleven subjects.

Also see box-plot in the summary of clinical pharmacology findings.

3.2.4 Synopsis of Study OXP3003 Pediatric age group 5 – 16 yrs.

<table>
<tr><td colspan="2">Name of Sponsor/Company:
Purdue Pharma L.P.</td><td>Protocol No.
OXP3003</td></tr>
<tr><td colspan="2">Name of Finished Product:
Oxy Pediatric Liquid 1 mg/mL</td><td>Name of Active Ingredient:
Oxycodone hydrochloride</td></tr>
<tr><td colspan="2">IND No.: 29,038</td><td></td></tr>
<tr><td colspan="3">Indication: Acute moderate to severe pain in children aged 5 to ≤ 16 years.</td></tr>
<tr><td colspan="3">Title of the Study: Multicenter, Double-blind, Randomized, Dose-ranging Study, in Pediatric Patients 5 to ≤ 16 Years of Age Receiving Morphine As Standard Supplemental Pain Medication, to Evaluate Pharmacokinetics, Efficacy and Safety of Oxy Pediatric Liquid (1 mg/mL) vs Placebo in the Treatment of Acute Moderate to Severe Pain</td></tr>
<tr><td colspan="3">Investigator(s), Site(s): This is a multicenter multinational trial at 30 sites. (US, Canada, EU [England, Finland, The Netherlands]). The list of investigators is provided in Appendix 16.1.4.</td></tr>
<tr><td colspan="3">Publication (Reference): None</td></tr>
<tr><td>Study period (Dates):
31-Jan-2003 (FPFV) to 03-Apr-2004 (LPLV)</td><td>Study Status:
Completed.
This study was terminated early on 31-Mar-2004 for administrative reasons other than safety or efficacy.</td><td>Phase of Development:
Phase 3</td></tr>
<tr><td colspan="3">Objectives:
Primary
• To characterize the pharmacokinetics of Oxy Pediatric Liquid 1 mg/mL, (using a population PK approach), after the first dose and after repeated dosing, in pediatric patients aged 5 to ≤ 16 years.
• To evaluate the safety of Oxy Pediatric Liquid 1 mg/mL in pediatric patients aged 5 to ≤ 16 years.
Secondary
• To characterize the efficacy of Oxy Pediatric Liquid 1mg/mL based on supplemental analgesic requirements and pain scores in pediatric patients aged 5 to ≤ 16 years.</td></tr>
<tr><td colspan="3">Methodology: This was a multicenter, double-blind, randomized, placebo-controlled, dose-ranging study to evaluate the pharmacokinetics (using the population PK approach), safety, and efficacy of Oxy Pediatric Liquid 1mg/mL when compared to placebo, after the first dose and after repeated dosing, in pediatric patients aged 5 to ≤ 16 years who received morphine as standard supplemental pain medication. Pediatric patients were stratified into 2 age groups (5 years to < 12 years and 12 years to ≤ 16 years) and randomized to receive either 0.1 mg/kg Oxy Pediatric Liquid, 0.2 mg/kg Oxy Pediatric Liquid, or placebo every 6 hours for 18 to 24 hours (4 to 5 doses) according to a randomization ratio of 3:3:2.

All patients were permitted to receive patient controlled analgesia (PCA) or oral morphine sulfate (if the intravenous route stopped functioning) as supplemental pain medication during double-blind treatment. If patients were unable to take morphine they were not eligible to participate in the study.
Note: wording of the previous paragraph was changed by Amendment 1 (13-Nov-2002) to include the whole double-blind treatment rather than the first 18 hours for PCA.</td></tr>
<tr><td colspan="3">Number of Patients:
Planned: At least 100 PK evaluable patients, with an approximately equal number of patients in each of the age groups
Enrolled: 74
Screen failures: 6
Randomized: 68
Discontinued early: 14
Completed: 54</td></tr>
</table>

Name of Sponsor/Company:	**Protocol No.**
Purdue Pharma L.P.	OXP3003
Name of Finished Product:	**Name of Active Ingredient**:
Oxy Pediatric Liquid 1 mg/mL.	Oxycodone hydrochloride

Indication and Main Criteria for Inclusion/Exclusion:

Male and female pediatric patients from 5 to ≤ 16 years old who were opioid naïve at study entry or preoperatively (for surgical patients) were included in the study. Patients had to be inpatients at the time of enrollment. Patients either had or were anticipated to have moderate to severe pain requiring opioid analgesics for at least 2 days. Patients with clinically significant hepatic or renal dysfunction were excluded from the study. *Note: the preceding paragraph deleted the requirement of PCA or nurse-administered analgesia with opioids for moderate to severe pain for ≥ 4hours in Amendment 2 (20-Nov-2002).*

Test Product, Dose, Mode of Administration, and Batch Number:

Test Treatment	**Dose**	**Dosage Form**	**Lot Number**
Oxy Pediatric Liquid 1 mg/kg	0.1 mg/kg q6h	Oral Solution	**CB-2002-11**
Oxy Pediatric Liquid 1 mg/kg	0.2 mg/kg q6h	Oral Solution	**CB-2002-11**

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

Placebo	N/A	Oral Solution	**CB-2002-10** **CB-2003-39**

Supplemental Analgesia:

Morphine	PCA	IV, oral	N/A
Acetaminophen	prn	Oral	N/A

Duration of Treatment: Up to 2 days.

Criteria for Evaluation:

Efficacy

Supplemental pain medication was recorded by exact clock time for each attempt, dose in milligrams, and route of administration on the case report form.

Note: wording of the previous sentence was changed by Amendment 1 (13-Nov-2002) to: All doses of PCA morphine were recorded by the total amount of morphine (mg) administered in a 1-hour period, number of doses in a 1-hour period, and route of administration. All other supplemental pain medications were recorded by the exact clock time for each dose, the dose in mg, and the route of administration on the case report form.

Pain intensity scores were obtained as follows: at baseline (before administration of study drug; after the first dose, at 0.5, 1, 2, and 3 hours postdose, immediately prior to and 1 hour after each subsequent dose, and at the end of the study. Additionally, pain intensity scores were recorded when nurse administered PCA was given. Scores were recorded on a numerical rating scale of 0 to 10.

Pharmacokinetics

A maximum of 8 blood samples, when feasible, of 1 mL each was collected over the entire study period. Blood samples for concentrations of oxycodone, oxycodone metabolites, and morphine were obtained from indwelling cannula or from a previously inserted central venous catheter or arterial catheter. If access was otherwise not available, finger stick or venipuncture could be used if acceptable to the patient/guardian. It was required that there be at least a 1-hour interval between each blood sample.

Safety

Safety was assessed using reports of adverse events (AEs), clinical laboratory tests, vital sign measurements, physical examinations, hemoglobin-oxygen saturation evaluations, and somnolence evaluations.

Name of Sponsor/Company:	**Protocol No.**
Purdue Pharma L.P.	OXP3003
Name of Finished Product:	**Name of Active Ingredient**:
Oxy Pediatric Liquid 1 mg/mL	Oxycodone hydrochloride

Bioanalytical Methods

Serum samples were prepared using solid phase extraction and the concentrations of oxycodone, oxycodone metabolites, and morphine were quantified by LC-MS/MS analysis. The instrument was run under positive electron spread and multiple-reaction mode (MRM).

Statistical Methods:

Demographic and Baseline Characteristics

Demographic and baseline variables included age, sex, race, ethnicity, height, weight, and tanner puberty stage. Demographic and baseline characteristics were summarized descriptively by treatment group, overall, and by age group.

Dosing and Extent of Exposure

A data listing of the study drug dosage administration was provided for each patient. Descriptive statistics were provided to summarize the number of doses and the length of exposure (in hours) in each treatment group, overall, and by age group.

Sample Size Rationale

In study OC96-0602, the observed total standard deviation of the log transformed oxycodone AUCt, after adjusting for both dose level and weight, was 0.45, or the approximate coefficient of variation (CV) was 45%. The similar number for C_{max}, after adjusting for weight, was 0.40 for an approximate CV of 40%. Thus the larger of these two CV's is approximately 45%. When estimating parameters using the population PK approach, it is reasonable to assume that the variability will be larger, eg, a CV of 75%. Assuming a total variability (CV) equal to 75%, it is estimated that the 95% confidence interval from 75 patients will have a length of 0.34 times the mean, or that the CI will be approximately Xbar +/- 0.17*Xbar.
Although the primary objective of the study was pharmacokinetics, a sample size evaluation based on safety was also presented (see Statistical Analysis Plan, Appendix 16.1.9).

Efficacy Analyses

Efficacy variables consisted of supplemental pain medication and pain scores.

Supplemental pain medication consisted of PCA morphine medication, non-PCA opioid supplemental pain medication, and acetaminophen usage. Total opioid medication was obtained by adding the PCA morphine supplemental medication usage to the non-PCA opioid supplemental pain medication usage (in IV morphine equivalence). Dose-response for these derived variables within each dose interval was evaluated using the Jonckheere-Terpstra test. Additionally, the number and percentage of patients who received at least 1 dose of acetaminophen supplemental pain medication was summarized by treatment group overall, by age group, and by dose interval. Approximate 95% confidence intervals (CIs) were obtained.

Pain score variables consisted of pain scores recorded at scheduled time points and prior to nurse administered PCA. Statistical analysis was performed for the average and the maximum pain score for each dose interval and the overall average of the 1 h and 6 h postdose pain scores. Non-increasing dose-response was evaluated using a Jonckheere-Terpstra test.

Exploratory efficacy analyses were performed to examine the effect of age group on the efficacy variables. These analyses consisted of descriptive summaries (N, mean, minimum, maximum, median and standard deviation).

Population PK Analyses

Population PK modeling approach was applied to the plasma oxycodone concentrations obtained during treatment. Methodology and results of the population PK analyses will be contained in a separate report.

Name of Sponsor/Company:	Protocol No.
Purdue Pharma L.P.	OXP3003
Name of Finished Product:	**Name of Active Ingredient**:
Oxy Pediatric Liquid 1 mg/mL	Oxycodone hydrochloride

Safety Analyses

Variables analyzed were adverse events, laboratory tests, vital signs, hemoglobin oxygen saturation, and somnolence.

Adverse Events: All adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 13.0) Coding Dictionary. Treatment-emergent adverse events (TEAEs) were summarized to examine overall incidence of TEAEs and the incidence of TEAEs by relationship to study drug and maximum severity.

Clinical Laboratory: Laboratory data were summarized using mean and mean changes from baseline and shifts from baseline using the LNH classification according to whether the value was below (L), within (N), or above (H) the laboratory reference range. Clinical laboratory results for each patient were evaluated to determine whether they were markedly abnormal.

Vital Signs: Descriptive statistics for vital sign parameters at each assessment time were summarized. Mean and mean changes from baseline to end of study were also summarized. Statistical analysis was performed for respiratory rate to test for nonincreasing or nondecreasing dose response.

Hemoglobin-Oxygen Saturation: Statistical analysis of SpO_2 was performed similar to what was done for the pain assessments. Nonincreasing dose response was assessed using a Jonckheere-Terpstra test. The number and percent of patients experiencing desaturation was summarized.

Somnolence: Statistical analysis was performed to assess nondecreasing dose response.

Analysis Populations

The enrolled population was defined as all patients who signed the informed consent form.
The safety population was defined as those patients who had received at least 1 dose of study drug and had at least 1 subsequent safety assessment
The full analysis population for pharmacokinetics (PK) was defined as those patients who received at least 1 dose of study drug, and had at least 1 quantifiable PK sample.
The full analysis population for efficacy was defined as those patients who received at least 1 dose of study drug, and had at least 1 subsequent efficacy evaluation (pain measurement or supplemental pain medication).

Results:

Disposition of Patients

Seventy-four patients were enrolled into the study. Of these, 6 patients were screening failures and 68 patients were randomized into the study. Three patients discontinued early, all without being dosed, leaving 65 patients in the safety and the full analysis for efficacy populations. Fifty-four patients completed the study; 11 patients (16.9%) discontinued, 2 (3.1%) due to adverse events, 2 (3.1%) due to administrative reasons, and 7 (10.8%) due to subject's choice.

Concomitant Medications

The most common opioid supplemental medications used by patients during the study were fentanyl (91%) and morphine products (95%).

Demographic and Baseline Characteristics

- Sixty-three percent of patients were female.
- Seventy-four percent of patients were white.
- The mean age of the patients was 11.4 years (range, 5 to 16 years).

Name of Sponsor/Company:	**Protocol No.**
Purdue Pharma L.P.	OXP3003
Name of Finished Product:	**Name of Active Ingredient**:
Oxy Pediatric Liquid 1 mg/mL	Oxycodone hydrochloride

Efficacy:

When examined across all dose intervals including the first, the following conclusions are drawn:

- Supplemental PCA morphine medication use was statistically significantly less in the active treatment groups compared to the placebo group.
- Total opioid supplemental medication use was less in the active treatment groups compared to the placebo groups, but this difference was not statistically significant. The overall pattern of usage for total opioid supplemental pain medication was similar to that of total supplemental PCA morphine.
- Patients who received active treatment used statistically significantly less supplemental acetaminophen than patients who received placebo.

Overall, pain scores were statistically significantly lower in the active treatment groups compared to the placebo group, and this difference was observed following single as well as multiple dosing.

Pharmacokinetics

Population PK results will be presented in a separate report.

Safety:

Dosing and Extent of Exposure

- The mean exposure to Oxy Pediatric Liquid was 18.6 hours overall.
- All patients in the safety population received at least 1 dose, while 91% of patients received at least 2 doses, 89% received at least 3 doses, 86% received at least 4 doses, and 38% received 5 doses.

Adverse Events

- The most common TEAEs in ≥ 5% of all patients were nausea, vomiting, pyrexia, headache, and pruritus.
- A total of 36/65 patients (55.4%) in the safety population had TEAEs, most of which (26) were mild in intensity, and there were 3 severe events.
- No patient died during the study. Four patients experienced 5 SAEs: pericardial effusion; cholangitis and bile duct stone; pneumonia; and pyrexia, and recovered from the events.
- Following administration of study drug, 1 patient discontinued study drug due to TEAEs (SAEs of cholangitis and bile duct stone). Narratives for serious adverse events and AEs leading to discontinuation are contained in section 14.3.3.

Incidence of Deaths, Serious Adverse Events and Other Significant Adverse Events by Dosage Group: Safety Population

Category	Placebo (n = 19) n (%)	0.1 mg/kg (n = 24) n (%)	0.2 mg/kg (n = 22) n (%)	Total (N = 65) n (%)
Deaths	0	0	0	0
Other Serious Adverse Events	1 (5.3)	1 (4.2)	2 (9.1)	4 (6.2)
AEs Leading to Treatment Discontinuation	1[a] (5.3)	1 (4.2)	0	2 (3.1)
AEs Leading to Treatment/Dose Reduction	0	1 (4.2)	0	1 (1.5)
AEs Leading to Dose Interruption	0	0	1 (4.5)	1 (1.5)

Cross-references: Table 14.3.2.1, 14.3.2.2, 14.3.2.3, 14.3.2.4, 14.3.2.5, 14.3.2.6, Appendix 16.2.7.1.
Note: Percentages are based on N. Multiple occurrences of the same adverse event in one individual are counted only once.
[a]The patient experienced a pretreatment-emergent AE (vomiting) before placebo administration.

Clinical Laboratory Evaluations

Clinical laboratory evaluations did not reveal any unanticipated safety findings.

Vital Signs and Other Observations Related to Safety

- There were no appreciable changes in blood pressure for the 0.1 and 0.2 mg/kg treatment groups from baseline to end of study. Two AEs were reported for increased blood pressure.
- Respiratory rates and hemoglobin-oxygen saturation values were similar across treatment groups throughout the dose intervals. No statistically significant dose response was observed. Eight patients experienced desaturation at some point during the study: 3 in the placebo group and 5 in the 0.2 mg/kg group.
- The mean somnolence scores for the 1 hour and 6 hour postdose evaluations overall were low (below 1) with no significant difference between dose groups. One patient had a somnolence score of 4.0.

Conclusions:

- The population PK results will be presented in a separate report.
- Overall it appears that patients in the active treatment groups had less pain based on less supplemental medication use and lower pain scores.
- Under the conditions of this study, there were no unexpected safety findings when Oxy Pediatric Liquid (1 mg/mL) was administered at 0.1 and 0.2 mg/kg doses to pediatric patients from 5 to ≤ 16 years of age with acute moderate to severe pain.

Date of the Report: 25-Apr-2011

3.2.5 Synopsis of Study OTR3001, Pediatric Study of OxyContin (ORF) in 6 – 16 yrs.

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

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).

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

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.

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:

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.

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.

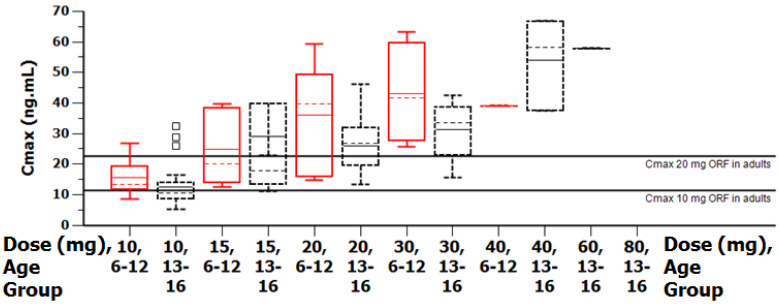
Overall, based on changes from baseline in pain right now scores, supplemental analgesic usage (opioid and nonopioid), and changes from baseline in FDI and PGIC ratings in these opioid-tolerant, pediatric patients:

- 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.

Figure: Note the higher Cmax for OxyContin (10 – 30 mg) strengths in pediatric patient's ages 6-12 yrs. Vs. 13 – 16 yrs.



The bodyweight impact on Cmax is described in the summary of clinical pharmacology findings above.

3.2.6 Synopsis of Pediatric Study in 6 – 16 yrs. age (OXP3004):

Name of Company Purdue Pharma L.P.	**Protocol Number** OXP3004	
Name of Finished Product OxyIR,® OxyContin®	**Name of Active Ingredient** Oxycodone Hydrochloride	
IND No. 29,038		
Title of the Study Multicenter, Open-Label, Multiple-Dose Study of the Conversion From Immediate Release Oxycodone (OxyIR®) to Controlled-Release Oxycodone (OxyContin®) to Evaluate Pharmacokinetics and to Characterize Safety and Efficacy in Pediatric Patients Aged 6 to ≤ 16 Years		
Investigators/Centers: Multicenter		
Publication (Reference) None		
Study Dates (FPFV) 31-Mar-2003 to (LPLV) 29-Feb-2004	**Study Status** Terminated early due to administrative reasons not related to efficacy or safety, with 10 patients enrolled.	**Phase of Development** Phase 3

Objectives

Conversion Phase

Primary

- To evaluate the safety of the approved adult conversion ratio (1:1) from OxyIR q6h to OxyContin q12h in pediatric patients aged 6 to ≤ 16 years.

Secondary

- To define the pharmacokinetics (using population PK method) of OxyIR (q6h) and OxyContin (q12h) in pediatric patients aged 6 to ≤ 16 years
- To evaluate the safety of OxyIR and OxyContin in pediatric patients aged 6 to ≤ 16 years
- To characterize efficacy based on supplemental analgesic requirements and pain scores in pediatric patients aged 6 to ≤ 16 years.

Long-Term Phase

- To monitor the safety of OxyContin q12h in pediatric patients aged 6 to ≤ 16 years.

Methodology

There were 3 phases in this study: pretreatment phase (which included the screening period and the baseline period), conversion phase, and the long-term phase (Amendment 3, 20-Mar-2003).

The conversion phase consisted of open-label, multiple-dose treatment that continued up to 3 days. Patients transitioned from their current opioid therapy to oral OxyIR capsules q6h. The conversion from OxyIR to OxyContin was the recommended adult conversion ratio of 1:1 provided in the approved OxyContin tablets package insert.

All patients were allowed to receive PCA morphine, IV or oral morphine as needed. NSAIDs and acetaminophen were also allowed as supplemental pain medication.

The long-term phase consisted of up to 3 months of treatment with OxyContin for patients who completed the conversion phase. Patients who required treatment with OxyContin for more than 3 months were evaluated on a case-by-case basis (Amendment 3, 20-Mar-2003).

Patients may have continued to receive the same dose of OxyContin that they received in the conversion phase or the investigator may have changed the dose of OxyContin based on their assessment of the patient.

Name of Company Purdue Pharma L.P.	Protocol Number OXP3004
Name of Finished Product OxyIR,® OxyContin®	Name of Active Ingredient Oxycodone Hydrochloride

Number of Patients

Conversion phase

Planned: Approximately 100 patients, with approximately 40 patients in the 6 to < 12 year old age group and approximately 60 patients in the 12 to ≤ 16 year old age group

Enrolled: 10

Completed: 7.

Long-term phase

Planned: Approximately 100 patients (Amendment 3, 20-Mar-2003)

Enrolled: 7

Completed: 6.

Indication and Main Criteria for Inclusion/Exclusion The conversion phase included male and female pediatric inpatients aged 6 to ≤ 16 years who were currently receiving an opioid analgesic and had demonstrated that they could tolerate an opioid analgesic for moderate to severe pain associated with conditions such as cancer, other chronic conditions, or postoperative pain which was expected to be moderate to severe, persist for approximately 3 weeks or longer, and required treatment with an around-the-clock oral opioid analgesic for approximately 3 weeks or longer (Amendment 3, 20-Mar-2003).

Patients were excluded in the study's long-term phase if they had a history of sleep apnea, the use of opioids was contraindicated (Amendment 2, 20-Nov-2002), had known clinically significant renal or hepatic disease or dysfunction, or malabsorption syndromes.

Treatments:

United States				
Test Treatment	**Dose**	**Mode**	**Dosage Form**	**Lot Number**
Conversion phase				
OxyIR	5 mg	oral	Capsule	CB41, DH61
OxyContin	10 mg	oral	Tablet	DR61, EB3N1
Long-term phase				
OxyContin	10 mg	oral	Tablet	DR61, EB3N1

France				
Test Treatment	**Dose**	**Mode**	**Dosage Form**	**Lot Number**
Conversion phase				
OxyIR	5 mg	oral	Capsule	DH61
OxyContin	10 mg	oral	Tablet	MG51
Long-term phase				
OxyContin	10 mg	oral	Tablet	MG51

Reference Treatment, Dose, and Mode of Administration: N/A

Supplemental Analgesia	**Dose**	**Mode**	**Dosage Form**	**Lot Number**
Morphine	PCA	IV, Oral	IV, Tablet	N/A
Acetaminophen	prn	Oral	Tablet	N/A

Duration of Treatment: Conversion phase, 3 days. Long-term phase, up to 3 months.

Treatment Schedule

Conversion phase

Pediatric patients who were receiving around-the-clock morphine or other opioids were transitioned from their opioid therapy to oral open-label OxyIR capsules q6h using dosing guidelines and conversion ratios as outlined in the protocol (Appendix 16.1.1). The investigator chose the starting dose of OxyIR based on the opioid requirement of the patient (Amendment 1, 13-Nov-2002).

Name of Company Purdue Pharma L.P.	Protocol Number OXP3004
Name of Finished Product OxyIR,® OxyContin®	Name of Active Ingredient Oxycodone Hydrochloride

The dose of OxyIR was adjusted based on the patient's pain scores and on his/her requirement for supplemental pain medication or based on the investigator's assessment of the patient. No subsequent dose changes were permitted. If patients were able to tolerate OxyIR and had stable pain control, then after 18 to 24 hours (4 or 5 doses), patients were converted to OxyContin q12h for the next 36 hours (4 doses). The conversion from OxyIR to OxyContin was the 1:1 ratio recommended for adult patients. Patients who required less than 5 mg q6h of OxyIR were not converted to OxyContin.

Long-term phase.

Patients continued to receive the same dose of OxyContin that they were receiving at the end of the conversion phase or the dose could have been adjusted based on the investigator's assessment of the patient.

Criteria for Evaluation

Efficacy

During the conversion phase, efficacy of OxyIR and OxyContin was characterized based on the pain scores ("pain right now") measured using the Faces Pain Scale – Revised (FPS-R). The FPS-R consists of 6 facial expressions that reflected the patient's pain. The end points are 0 = no pain to 10 = very much pain (Administrative Change 2, 04-Nov-2002).

Efficacy was also characterized by the doses of supplemental analgesic administered in a 1-hour period, and route of administration.

There were no efficacy measurements during the long-term phase.

Pharmacokinetics

A maximum of 15 blood samples (when feasible) of 1 mL each were collected over the 3-day duration of the conversion phase. See protocol (Appendix 16.1.1) for description of PK measurements.

There were no pharmacokinetic measurements during the long-term phase.

Safety

During the conversion phase, safety was assessed using reports of adverse events, clinical laboratory results, vital sign measurements, physical examinations, hemoglobin-oxygen saturation scores, and somnolence scores.

During the long-term phase, safety was assessed using reports of adverse events, clinical laboratory results, vital sign measurements, and physical examinations.

Bioanalytical Methods

Concentrations of oxycodone and metabolites were quantified by LC-MS/MS. Sparse blood samples (1 mL each) were obtained in multiple time windows after the first dose, at steady state, and after the last dose to determine the concentration of plasma oxycodone and its metabolites.

Statistical Methods

The study was terminated early with 10 patients enrolled. As such, the planned statistical analyses stated in the protocol were not implemented. Summary tabulations for key efficacy variables and safety data are provided.

Demographic and Baseline Information

Demographic and baseline variables summarized for all patients in the safety population included age, sex, race, vital sign information, hemoglobin-oxygen saturation, somnolence scores, and pain scores.

Dosing and Extent of Exposure

A summary of dosing and extent of exposure is described in the Statistical Analysis Plan (Appendix 16.1.9).

Name of Company Purdue Pharma L.P.	Protocol Number OXP3004
Name of Finished Product OxyIR,® OxyContin®	Name of Active Ingredient Oxycodone Hydrochloride

Sample Size Rationale

The primary objective of the study was the safety of conversion from OxyIR to OxyContin; therefore, sample size rationale was based on safety. If an adverse event occurs in 3.0% of the population, there is a 95% chance that at least 1 such event will be observed in a sample size of 100. If an event occurs in 1.6% of the population, there is a 80% chance that at least 1 such event will be observed in a sample size of 100.

The study was terminated early for administrative reasons not related to safety and efficacy, with 10 patients enrolled.

Efficacy and Pharmacokinetic (PK) Analyses

Efficacy

Efficacy variables include supplemental pain medication usage and pain intensity scores. Data were summarized by treatment for all patients with available data in the conversion phase for the first 12 hours, overall excluding the first 12 hours, and overall including the first 12 hours.

Population PK Analyses

A population PK modeling approach was applied to the plasma oxycodone concentrations obtained during the course of treatment. Results of the PK analyses will be presented in a separate report.

Safety

Safety variables summarized were adverse events, clinical laboratory tests, vital signs, hemoglobin-oxygen saturation, and somnolence. Safety summaries were provided for the conversion phase and the long-term phase.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Coding Dictionary (version 13.0). Treatment-emergent adverse events (TEAEs) were summarized to examine overall incidence of TEAEs and the incidence of TEAEs by relationship to study drug and maximum severity.

Clinical laboratory data were summarized using mean and mean changes from baseline, and shifts from baseline using the LNH classification according to whether the value was below (L), within (N), or above (H) the laboratory reference range. Clinical laboratory results for each patient were evaluated to determine whether they were markedly abnormal using the toxicity grade scheme (Division of AIDS Toxicity Table for Grading Severity of Pediatric Adverse Events Dec, 2004).

Vital signs at each assessment time were summarized. Mean and mean changes from baseline to end of study were also summarized. Statistical analysis was performed for respiratory rate to test for nonincreasing or nondecreasing dose response.

Hemoglobin-oxygen saturation (SpO_2) values were summarized by treatment and time interval postdose.

Somnolence scores using the University of Michigan Sedation Scale (UMSS) were summarized by treatment and time interval postdose. Statistical analysis was performed to assess nondecreasing dose response.

Analysis Populations

The enrolled population consisted of all patients who signed informed consent.

The safety population was defined as all patients who received at least 1 dose of study drug.

Results

Disposition

There were 10 patients treated in the conversion phase and 7 patients treated in the long-term phase. Six patients completed the study through the long-term phase. One patient each discontinued due to an AE in the conversion phase and the long-term phase. One patient discontinued due to patient's choice in the conversion phase, and 1 patient completed the conversion phase but did not enter the long-term phase.

Name of Company Purdue Pharma L.P.	Protocol Number OXP3004
Name of Finished Product OxyIR,® OxyContin®	Name of Active Ingredient Oxycodone Hydrochloride

Results (continued)

Demographic and Baseline Characteristics

The median age of the patients in both the conversion and long-term phases was 12 years. In the conversion phase 4 patients were in the 6 years to < 12 years age group, and 6 patients were between 12 and 16 years of age. Seventy percent of the patients in the conversion phase were white.

Efficacy

Statistical analyses of the efficacy variables were not performed. No efficacy conclusions can be made due to the small number of patients.

Pharmacokinetics

Population PK results will be presented in a separate report.

Safety

Dosing and Extent of Exposure

- In the conversion phase 100% of patients received OxyIR and 44% of patients received at least 4 doses of OxyContin. The mean number of OxyContin doses was 3.2 doses, and the time from first to last dose of OxyContin was 26.7 hours.
- In the long-term phase, 6 patients (85.7%) remained in the study for at least 3 weeks, ingesting a mean of 102 doses, and the time from first to last dose was 25.9 days.

Adverse Events

- TEAEs in the conversion phase were abdominal pain upper, constipation, gastroesophageal reflux disease, nausea, oral pruritus, and vomiting (1 patient [10%] each). In the long-term phase, the TEAEs were constipation and pyrexia (2 patients [29%] each). Most events were mild or moderate in intensity.
- No patient died during the study. Two patients had serious adverse events (SAEs) consisting of pyrexia (1 patient) and febrile neutropenia, pseudomonal sepsis, pyrexia, candida sepsis, and sepsis (1 patient) that were not associated with the study drug, and the patients recovered from the events.
- Two patients discontinued study drug treatment due to adverse events (1 patient receiving OxyIR in the conversion phase discontinued due to an AE [vomiting], and 1 patient receiving OxyContin in the long-term phase discontinued due to AEs [bone pain, disease progression]).

Narratives for SAEs and AEs leading to discontinuation are contained in section 14.3.3.

Name of Company Purdue Pharma L.P.	Protocol Number OXP3004
Name of Finished Product OxyIR,® OxyContin®	Name of Active Ingredient Oxycodone Hydrochloride

Incidence of Deaths, Serious Adverse Events, and Other Significant Events by Dosage Group

	Conversion Phase			Long-Term Phase
Category[a]	OxyIR (n = 10) n (%)	OxyContin (n = 9) n (%)	Total (N = 10) n (%)	OxyContin (N = 7) n (%)
Deaths[b]	0	0	0	0
Serious Adverse Event(s)	0	0	0	2 (28.6)
Total Adverse Events	3 (30)	4 (44.4)	5 (50)	5 (71.4)
Other Significant Events				
Adverse Events Leading to Discontinuation	1 (10)	0	1 (10)	1 (14.3)[b]
Adverse Events Requiring Reduction in Dose of Study Drug	0	0	0	0

Cross references: Tables 14.3.1.1, 14.3.2.1.
[a]A patient may have had more than 1 other significant event; patients with other significant events may have also had a serious adverse event or died.
[b]One patient died after discontinuing from the study.

Clinical Laboratory Evaluations did not reveal any unanticipated safety findings.

Vital Signs and Other Observations Related to Safety

Vital sign measurements throughout the study remained within normal ranges, with few exceptions. Average hemoglobin-oxygen saturation scores and somnolence scores, measured during the conversion phase, remained within normal ranges.

Conclusions

The study was terminated early for administrative reasons unrelated to safety and efficacy. Conclusions are, therefore, limited based on the small number of patients in the study.

There were no unanticipated safety findings. No patient died during the study. Two SAEs occurred during the study and were not associated with study drug.

Date of the Report: 21-Apr-2011

3.2.7 Synopsis of Pediatric Study with patient's age birth to 4 yrs. (OXP1005):

Name of Company: Purdue Pharma L.P.	**Protocol Number:** OXP1005	
Name of Finished Products: Oxy Pediatric Liquid 1 mg/mL	**Name of Active Ingredients:** Oxycodone hydrochloride	
IND Number: 29,038		
Indication: For moderate to severe pain in children from birth to 4 years of age.		
Title of the Study: A Multicenter, Inpatient, Open-Label, Dose-Ranging Study to Characterize the Pharmacokinetics and Safety of an Oral Liquid Formulation of Oxycodone in Patients From Birth to 4 Years, Who Require Opioid Analgesia		
Investigator/Center: This was a multicenter, multinational trial at 26 sites (US, Canada, EU [Finland, Scotland, Netherlands, England]). The list of investigators is provided in Appendix 16.1.4.		
Publications (Reference): None.		
Study Dates: 22-Jan-2003 (FPFV) to 03-Apr-2004 (LPLV)	**Study Status:** Completed This study was terminated early on 31-Mar-2004 due to administrative reasons not related to efficacy or safety.	**Phase of Development:** Phase 1
Objectives: Primary • To characterize the pharmacokinetics of Oxy Pediatric Liquid 1 mg/mL (oxycodone hydrochloride oral solution) after the first dose and after repeated dosing in pediatric patients from birth to ≤ 4 years of age. • To evaluate the safety of Oxy Pediatric Liquid 1 mg/mL in pediatric patients from birth to ≤4 years of age. Secondary • To assess the efficacy of Oxy Pediatric Liquid 1 mg/mL in pediatric patients from birth to ≤4 years of age using supplemental analgesic requirement as the endpoint.		
Methodology: This was a multicenter, inpatient, open-label, group-sequential, ascending dose study to evaluate the pharmacokinetics of Oxy Pediatric Liquid (1mg/mL), using a population PK approach, after first dose, and after repeated dosing. Pediatric patients were stratified into 3 age groups: birth to 30 days, 31 days to ≤ 6 months, and 7 months to ≤ 4 years. Patients were to be approximately evenly distributed over the entire age range in each stratum and across both genders (Amendment 2, 20-Nov-2002). The duration of the study was up to 2 days. All patients were permitted to receive opioids, preferably PCA morphine (or oral morphine if the patient no longer had intravenous access) as supplemental medication for pain relief. NSAIDS and acetaminophen were also permitted.		
Number of Patients: Planned: At least 60 evaluable patients Enrolled: 66 Screen failures: 6 Discontinued early: 10 Completed: 50		

Indication and Criteria for Inclusion/Exclusion:
Male and female pediatric patients from birth to ≤ 4 years who had or were anticipated to have moderate to severe pain requiring opioid analgesics for at least 2 days were included in the study. Patients had to be opioid naïve prior to study entry or preoperatively (for surgical patients) (added per Amendment 2, 20-Nov-2002). Patients aged ≤ 1 year had to have a gestational age ≥ 36 weeks and body weight ≥ 2.5 kg. All patients had to be inpatients at the time of enrollment and sufficiently alert to be assessed for treatment-related side effects and level of pain. Exclusion criteria included clinically significant hepatic or renal dysfunction, impaired respiratory reserve, or impaired cardiovascular stability.

Treatments:

Test Treatment	Dose	Dosage Form	Lot Number
Oxy Pediatric	0.05 mg/kg	Oral Liquid	CB-2002-11
Oxy Pediatric	0.1 mg/kg	Oral Liquid	CB-2002-11
Oxy Pediatric	0.2 mg/kg	Oral Liquid	CB-2002-11
Reference Treatment			
None			
Supplemental Analgesia			
Morphine	PCA	IV, oral	N/A
NSAIDS, acetaminophen	Prn	oral	N/A

Treatment Schedule:
The first dose of Oxy Pediatric Liquid was permitted when the patient was ready to take oral liquid, preferably at 8 AM. The study drug was given q6h for up to 7 doses. If the study drug was not sufficient to relieve the pain, supplemental pain medication was given, preferably morphine.

Duration of Treatment: Up to 2 days.

Criteria for Evaluation:

Efficacy
Supplemental Pain Medication was recorded by exact clock time for each attempt, dose, and route of administration on the case report form.

Pain intensity ("pain right now") was assessed using a numerical scale ranging from 0 to 10, where 0 indicates "no pain" and 10 indicates "very much" or "unbearable pain." Scores were obtained as follows: at baseline (before administration of study drug; after the first dose, at 0.5, 1, 2, and 3 hours postdose, immediately prior to and 1 hour after each subsequent dose, and at the end of the study (Administrative Change 1, 12-Nov-2002). Additionally, pain intensity scores were recorded when nurse administered PCA was given.

Pharmacokinetics
Blood samples (1 mL each) for serum oxycodone and metabolite concentrations were obtained from an indwelling cannula inserted in a forearm or from a previously inserted central venous catheter or arterial catheter. If access was otherwise not available, venipuncture could be used if acceptable to patient/guardian ("fingerstick" deleted per Amendment 1 [Netherlands], 05-Jun-2003]). A total of 9 blood samples were collected from each patient with body weight > 5 kg. For patients with body weight ≤ 5 kg, only 4 blood samples were collected. Blood samples were collected in accordance with the time windows specified in the protocol (Appendix 16.1.1). The protocol required that there must be at least a 1-hour interval between each sample.

Safety
Safety was assessed using reports of adverse events (AEs), clinical laboratory tests, vital sign measurements, hemoglobin-oxygen saturation evaluations, somnolence evaluations, and physical examinations

Bioanalytical Methods:
Serum samples were prepared by using solid phase extraction, and the concentrations of oxycodone and its metabolites were quantified by LC-MS/MS analysis. The LOQ was at least 1 ng/mL and the linear range was up to at least 50 ng/mL. The instrument operated under positive electron spread and multiple-reaction mode (MRM). A calibration curve was constructed for the quantitation based on the peak area ratio of drug/international standard (IS).

Statistical Methods:

Demographic and Baseline Characteristics
Demographic and baseline variables included age, sex, race, weight, vital sign measurements, and surgical stress scores, and medical history.
Continuous variables were summarized using mean, standard deviation (SD), median, minimum and maximum values, and categorical variables were summarized using frequency and percent.

Dosing and Extent of Exposure
The number of doses and the length of exposure (number of hours from first to last dose) in each treatment group, overall, and by age group, were summarized.

Sample Size Rationale
In study OC96-0602, the observed total standard deviation of the log transformed oxycodone AUC_t, after adjusting for both dose level and weight was 0.45, or the approximate coefficient of variation (CV) was 45%. The similar number for C_{max}, after adjusting for weight, was 0.40 for an approximate CV of 40%. Thus the larger of these two CV's is approximately 45%. When estimating parameters using the population PK approach, it was reasonable to assume that the variability will be larger, eg, a CV of 75%. Assuming a total variability (CV) equal to 75%, it was estimated that the 95% confidence interval from 60 patients would have a length of 0.38 times the mean.

Efficacy and Pharmacokinetic (PK) Analyses
Efficacy variables consisted of supplemental pain medication use and pain intensity scores.
Supplemental pain medication consisted of PCA morphine supplemental pain medication, nonPCA opioid supplemental pain medication, and acetaminophen usage. Total opioid supplemental pain medication was obtained by adding the PCA morphine supplemental medication usage to the nonPCA opioid supplemental pain medication usage (in IV morphine equivalence). Dose-response for these derived variables within each dosing interval was evaluated using the Jonckheere-Terpstra (J-T) test. Additionally, the number and percentage of patients who received at least 1 dose of acetaminophen supplemental pain medication was summarized by treatment group overall, by age group, and by dose interval. Approximate 95% confidence intervals (CIs) were obtained.

Pain intensity scores obtained at scheduled postdose intervals as well as prior to nurse- administered PCA were analyzed. Statistical inference examining nonincreasing dose response was evaluated using a J-T test for the average and maximum pain scores during the first dose interval and overall average of the 1 h and 6 h postdosing scores excluding and including the first dose interval.

Exploratory efficacy analyses were performed to examine age group differences. No formal statistical comparisons were done; however, data were summarized by age group.

Population PK Analyses: The population mean and population variability for oxycodone PK parameters were estimated using a nonlinear mixed effects model, ie, a population PK approach. Methodology and results of the population PK analyses will be presented in a separate report.

Safety

Safety variables analyzed were adverse events, laboratory tests, vital signs, hemoglobin-oxygen saturation, and somnolence. All safety analyses were conducted on the safety population.

Adverse events: All adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Coding Dictionary (version 13.0).

Treatment-emergent adverse events (TEAEs) were summarized to examine overall incidence of TEAEs and the incidence of TEAEs by relationship to study drug and maximum severity.

Clinical laboratory: Laboratory data were summarized using mean and mean changes from baseline, and shifts from baseline using the LNH classification according to whether the value was below (L), within (N), or above (H) the laboratory reference range. Clinical laboratory results for each subject were evaluated to determine whether they were markedly abnormal using the toxicity grade scheme (Division of AIDS Toxicity Table for Grading Severity of Pediatric Adverse Experience, Dec, 2004).

Vital Signs: Descriptive statistics for vital sign parameters at each assessment time were summarized. Mean and mean changes from baseline to end of study were also summarized. Statistical analysis was performed for respiratory rate to test for nonincreasing or nondecreasing dose response.

Hemoglobin-Oxygen Saturation: Statistical analysis of SpO_2 was performed similar to that performed for the pain assessments. Nonincreasing dose response was assessed using a J-T test. The number and percent of patients experiencing desaturation was summarized.

Somnolence: Statistical analysis was performed to assess nondecreasing dose response.

Analysis Populations

The enrolled population was defined as all patients who signed the informed consent form.

The safety population was defined as those patients who received at least 1 dose of Oxy Pediatric Liquid.

The full analysis population for PK was defined as those patients who received at least 1 dose of Oxy Pediatric Liquid, and had at least 1 valid quantifiable PK sample.

The full analysis population for efficacy was defined as those patients who received at least 1 dose of Oxy Pediatric Liquid, and at least 1 subsequent efficacy evaluation (pain measurement or supplemental pain medication).

Results:

Disposition

Sixty patients received treatment in this study. Of these, 50 patients completed the study: 10 patients in the ≤ 30 day age group, 20 patients each in the 31 days to ≤ 6 months and 7 months to ≤ 4 years age groups. Ten patients (17%) discontinued: 3 (5%) due to adverse events, 5 (8%) due to administrative reasons, and 2 (3%) due to subject's choice.

Concomitant Medications

The most common opioid supplemental medications used by patients during the study were fentanyl (80%) and morphine (68%).

Demographics and Baseline Characteristics

- Fifty-two percent of the patients were female
- Seventy percent of the patients were white
- Overall postsurgical pain scores were generally low (mean 1.8 = mild pain)

Efficacy Results

- Use of supplemental PCA morphine increased with increasing doses of Oxy Pediatric Liquid.
- Total opioid supplemental pain medication use was higher in the higher dose groups, particularly the 0.2 mg/kg group, than in the 0.05 mg/kg group.
- In the initial dosing period (first 6 h dosing interval), more patients in the Oxy Pediatric Liquid 0.1 mg/kg group used acetaminophen than in the other dose groups, but less supplemental acetaminophen overall compared to the 0.05 mg/kg and 0.2 mg/kg groups.
- Across all dosing intervals, mean pain intensity scores were low for all dose groups. Pain intensity scores were higher for the higher dose treatment groups.

Pharmacokinetics

Population PK results will be presented in a separate report.

Safety

Dosing and Extent of Exposure

- The mean exposure time from first to last dose of study drug for all patients was 28 hours and the mean number of doses was 5.6.
- Eighty-seven percent of patients were administered at least 6 doses of study drug.

Adverse Events

There were no deaths during the study. Two patients had treatment-emergent serious adverse events (SAEs) consisting of obstructive apnea (1 patient), and loss of appetite, abdominal pain, and pyrexia (1 patient). One SAE (myocardial ischemia, Patient 73001) occurred prior to satisfying all enrollment criteria or receipt of study drug and was not a treatment-emergent event. Three patients discontinued due to adverse events of sedation, vomiting NOS, and obstructive sleep apnea syndrome. Narratives for SAEs and AEs leading to discontinuation are contained in section 14.3.3.

3.2.8 Synopsis of Pediatric Study of OxyContin (ORF) in age group 6 – 16 yrs. (OTR1020).

Name of Company: Purdue Pharma L.P.		**Protocol Number:** OTR1020
Name of Finished Products: Oxycodone hydrochloride q12h controlled release tablets (ORF)		**Name of Active Ingredients:** Oxycodone hydrochloride
IND Number: 29,038		
Indication: NA		
Title of the Study: An Open-label Study to Characterize the Pharmacokinetics and Safety of Oxycodone Hydrochloride q12h Controlled-Release Tablets (ORF) in Pediatric Patients Aged 6 to 16 Years Inclusive, Who Require Opioid Analgesia		
Investigator/Center: This was a multicenter, multinational trial at 11 sites (US and AUS). The list of investigators is provided in Appendix 16.1.4.		
Publications (Reference): None.		
Study Dates: 18-Aug-2010 (FPFV) to 16-Aug-2011 (LPLV)	**Study Status:** Completed	**Phase of Development:** Phase 1
Objectives: Primary • To characterize the pharmacokinetics (PK) of single-dose ORF tablets in pediatric patients aged 6 to 16 years, inclusive. • To characterize the safety of ORF tablets in pediatric patients aged 6 to 16 years, inclusive. Secondary • To examine ORF multiple-dose PK in pediatric patients aged 6 to 16 years, inclusive.		
Methodology: This was an open-label study to characterize the PK and safety of ORF tablets in pediatric patients of both genders aged 6 to 16 years, inclusive. Patients were permitted to receive supplemental medication for pain relief (except OxyContin® or other oxycodone products), as deemed appropriate by the investigator.Study duration lasted from 1 day up to 27 days. (Amendment 6, 09-Feb-2011, added the following [4 sentences]: The screening period was up to 14 days prior to first dose of ORF. Postsurgical patients were not permitted to be dosed with study drug until at least 96 hours after surgery. All patients were required to be treated with an opioid for at least 96 hours prior to the first dose of ORF. Oxycodone was prohibited within 24 hours prior to administration of ORF.) Patients were screened within 14 days and up to 1 hour prior to administration of ORF (prior to surgery for surgical patients and prior to first dose for nonsurgical patients) and up to 1 hour prior to administration of ORF (Amendment 6, 09-Feb-2011, deleted: prior to surgery for surgical patients and prior to first dose for nonsurgical patients). Screening procedures were permitted to be performed independently or in combination with the baseline visit. In the event that the screening and baseline visits were combined, patients were permitted to be screened up to 1 hour prior to dosing. Study treatment lasted from 24 hours (single dose) to 72 hours (5 doses). (Amendment 6, 09-Feb-2011, changed this to read: Study treatment could last from 12 hours [single dose] to 72 hours [5 doses]). An end-of-study (EOS) visit occurred 24 hours post final dose. A follow-up phone call was made 7 to 10 days post the last dose of ORF. All patients' caregivers received a follow-up phone call 7 to 10 days post final dose to assess for any additional AEs.		
Number of Patients: Planned: 36 patients Enrolled: 42 Screen failures: 12 Treated: 30 Discontinued early: 2 Completed: 28		

Indication and Criteria for Inclusion/Exclusion:

Postoperative and nonsurgical pediatric patients, of either gender, aged 6 to 16 years, inclusive, who were clinically stable and tolerating oral fluids were permitted to enroll. Patients were required to have or were expected to have had moderate to severe pain requiring oral opioid analgesic treatment for at least 24 hours. (Amendment 6, 09-Feb-2011, changed this to read: Patients were required or were expected to have moderate to severe pain for an extended period of time requiring inpatient oral opioid analgesic treatment for at least 12 hours as this was the minimum duration of study period treatment. Eligible postsurgical patients were not permitted to be dosed with study drug until at least 96 hours after surgery. All patients were required to be treated with an opioid for at least 96 hours prior to the first dose of ORF.) Patients were required to be inpatient for the treatment period of the study. The patient's anticipated opioid analgesic requirement over the first 12 hours that followed administration of ORF was required to be equivalent to at least 10 mg of intravenous (IV) morphine. The patients were required to have adequate pain control during the 6 hours prior to study drug administration, based on appropriate clinical assessment. To receive the first oral dose, patients were required to have a sustained pulse oximetry (SpO_2) of at least 92% with or without supplemental oxygen during the 15 minute period just prior to dosing. A 1:1 ratio of minimum cumulative 12-hour IV morphine sulfate dose to q12h oral ORF dose was used for this study.

Treatments:

Single oral dose of ORF tablets (10 mg, 15 mg or 20 mg) were administered after the patient began taking oral fluids. The patient's anticipated opioid analgesic requirement over the first 12 hours following administration of ORF was equivalent to at least 10 mg of IV morphine.

Multiple doses: At the investigator's discretion, additional oral doses of ORF tablets were given at 12, 24, 36, and at 48 hours post initial dose (up to 5 doses). These subsequent doses were permitted to be adjusted upward or downward based on the patient's clinical course and/or changing analgesic requirements.

Doses were administered with sips of water or other appropriate clear liquid. (Amendment 5, 02-Nov-2010, changed this to read: Doses were administered with enough water or other appropriate liquid.) Tablets were required to be swallowed whole without chewing and were not to be crushed.

Lot numbers CB-2010-03, CB-2010-04, and CB-2009-15 were used in this study.

Test Treatment:	**Dose**	**Dosage Form**	**Lot Number**
Oxycodone HCl 10 mg TR	10 mg	Oral Tablets	CB-2010-03
Oxycodone HCl 15 mg TR	15 mg	Oral Tablets	CB-2010-04
Oxycodone HCl 20 mg TR	20 mg	Oral Tablets	CB-2009-15
Reference Treatment:			
None			

Concomitant Medication Including Rescue:

No oxycodone product was permitted 24 hours predose. All patients were permitted to receive supplemental medication (except oxycodone) for pain relief, as prescribed by their physician.

Treatment Schedule:

Screening/Baseline Period (from 14 days up to 1 hour prior to study drug administration): The screening procedures were performed either independently or in combination with the baseline visit; these were physical exam, vital signs, SpO_2, medical/ surgical history, clinical laboratory testing, prior and concomitant medications/therapies, and evaluation of inclusion/exclusion criteria.

Oral Treatment Period: Initial administration of the ORF tablet occurred when the patient was able to tolerate oral fluids, preferably at 8 AM. (Amendment 6, 09-Feb-2011, changed this to read: Initial administration of the ORF tablet occurred at least 96 hours following surgery (for surgical patients) and when the patient was able to tolerate oral fluids. Both surgical and nonsurgical patients were required to be treated with an opioid for a minimum of 96 hours prior to the first dose of ORF.)

The investigator determined the timing of the first dose based on each patient's clinical condition (8 AM was preferable to accommodate PK blood sampling) (Amendment 6, 09-Feb-2011, changed this to read:

Once the patient was eligible to be dosed with ORF, the investigator determined the timing of the first dose based on each patient's clinical condition [8 AM was preferable to accommodate PK blood sampling]). Up to 4 additional doses of ORF were permitted on a q12h schedule.

Supplemental analgesics (except oxycodone) were permitted.

End–of-Study (EOS; at time of study completion or early discontinuation): This visit occurred 24 hours post final dose, or at the time of discontinuation for all patients who had received their last dose of ORF but discontinued the study before the 24-hour postdose time point. End–of-study/ early termination procedures included a physical exam, vital signs, SpO_2, laboratory tests, pain and somnolence assessments, evaluation of concomitant medications/therapies, AE collection, and final PK sample collection.

Follow-up: A follow-up phone call was made 7 to 10 days post final dose to query for any additional AEs. The analgesic treatment after the EOS visit was determined by the patient's physician based on the patient's clinical condition.

Duration of Treatment:

Study duration lasted from 1 day up to 27 days. (Amendment 6, 09-Feb-2011, added the following [4 sentences]: The screening period was up to 14 days prior to first dose of ORF. Postsurgical patients were not permitted to be dosed with study drug until at least 96 hours after surgery. All patients were required to be treated with an opioid for at least 96 hours prior to the first dose of ORF. Oxycodone was prohibited within 24 hours prior to administration of ORF.)

Criteria for Evaluation:

Pharmacokinetics (PK):

Oxycodone Concentration Measurements: Blood samples (1 mL) for determining oxycodone concentrations were obtained immediately before dosing (0 hour), 1.5h, 3h, 4.5h, 6h, and 12h post first dose. For patients who received multiple dosing, additional PK blood time points for the secondary PK analysis were just prior to dosing for doses 2 (same sample as 12-hour post initial dose), 3, 4 and 5. A final PK blood sample was taken between 12 and 24 hours after the final dose in all patients.

Plasma concentration of oxycodone was analyzed to determine single and multiple dose PK metrics.

Safety:

Physical examinations were performed during the screening period and EOS. Vital signs, SpO_2, reports of AEs, and somnolence using the University of Michigan Sedation Scale (UMSS), were obtained at multiple times during the study. Sedation scores, using the UMSS, and pain scores were collected at baseline, during treatment, and at EOS at the same time as vital sign collection. 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 100-mm visual analogue scale (VAS). (Amendment 2, 27-May-2010, deleted the following sentence: The 100-mm VAS was completed by the parent/caregiver for patients aged 6 to < 12 years.) Clinical laboratory tests, including hepatic enzymes, were obtained prior to initial administration of study drug and at EOS.

Bioanalytical Methods:

Plasma concentrations of oxycodone and its metabolites (noroxycodone, oxymorphone, and noroxymorphone) were quantified by a validated liquid chromatography tandem mass spectrometric method.

Statistical Methods:

Demographic and Baseline Characteristics

Patient demographics and baseline characteristics were summarized descriptively for all patients overall and by age group (6 to < 12 years and ≥ 12 to ≤ 16 years). Demographics and baseline characteristics were summarized for the safety and full analysis for PK populations.

For continuous demographic and baseline variables, descriptive statistics (n, mean, standard deviation [SD], minimum, and maximum values) were displayed. For categorical (nominal) variables, the number and percentage of patients were displayed.

Dosing and Extent of Exposure

The number and percent of patients taking each dose of study drug were presented overall and by age group based on the initial dose level. Summaries included descriptive statistics (mean, SD, median, minimum, and maximum) for the number of doses and the time from first to last dose in hours. In addition, the average daily dose for each age group was calculated.

Extent of exposure was summarized for the safety population.

The total morphine equivalent (MEQ) dose used within the first 12 hours prior of first dose was summarized (n, mean, SD, minimum, and maximum values) for each medication overall and by age group.

Sample Size Rationale

It was planned for this study to dose 36 patients. No formal statistical power calculations were performed. However, assuming a 40% coefficient of variation (CV), the choice of 36 patients was expected to provide a 95% confidence interval (CI) for the PK exposure metrics with interval width up to 0.262 times the sample mean.

Pharmacokinetic (PK) Analyses

Descriptive statistics were tabulated overall and by age group as applicable, for all plasma concentrations and PK metrics.

PK metrics (AUC_t, AUC_{inf}, C_{max}, t_{max}, λ_Z, $t_{1/2Z}$, and t_{lag} for single dose patients, C_{min} for multiple dose patients, and $AUC_{(0-12)}$, $C_{max(0-12)}$, $t_{max(0-12)}$, and $t_{lag(0-12)}$ for all patients (ie, single and multiple dose patients), nonnormalized and normalized by body weight and dose, were summarized using means and associated 95% (CIs).

For the normalized data, a general linear model approach was utilized to provide a 90% CI for the ratio of oxycodone exposure metrics among pediatric age groups.

(Amendment 6, 09-Feb-2011, deleted the following: The PK data obtained in this pediatric population could be compared with previous data obtained in adults.)

Safety Analyses (Amendment 3, 10-Jun-2010, changed this to read: **Safety and Pain Analyses)**

All data (AEs, clinical laboratory results, vital signs, somnolence, SpO_2) were listed for patients in the safety population. (Amendment 3, 10-Jun-2010, changed this to read: All data (AEs, clinical laboratory results, vital signs, somnolence, SpO_2) and pain (FPS-R, 100-mm VAS) data were listed for patients in the safety population.) Summaries of safety data were presented overall, by age group and time point where applicable and by dose within an age group. (Amendment 6, 09-Feb-2011, deleted the following: Summary tabulations for safety data will include incidence rates for respiratory depression and hypotension.)

Supplemental Pain Medication: Supplemental pain medications (opioids and nonopioids) were coded according to WHODrug (WHO-DD2010MAR01 [basic]). The number and percent of patients with an opioid and nonopioid medication was summarized by age group and overall.

Opioid analgesic medication usage (including PCA supplemental pain medication usage) was converted to IV morphine dosage equivalence. Mean total dose (mg/day) of supplemental opioids pain medication (in IV morphine dosage equivalents) was calculated by 12 hours. Descriptive statistics (n, mean, SD, median, minimum, and maximum) were displayed overall and with each age group.

Pain Analyses: Pain assessments were summarized (number of patients, mean, standard error (SE), minimum, median, and maximum) for single dose patients at baseline, 0.75, 1.5, 3, 4.5, 6 and 12 hours postdose and at the EOS/early termination for single dose patients and for multiple dose patients at baseline, 0.75, 1.5, 3, 4.5, and 6 hours after the first dose, prior to doses 2, 3, 4 and 5 and 3 hours postdose 2, 3, 4 and 5. Also, pain assessments were captured 6 hours post fifth or final dose, whichever came first. A final pain assessment was taken 24 hours post final dose or at the time of early termination. Amendment 3, 10-Jun-2010, added: Pain scores were summarized overall and by age group, and by time point.

For patients 6 to < 12 years of age, the FPS-R data were listed and summarized using n, mean, SE, minimum, median, and maximum. Patients aged ≥ 12 to ≤ 16 years completed the VAS questionnaire and their data were listed and summarized using n, mean, SE, minimum, median, and maximum.

(Amendment 2, 27-May-2010, deleted the following: The 100-mm VAS was completed by the parent/caregiver for patients aged 6 to < 12 years.)

All pain data collected were listed.

Adverse events: All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 13.0 or higher.

All reported AEs (including nontreatment emergent events) were listed and only treatment-emergent AEs (TEAEs) were summarized by number and percentage of patients experiencing at least 1 AE by age group within single and multiple dose groups and overall by dose level within each age group and overall, by maximum severity and by relationship to study drug.

Clinical laboratory: Clinical laboratory values were evaluated by patient using the LNH classification according to whether the value was below (L), within (N), or above (H) the laboratory reference range. Abnormal laboratory values were identified as those outside (above or below) the normal range and were flagged in the patient listings.

Vital Signs:

Summary statistics (n, mean, SD, minimum, maximum, and median values) for baseline, and each schedule timepoint and change from baseline values were produced for each continuous vital sign parameter overall and by age group.

Somnolence: Somnolence scores were listed by patient and summary tables included the number and percent of responses in the various categories and descriptive statistics (n, mean, SD, median, minimum, and maximum) at baseline and each schedule timepoint for the safety population overall and by age group. In addition, descriptive statistics for change from baseline were provided.

Hemoglobin-Oxygen Saturation: SpO_2 was summarized (n, mean plus SD, median, minimum, and maximum at baseline, EOS, and change from baseline) overall and by age group, dose number and dose level, respectively.

Analysis Populations

The enrolled population (N = 42) was defined as the group of patients who signed the informed consent form.

The safety population (N = 30) was defined as the group of patients who received study drug.

The full analysis population for PK (N = 30) was defined as those patients who received at least 1 dose of oral study drug and had at least 1 valid, quantifiable PK metric. PK metrics from patients experiencing emesis within 12 hours after dosing were permitted to be excluded from PK analysis. Patients and profiles/metrics excluded from the analysis set were documented in the final SAP prior to database lock.

Results:

Disposition

There were 42 pediatric patients enrolled in the study. The safety and full analysis for PK populations consisted of 30 patients (5 aged 6 to < 12 and 25 aged ≥ 12 to ≤ 16), with 28 patients completing the study. Two patients (6.7%) in the ≥ 12 to ≤ 16 age group discontinued the study due to subject's choice (loss of vascular access and unwillingness to have additional access). All 30 patients met the inclusion and exclusion criteria.

Demographics and Baseline Characteristics

There were more patients in the the older age group (≥ 12 to ≤ 16 years; n = 25) than in the younger age group (6 to < 12 years; n = 5). Overall, in both age groups, there were slightly more female patients than male patients (56.7% vs 43.3%, respectively), 83.3% of the patients were white, and 96.7% were not Hispanic or Latino. The mean BMI was approximately the same between age groups (21.82 kg/m^2 and 21.19 kg/m^2, respectively).

Concomitant Medications

Within the nervous system anatomic class, the most common pharmacologic subclasses of concomitant

medications and therapies used by patients were opioids (96.7%) and other analgesics and antipyretics (90.0%), followed by anxiolytics (33.3%) and hypnotics and sedatives (30.0%). The most commonly used supplemental pain opioids were hydromorphone (43.3%), morphine (36.7%), and Vicodin® (16.7%). All 30 patients were taking either an opioid or nonopioid analgesic other than study drug at some point during the study.

Efficacy Results

- A similar proportion of patients used supplemental opioid pain medication between age groups.
- Overall, total opioid supplemental pain medication usage in IV morphine dosage equivalents was similar between doses and was generally higher in the older age group compared to the younger age group.
- In the younger age group, the mean pain score was low, as measured by the FPS-R scale. In the older age group, the mean pain score was also low and generally consistent between doses.

Pharmacokinetics

PK results will be presented in a separate report.

Safety

Dosing and Extent of Exposure

The mean number of doses for all patients was 2.3 and the mean time from first to last dose was 27.99 hours. Eighteen patients (60%) were administered a single dose of study drug and 12 patients (40%) received multiple doses of study drug. The mean daily dose for patients taking multiple doses of study drug was slightly higher in the older age group than in the younger age group (30.0 vs 25.0 mg, respectively).

Incidence of Deaths, Serious Adverse Events (SAEs) and Other Significant Adverse Events (AEs) by Dosage Group

	Age Group		
Category	**6 to < 12 Years (N=5) n (%)**	**≥ 12 to ≤ 16 Years (N=25) n (%)**	**Total (N=30) n (%)**
Deaths	0	0	0
Serious Treatment-Emergent Adverse Events	0	1 (4.0)	1 (3.3)
Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation	0	0	0
Treatment-Emergent Adverse Events Leading to Dose Reduction	0	0	0

Cross-reference: Table 14.3.2.1

Note: Death included both treatment emergent and nonTEAEs. Patients who experienced 2 or more AEs within the same category are counted only once. All AEs were coded using the MedDRA version 13.0 dictionary. A TEAE is defined as an event that emerges during treatment, having been absent at pretreatment, or reemerges during treatment, having been present at baseline but stopped prior to treatment, or worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Safety Results

- A total of 24 patients (80.0%) in the safety population experienced a TEAE: 5 patients (100%) in the younger age group (6 to ≤ 12 years) and 19 patients (76.0%) in the older age group (≥ 12 to ≤ 16 years). Twenty patients (66.7%) in the safety population experienced a TEAE that was reported in ≥ 10% patients: 5 patients (100%) in the younger age group and 15 patients (60%) in the older age group.
- The most commonly reported TEAEs in ≥ 10% patients were constipation and vomiting (each, 23.3%), respiratory rate decreased (16.7%), nausea (13.3%), and dizziness and pruritus (each, 10.0%).
- No patient died during the study. One patient had 1 SAE and no patient experienced AEs leading to treatment discontinuation. No patient experienced a severe AE.
- Clinical laboratory evaluations did not reveal any unanticipated safety signals. There were 4 AEs due to decreased hemoglobin, none of which resulted in discontinuation:
- Mean respiratory rates were generally unchanged in the older age group from predose through 12 hours after the first dose and were similar to those of the younger age group
- Four patients experienced treatment-emergent clinically significant respiratory depression; 3 patients in the older age group and 1 patient in the younger age group. In all cases, the decreases in respiratory rates were considered mild and possibly related to study drug. All 4 patients recovered without treatment.
- Mean hemoglobin-oxygen saturation values were generally unchanged in the older age group from predose through 12 hours after the first dose and were similar to those of the younger age group. No patient experienced treatment-emergent clinically significant SpO_2.
- Mean somnolence scores were low and generally unchanged in the older and younger age groups. No patient experienced treatment-emergent clinically significant somnolence.

Conclusions:

Treatment with ORF tablets in pediatric patients of ages 6 to 16 years old who required opioid analgesia did not reveal any unusual safety results of concern. Note that the characterization of the pharmacokinetics of ORF PK (population PK results) will be presented ina separate report.

Date of the Report: 05-Dec-2011

3.2.9 Synopsis of bioavailability study comparing IR oxycodone and original OxyContin in adults (OC94-0101).

I. TITLE/INVESTIGATOR/TRIAL DATES: A Single-Dose Pharmacokinetic Study in Healthy Adult Males of One (1) Oxycodone Controlled-Release 10 mg Tablet, Two (2) Immediate-Release Oxycodone 5 mg Tablets and Immediate-Release Oxycodone Oral Solution 10 mg/Roger L. Nation, Ph.D., Principal Investigator/February 11, 1995 - March 5, 1995.

II. OBJECTIVE/STUDY DESIGN: To characterize the pharmacokinetic (PK) profile of oxycodone when administered as a single controlled-release (OxyContin™) 10 mg tablet compared with two 5 mg tablets of immediate-release (IR) oxycodone (Endone™) and 10 mL of IR oxycodone oral solution (Roxicodone™) 5 mg/5 mL given as a single oral dose. In addition, the IR oxycodone 2×5 mg tablets were compared to the IR oxycodone 10 mL solution. Plasma oxycodone levels were used to calculate: (a) maximum plasma concentration (Cmax), (b) time to maximum plasma concentration (Tmax), (c) area-under-the-curve (AUC), (d) half-life of elimination (t½(elim)), (e) half-life of absorption (t½(abs)), (f) Wagner-Nelson 50% drug absorbed, and (g) peak width at 50% Cmax.

III. STUDY DRUG: Test: CR oxycodone (OxyContin™) tablets each containing 10 mg oxycodone hydrochloride. Reference: (a) IR oxycodone tablets (Endone™) each containing 5 mg oxycodone hydrochloride, (b) IR oxycodone oral solution (Roxicodone™) 5 mg/5 mL.

IV. STUDY POPULATION/DISPOSITION: A total of 22 healthy adult males 20 to 35 years of age were enrolled in this single-dose, three-way crossover, randomized, open-label, analytically-blinded, pharmacokinetic study. Subjects 1, 7, and 12 did not have blood samples drawn in Treatment Period 3 and were excluded from the pharmacokinetic analyses; however, they were included in the safety analyses.

V. RESULTS: This was a three-way crossover study. Each subject received CR oxycodone 10 mg, IR oxycodone 2×5 mg, and IR oxycodone oral solution 10 mL in the order determined by the randomization sequence. Figure S.1 shows that the mean plasma concentration for CR oxycodone 10 mg tablets was much lower from 0.25 to 5 hours, and much higher from 8 to 36 hours when compared with the IR oxycodone products.

The following table summarizes the pharmacokinetic results for oxycodone for the three treatments. Geometric means are presented for the values of $AUC_{0,36}$, $AUC_{0,\infty}$, and Cmax. Arithmetic means are presented for the values of t½(elim), t½(abs), Tmax, peak width @ 50% Cmax, and Wagner-Nelson 50% drug absorbed.

PK Parameters	CR Oxy 10 mg	IR Oxy 2x5 mg	Ratio (%)[a] (CR/IR)	90% Confidence Interval
$AUC_{0,36}$ (ng-hr/mL)	111.70	111.93	99.69	94.88-104.75
$AUC_{0,\infty}$ (ng-hr/mL)	113.42	111.93	101.22	96.33-106.37
Cmax (ng/mL)	9.18	29.00	31.53	27.67-35.92
t½(abs) (hrs)	0.94	0.99	94.34	72.24-121.03
t½(elim) (hrs)	6.44	1.97	326.34	299.54-350.78
Tmax (hrs)	2.33	0.83	280.95	235.57-325.76
Peak width @ 50% Cmax (hrs)	9.82	2.09	470.39	421.82-490.83
Wagner-Nelson 50% (hrs)	5.20	0.63	819.70	691.62-849.24

	CR Oxy 10 mg	IR Oxy Solu 10 mL	Ratio (%)[a] (CR/IR Solu)	90% Confidence Interval
$AUC_{0,36}$ (ng-hr/mL)	111.70	109.26	102.69	97.73-107.90
$AUC_{0,\infty}$ (ng-hr/mL)	113.42	109.26	104.29	99.24-109.59
Cmax (ng/mL)	9.18	25.99	35.14	30.84-40.05
t½(abs) (hrs)	0.94	0.48	193.71	144.66-242.38
t½(elim) (hrs)	6.44	2.09	308.11	285.48-334.31
Tmax (hrs)	2.33	0.76	305.71	262.13-362.50
Peak width @ 50% Cmax (hrs)	9.82	2.34	418.88	387.48-450.87
Wagner-Nelson 50% (hrs)	5.20	0.62	839.49	737.31-905.36

	IR Oxy 2x5 mg	IR Oxy Solu 10 mL	Ratio (%)[b] (IR/IR Solu)	90% Confidence Interval
$AUC_{0,36}$ (ng-hr/ml)	111.93	109.26	103.01	98.03-108.23
$AUC_{0,\infty}$ (ng-hr/ml)	111.93	109.26	103.03	98.04-108.26
Cmax (ng/ml)	29.00	25.99	111.48	97.83-127.02
t½(abs) (hrs)	0.99	0.48	205.35	151.39-249.11
t½(elim) (hrs)	1.97	2.09	94.41	70.89-119.72
Tmax (hrs)	0.83	0.76	108.62	61.09-161.46
Peak width @ 50% Cmax (hrs)	2.09	2.34	89.05	60.16-123.56
Wagner-Nelson 50% (hrs)	0.63	0.62	102.41	22.59-190.63

(Cross-reference: Table 18 and Appendix IV)
a Ratio (%) = (test mean/reference mean) × 100%
b Ratio (%) = (IR mean/IR Solu mean) × 100%

Note: For AUC(0,36), AUC(0,∞) and Cmax, geometric means are given. For all other parameters, arithmetic means are given.

Table Relative Bioavailability of Oxycodone: Summary of Point Estimates of PK Metrics and 90% Confidence Intervals of original OxyContin Tablet (OC) and Immediate Release Oxycodone (IR) Tablets - Study OC94-0101

PK Metric	Geometric Mean		Ratio (%)	(90% CI)
	OC (Test) 10 mg	IR (Reference) 2x5 mg	Test / Reference	
AUC0-36hr (ng.hr/mL)	111.7	111.9	99.7	(94.9 – 104.8)
AUCinf (ng.hr/mL)	113.4	111.9	101.2	(96.3 – 106.4)
Cmax (ng/mL)	9.2	29.0	31.5	(27.7 – 35.9)
Tmax (hr)[a]	2.3	0.8	NA	NA

Source: CSR OC94-0101, Table 3.4.2
[a] Arithmetic mean; NA = Not Applicable.

Table Relative Bioavailability of Oxycodone: Summary of Point Estimates of PK Metrics and 90% Confidence Intervals of Original OxyContin Tablet (OC) and IR Oxycodone Solution - Study OC94-0101

PK Metric	Geometric Mean		Ratio (%)	(90% CI)
	OC (Test) 10 mg	IR (Reference) Solution (10 mg/10 mL)	Test / Reference	
AUC0-36hr (ng.hr/mL)	111.7	109.3	102.7	(97.7 – 107.9)
AUCinf (ng.hr/mL)	113.4	109.3	104.3	(99.2 – 109.6)
Cmax (ng/mL)	9.2	26.0	35.1	(30.8 – 40.1)
Tmax (hr)[a]	2.3	0.8	NA	NA

Source: CSR OC94-0101, Table 3.4.2
[a] Arithmetic mean; NA = Not Applicable.

Table Relative Bioavailability of Oxycodone: Summary of Point Estimates of PK Metrics and 90% Confidence Intervals of Immediate Release Oxycodone Tablet (IR) and IR Oxycodone Solution - Study OC94-0101

PK Metric	Geometric Mean		Ratio (%)	(90% CI)
	IR (Test) 2 x 5 mg	IR (Reference) Solution (10 mg/10 mL)	Test / Reference	
AUC0-36hr (ng.hr/mL)	111.9	109.3	103.0	(98.0 – 108.2)
AUCinf (ng.hr/mL)	111.9	109.3	103.0	(98.0 – 108.3)
Cmax (ng/mL)	29.0	26.0	111.5	(97.8 – 127.0)
Tmax (hr)[a]	0.8	0.8	NA	NA

Source: CSR OC94-0101, Table 3.4.2
[a] Arithmetic mean; NA = Not Applicable.

CR oxycodone 10 mg tablet was equally bioavailable to IR oxycodone 2×5 mg tablets and to IR oxycodone 10 mL oral solution with respect to the extent of absorption, based on the AUC 90% confidence intervals, but was not comparable to these products with respect to the rate of absorption, based on the Cmax 90% confidence intervals. The Cmax of the CR tablet was approximately one-third that observed with the IR products. Mean t½ (elim), Tmax, peak width @ 50% Cmax, and Wagner-Nelson 50% drug absorbed were significantly ($p<0.05$) longer for CR oxycodone 10 mg tablet than for either IR oxycodone 10 mL oral solution or IR oxycodone 2×5 mg tablets. CR oxycodone 10 mg tablet had a significantly ($p\leq0.05$) longer t½(abs) than IR oxycodone 10 mL oral solution.

IR oxycodone 2×5 mg tablets and IR oxycodone 10 mL oral solution were equally bioavailable with respect to the extent of absorption, based on the AUC 90% confidence intervals, but were not comparable with respect to the rate of absorption, based on the Cmax 90% confidence intervals (98%-127%). IR oxycodone 10 mL oral solution had significantly ($p<0.05$) shorter mean t½(abs) than IR oxycodone 2×5 mg tablets.

None of the adverse experiences were serious or severe. At least one adverse experience was reported by 59% of subjects after taking CR oxycodone tablets, 68% after taking IR oxycodone tablets, and 82% after taking IR oxycodone solution; the differences were not statistically significant ($p>0.05$). Dizziness and nausea were reported more frequently with the IR oxycodone products than with CR oxycodone tablets. The numbers of reports of dizziness were 13 with the IR solution, 17 with IR tablets, and 2 with CR tablets; the numbers of reports of nausea were 7 with the IR solution, 6 with IR tablets, and 1 with CR tablets; the numbers of reports of somnolence were 10 with the IR solution; 5 with IR tablets; and 5 with CR tablets. All other adverse experiences had fewer than three reports per treatment. Most adverse experiences with any relationship to study medication were those commonly reported with the administration of opioid analgesics.

Clinically significant physical examination abnormalities that were not present pre-study were found in three subjects during the post-study physical examinations -- cold sore on lip (Subject 6), macular rash and decreased knee jerks bilaterally (Subject 9), and inactive psoriasis in neck and elbow and a 5-mm lymph node in left posterior (Subject 21). All electrocardiogram values were normal at screening and at end of study. Although some vital sign changes were statistically significant, they were not clinically significant. Most (93%) of the laboratory values were within normal ranges, and none of the abnormal values were considered clinically significant.

VI. CONCLUSIONS: CR oxycodone 10 mg tablet was equally bioavailable to IR oxycodone 2×5 mg tablets and to IR oxycodone 10 mL oral solution with respect to the extent but not the rate of absorption. The Cmax of the CR tablet was approximately one-third that observed with the IR products. The plasma oxycodone concentrations of CR oxycodone 10 mg tablet were much lower compared to IR oxycodone 2×5 mg tablets and to IR oxycodone 10 mL oral solution for the first 5 hours and much higher after 8 hours. Minor differences in the rate of absorption of IR oxycodone solution and tablets were not clinically significant. All of the treatments were well tolerated by healthy, adult, male volunteers.

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/s/

SRIKANTH C NALLANI
05/15/2015

KEVIN M KRUDYS
05/15/2015

YUN XU
05/15/2015

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**22-272 S-027**	**Brand Name**	**Oxycontin**
OCP Division (I, II, III, IV, V)	**DCP2**	**Generic Name**	**Oxycodone ER Tablets**
Medical Division	**DAAAP**	**Drug Class**	**Opioid**
OCP Reviewer	**Srikanth C. Nallani, Ph.D.**	**Indication(s)**	**Chronic Pain Management**
OCP Team Leader	**Yun Xu, Ph.D.**	**Dosage Form**	**Tablet**
Pharmacometrics Reviewer	**Srikanth C. Nallani, Ph.D., Kevin Krudys, Ph.D.**	**Dosing Regimen**	**BID**
Date of Submission	**12/10/2014**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**5/15/2015**	**Sponsor**	**Purdue Pharma LP**
Medical Division Due Date	**5/15/2015**	**Priority Classification**	**Priority**
PDUFA Due Date	**6/8/2015**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**2**		BE studies in healthy adult volunteers
multiple dose:				
Patients-				
single dose:	**X**	**1**		**In Pediatric Patients**
multiple dose:	**X**	**5**		**In Pediatric Patients**
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				

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ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	**X**	**1**		
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**9**		

On **initial** review of the NDA/BLA application for filing:

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements

No	Content Parameter	Yes	No	N/A	Comment
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)			X	
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?			X	
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			X	
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	X			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	X			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	X			

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
YES

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None Identified.
Purdue Pharma LP submitted a response to the Pediatric Written Request issued by the Agency. In addition, the sponsor has also submitted Oxycontin product label with changes to the Dosage and Administration (Section 2), Specific Populations, Pediatrics (Section 8); Clinical Pharmacology, Pharmacokinetics, Special Populations (Section 12.3). Data from five multiple dose and one single dose pediatric pharmacokinetic studies, and two single dose BA/BE studies in adults were submitted (listed below in the table) to support meeting the exclusivity requirements and the labeling changes proposed. The sponsor also refers to a previously completed safety, PK study (OC96-0602 from 1998) that evaluated relative bioavailability of Oxycontin (original formulation) compared to oral immediate release tablet in pediatric patients on other opioid medications. Additional reference is made to relative bioavailability study of Oxycontin (old and new formulations) with IR oxycodone solution/tablet for bridging PK information (OC94-0101 in attached synopsis, OTR1005, and OTR1502 in table below).

Study (Country)	Study Objective(s)	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID],	No. of Dosed Subjects. (M/F) Type Age: mean (range)
		PEDIATRIC		
OTR1020 (United States and Australia)	To characterize the single and multiple dose PK and safety of reformulated OxyContin tablets (OTR) of various strengths in pediatric patients	Multicenter, multinational, open-label, single- and multiple dose	OTR 10, 15 and 20 mg tablets, po [10 mg: CB-2010-03], [15 mg: CB-2010-04], [20 mg: CB-2009-15]	30 (13M/17F) Pediatric patients 13.5 y (9-16y)
OTR3001 (Multinational) WR Study 3	To evaluate safety, efficacy and pharmacokinetics of OTR in opioid tolerant pediatric patients	Multicenter, multi-national, open-labeled, multiple-dose	OTR 10, 15, 20, 30, or 40 tablets, po [*]	155 (66M/89F) Pediatric patients 13.7 (6 to 16y)
OXP1005 (Multinational) WR Study 1	To characterize the PK and safety of oxycodone in pediatric patients following administration of IR oxycodone hydrochloride solution	Multicenter, multinational, open-label, multiple-dose, dose-ranging	Oxycodone HCl oral solution, 0.05 mg/kg, 0.1 mg/kg and 0.2 mg/kg, po [0.05 mg/kg:CB-2002-11], [0.1 mg/kg:CB-2002-11], [0.2 mg/kg:CB-2002-11]	60 (29M/31F) Pediatric patients 1.14y (birth to 4y)
OXP3003 (Multinational) WR Study 2	To characterize the PK and safety of oxycodone in pediatric patients following administration of IR oxycodone hydrochloride solution 0.1 to 0.2 mg/kg q6h	Multicenter, multinational, randomized, double-blind, multiple-dose, dose-ranging	Oxycodone HCl oral solution, 0.1 and 0.2 mg/kg, po [Oral solution: CB-2002-11],	65 (24M/41F) Pediatric patients 11.4y (5 to 16y)
OXP3004 (Multinational)	To evaluate safety and pharmacokinetics of the approved adult conversion ratio (1:1) from immediate release (IR) oxycodone q6h to OC q12h in pediatric patients	Multicenter, multinational, multiple-dose, dose-ranging	Immediate Release 5 mg capsule, po [CB41, DH61] OC 10 mg tablet , po [DR61, EB3N1]	7 (5M/2F) Pediatric patients 12.6y (7 to 16y)
OC96-0602 (United States)	To compare the relative bioavailabilities following single doses of IR oxycodone and OC in children	Single-center, randomized, open-label, two-way crossover, single-dose	OC 10 mg tablet, po [OC C25] Immediate Release 5 mg, po [IR Oxycodone 962438]	13 (7M/6F) Pediatric patients 9.6y (6 to 12y)
		ADULTS		
OTR1005 (United States)	To characterize the single-dose PK of oxycodone in healthy subjects and assess bioequivalence of OTR relative to OC	Single-center, randomized, open-label, single-dose, two-way crossover study	OTR 40 mg tablets, po [CB-2006-18] OC 40 mg tablets, po [W66G1]	92 (61M/31F) Healthy adult subjects under fasting and under naltrexone blockade, 31y (18-49y)
OTR1502 (United Kingdom)	To determine the bioequivalence of OTR (UK) and OTR (US) tablets; and bioequivalence of OTR(UK) and OC tablets	Single-center, open-label, multiple-dose, three-treatment, three-period, crossover	OTR (UK), OTR (US) and OC 80 mg tablets, po [OTR (UK) 80 mg: PN3369], [OTR (US) 80 mg: PN3374], [OC 80 mg: PN3350]	24 M Healthy adult subjects under naltrexone blockade, 31y (19-45y)

F=female; IR=immediate-release; M=male; OC= original OxyContin Tablets; OTR=reformulated OxyContin Tablets with abuse-deterrent properties; PK=pharmacokinetic(s); po=per os (by mouth); q12h=every 12 hours; WR=written request; y=years.
* Numerous lots were used in Study OTR3001,which was conducted over a 4-year period. For Product IDs please consult CSR OTR3001.

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Srikanth C. Nallani, Ph.D.

Reviewing Clinical Pharmacologist — Date

Kevin Krudys, Ph.D.

Pharmacometrics Team Leader — Date

Yun Xu, Ph.D.

Team Leader/Supervisor — Date

NDA 22272 S-027 Oxycontin response to PWR.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Appendix - Synopses of Past Bioavailability Studies (OC94-0101 and OC96-602):

Study OC94-0101

The following summary of Study OC94-0101 provides relative bioavailability information for OxyContin tablets, IR oxycodone tablets and IR oxycodone oral solution in adult male subjects.

Title: A Single-Dose Pharmacokinetic Study in Healthy Adult Males of one (1) Oxycodone controlled-Release 10 mg Tablet, Two (2) Immediate Release Oxycodone 5 mg Tablets and Immediate Release Oxycodone Oral Solution 10 mg

Study Objectives:

To characterize the pharmacokinetic (PK) profile of oxycodone when administered as a single controlled-release (Original OxyContin™, OC) 10 mg tablet compared with two 5 mg tablets of immediate-release (IR) oxycodone (Endone™) and 10 mL of IR oxycodone oral solution (Roxicodone™) 5mg/5 mL given as a single dose.

Methods and Treatments:

This was a single-center, single-dose, open-label, randomized, three-way crossover PK study in healthy adult males.

Out of 22 enrolled male subjects (20 to 35 years of age), none discontinued. Subjects 1, 7 and 12 did not have blood samples drawn in Treatment Period 3 and were excluded from the pharmacokinetic analyses; however they were included in the safety analyses.

One 10 mg dose of each oxycodone formulation was administered orally with 6 ounces (180 mL) of water to subjects in the fasted state; administrations were separated by a washout period of at least 7 days. The use of other concomitant medications during this trial was discouraged, unless necessary to treat AEs.

Blood Sampling for Pharmacokinetics:

Blood samples were taken for 36 hours after drug administration. Harvested plasma samples were analyzed for oxycodone using a validated gas chromatography / mass spectrometric method. Pharmacokinetic metrics included AUCt0-36hrs, AUCinf, Cmax and Tmax.

Results:

The PK metrics after single 10 mg oral administration of each of the three formulations in the fasted state are presented in Tables 2, 3, and 4.

Table 2 Relative Bioavailability of Oxycodone: Summary of Point Estimates of PK Metrics and 90% Confidence Intervals of original OxyContin Tablet (OC) and Immediate Release Oxycodone (IR) Tablets - Study OC94-0101

PK Metric	Geometric Mean		Ratio (%)	(90% CI)
	OC (Test) 10 mg	IR (Reference) 2x5 mg	Test / Reference	
AUC0-36hr (ng.hr/mL)	111.7	111.9	99.7	(94.9 – 104.8)
AUCinf (ng.hr/mL)	113.4	111.9	101.2	(96.3 – 106.4)
Cmax (ng/mL)	9.2	29.0	31.5	(27.7 – 35.9)
Tmax (hr)[a]	2.3	0.8	NA	NA

Source: CSR OC94-0101, Table 3.4.2

[a] Arithmetic mean; NA = Not Applicable.

Table 3 Relative Bioavailability of Oxycodone: Summary of Point Estimates of PK Metrics and 90% Confidence Intervals of Original OxyContin Tablet (OC) and IR Oxycodone Solution - Study OC94-0101

PK Metric	Geometric Mean		Ratio (%)	(90% CI)
	OC (Test) 10 mg	IR (Reference) Solution (10 mg/10 mL)	Test / Reference	
AUC0-36hr (ng.hr/mL)	111.7	109.3	102.7	(97.7 – 107.9)
AUCinf (ng.hr/mL)	113.4	109.3	104.3	(99.2 – 109.6)
Cmax (ng/mL)	9.2	26.0	35.1	(30.8 – 40.1)
Tmax (hr)[a]	2.3	0.8	NA	NA

Source: CSR OC94-0101, Table 3.4.2

[a] Arithmetic mean; NA = Not Applicable.

Table 4 Relative Bioavailability of Oxycodone: Summary of Point Estimates of PK Metrics and 90% Confidence Intervals of Immediate Release Oxycodone Tablet (IR) and IR Oxycodone Solution - Study OC94-0101

PK Metric	Geometric Mean		Ratio (%)	(90% CI)
	IR (Test) 2 x 5 mg	IR (Reference) Solution (10 mg/10 mL)	Test / Reference	
AUC0-36hr (ng.hr/mL)	111.9	109.3	103.0	(98.0 – 108.2)
AUCinf (ng.hr/mL)	111.9	109.3	103.0	(98.0 – 108.3)
Cmax (ng/mL)	29.0	26.0	111.5	(97.8 – 127.0)
Tmax (hr)[a]	0.8	0.8	NA	NA

Source: CSR OC94-0101, Table 3.4.2

[a] Arithmetic mean; NA = Not Applicable.

Conclusions:

Following oral administration in the fasted state, the OC 10 mg tablet was equally bioavailable to IR oxycodone 2x5 tablets and to IR oxycodone 10 mL oral solution with respect to the extent but not the rate of absorption. The Cmax of the controlled-release tablet was approximately one-third that observed with the IR products. All three treatments were well tolerated. There were no unexpected or clinically relevant safety findings. Overall, the safety profile of all was typical of that expected from oxycodone administration to healthy adult subjects. None of the adverse experiences were serious or severe. Dizziness or nausea was reported more frequently in the IR oxycodone tablets and solution than the controlled-release original OxyContin.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Synopsis of Study OC96-602:

2. SYNOPSIS

Name of Company: Purdue Pharma L.P.	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: OxyContin® (oxycodone HCl controlled-release) Tablets	Referring to Part IV of the Dossier	
Name of Active Ingredient: Oxycodone HCl	Volume: Page:	

Title of the Study: An Open-Label, Randomized, Crossover Comparison of Plasma Oxycodone Concentrations in Children After the Administration of Single Doses of Controlled-Release Oxycodone (OxyContin®) and Immediate-Release Oxycodone

Investigator: Jeffrey L. Blumer, PhD, MD

Publication (Reference): None

Study Dates:	**Study Status:**	**Phase of Development:**
11-Apr-1997 to 16-Nov-1998	Completed	Phase 1

Objectives: To compare the relative bioavailabilities following single doses of immediate-release (IR) oxycodone and controlled-release (CR) oxycodone (OxyContin®) in children.

Methodology: A single-dose, open-label, randomized, 2-period crossover pharmacokinetic (PK) study in children of both sexes aged 5 to 12 years.

Number of Subjects: Planned: 24 subjects (to complete 20). Enrolled: 13 subjects (results from the first 11 completed subjects provided sufficient study data, and so no additional subjects were enrolled). Completed: 11 subjects. All 13 subjects had valid PK data from at least 1 treatment and were considered evaluable for pharmacokinetic analysis. However, 2 subjects discontinued after completing the first period (subject 4 received only OxyContin® 10 mg, and subject 5 received only IR oxycodone 5 mg). All 13 subjects were included in the safety analysis.

Subject Demographics: Seven males and 6 females; 5 white and 8 black; all pediatric subjects, with a mean age of 9.6 (range, 6–12) years.

Diagnosis and Criteria for Inclusion: Children of both sexes aged 5 to 12 years who were hospitalized and receiving opiates other than oxycodone, who were expected to continue to need opiates for at least 4 days, and who met the inclusion/exclusion criteria specified in the protocol.

Drugs Supplied:

Product	Route	Dosage Form	Unit Strength	Lot Number
OxyContin®	Oral	Tablet	10 mg	C25
IR oxycodone	Oral	Tablet	5 mg	962438

Treatment Comparisons:

Test Treatment	Reference Treatment
OxyContin® 10 mg (CR)	IR oxycodone 5 mg (IR)

Treatment Schedule: One dose of each oxycodone formulation, separated by a washout period of at least 48 hours. Blood samples were taken for 12 hours after IR administration and for up to 36 hours after the CR (OxyContin®) administration.

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Criteria for Evaluation:

Pharmacokinetic Metrics: Plasma concentrations of oxycodone, oxymorphone, and noroxycodone and the following metrics: area under the curve to the last quantifiable plasma concentration (AUC_t), area under the curve from zero to infinity (AUC_∞), maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), apparent terminal phase half-life ($t_{½}$[elim]), and mean residence time (MRT). AUC_∞ is an index of total exposure and C_{max} is an index of peak exposure to the study drug or metabolite.

Safety: Reports of adverse events, clinical laboratory tests, vital signs, and physical examinations.

Bioanalytical Method: Plasma concentrations of oxycodone, oxymorphone, and noroxycodone were quantified by gas chromatography using negative chemical ionization mass spectrometry.

Statistical Methods: Log-transformed AUC_t, AUC_∞, and C_{max} values for oxycodone for test (OxyContin® 10 mg) and reference (IR oxycodone 5 mg) treatments were analyzed using an analysis of variance (ANOVA) model with terms for sequence, subject (sequence), period, and treatment. Relative bioavailability was assessed by comparing primary metrics (AUCt, AUC∞, and C_{max} [test vs reference treatment]) using the previously mentioned ANOVA model for a 2-way crossover design. Confidence intervals (90%) were estimated around ratios (test/reference) of geometric least squares means derived from logarithmic-transformed values of AUC_t and AUC_∞. Relative bioavailability was summarized by the percent ratios of the means for AUC_t and AUC_∞ with respect to the reference treatment, and the lower and upper limits of the 90% confidence interval were examined. In addition, summary statistics for AUC_t, AUC_∞, and C_{max} were presented by treatment for the parent compound and its metabolites. Secondary metrics (t_{max}, $t_{½}$, MRT) were presented as mean and standard deviation (SD), CV, minimum and maximum. Per protocol, after the completion of the first 13 subjects (with 11 completing both treatments), pharmacokinetic analysis was performed, which confirmed that the ratio of geometric mean AUC_∞ was within the CI of 70% to 143% (or as specified in the protocol as a difference of ±30%). As a result, the decision was made to stop study enrollment. Vital signs, laboratory tests, and physical examination results were tabulated, with abnormal values listed. Descriptive shift tables for each laboratory parameter and summary tables of adverse events by body system were prepared.

Results:

Pharmacokinetic: OxyContin® (CR oxycodone) produced relatively rapid increases to initial early peak plasma concentrations for oxycodone and its metabolites, followed by measurable concentrations that were sustained beyond 24 hours. IR oxycodone produced similar early peak plasma concentrations for oxycodone and metabolites, but plasma concentrations declined more rapidly. Plasma oxymorphone concentrations were negligible. The 90% CI of the geometric mean ratio of the test treatment (OxyContin®) to the reference treatment (IR oxycodone) in terms of total exposure (AUC_∞) to the study drug was within 80% to 125%. The dose-adjusted peak exposure (C_{max}) of OxyContin® was approximately one half that of IR oxycodone. Similarly, mean values of $t_{½}$ and MRT for parent oxycodone following IR oxycodone administration were approximately half, while t_{max} was two thirds those following OxyContin® administration. See Tables 2A and 2B.

Safety: Overall, 9 (69%) out of 13 subjects experienced 1 or more adverse events during the study. Over the course of the study, 5 (42%) of 12 subjects experienced adverse events during or after receiving IR oxycodone, while 7 (58%) of 12 subjects experienced adverse events during or after receiving OxyContin® (Table 2C). The most common adverse event was fever (IR oxycodone, 25%; OxyContin®, 33%), which was expected in a postoperative population and was not regarded as drug-related (Table 2D). All other adverse events occurred in 1 or 2 subjects each. Adverse events judged by the investigator to be drug-related (seen in only 4 subjects when receiving OxyContin®) were pruritus, nausea, and vomiting. There was no apparent difference between IR oxycodone and OxyContin® in the incidence or type of adverse events reported in this 2-way crossover study. No deaths or other serious adverse events occurred during the study. One subject (subject 4, oxycodone) discontinued prematurely due to an adverse event (moderate pruritus). One subject (subject 5, IR oxycodone) discontinued prematurely due to inability to obtain IV access. No safety concerns were raised from the results of laboratory tests, vital sign measurements, or physical examinations. In conclusion, no unexpected safety concerns for oxycodone, as either the IR or the CR formulation, were suggested by the present results.

Conclusions: For the parent compound (oxycodone), the 90% confidence interval around the dose-adjusted geometric mean ratio of the test treatment (OxyContin®) to the reference treatment (IR oxycodone) in terms of total exposure (AUC_∞) to the study drug was within 80% to 125%. Due to differences in the dosage forms, for oxycodone, the dose-adjusted peak exposure (C_{max}) of OxyContin® was approximately one half that of IR oxycodone. Mean values of t_{max}, $t_{½}$, and MRT (all not dose-adjusted) for parent oxycodone following IR oxycodone administration were approximately half those following OxyContin® administration. These PK results in pediatric subjects following administration of OxyContin® and IR oxycodone are consistent with the characteristics of CR and an IR dosage forms, respectively. The PK profiles of noroxycodone and oxymorphone were similar to that of the parent compound. Noroxycodone levels were approximately one half that of the parent compound, and oxymorphone levels were negligible. As noroxycodone possesses 1/100th of the analgesic potency of oxycodone, its contribution to analgesia is not clinically meaningful. Oxymorphone, with 10 times the potency of oxycodone, contributes 10% to 15% of the analgesia of oxycodone. No unexpected safety concerns for oxycodone in pediatric subjects aged 6 to 12 years, administered as either the IR or the CR formulation, were suggested by the present results.

Date of the Report: 16-May-2001

TABLE 2A.

Summary of Oxycodone Pharmacokinetic Metrics (N = 13 [a]), Not Dose-Adjusted

	Arithmetic Mean (SD)	
PK Metric	**IR Oxycodone** (5 mg)	**OxyContin®** (10mg)
AUCt (ng·h/mL)	83.2 (43.0)	201.0 (143.0)
AUC_∞ (ng·h/mL)	81.3 (39.1)[b]	174.6 (91.1)[c]
C_{max} (ng/mL)	20.2 (8.3)	22.0 (13.0)
t_{max} (h)	2.1 (0.9)	3.3 (1.7)
$t_{½}$ (h)	2.6 (1.0)[c]	5.2 (1.8)[c]
MRT (h)	4.2 (1.2)	8.7 (1.9)

[a]Thirteen subjects enrolled, with 2 subjects discontinuing after completing the first period. Subject 4 received only OxyContin®, and subject 5 only received IR oxycodone.
[b]Ten subjects.
[c]Eleven subjects.
Cross-references: Table 14.4.4; Appendix 16.2.6.1.

TABLE 2B.

Summary of Dose-Adjusted[a] AUC_t and AUC_∞ Means and Confidence Intervals for Oxycodone (N = 11 [b])

PK Metric	Geometric Least Squares Mean		Ratio (%)[c]	90% CI[d]
	IR Oxycodone (5 mg)	OxyContin® (10 mg)		
AUC_t (ng·h/mL)	75.7	78.7	104	87 to 126
AUC_∞ (ng·h/mL)	74.3	72.5	98	84 to 124

[a]Plasma concentrations for OxyContin® were dose-adjusted from 10 mg to 5 mg.
[b]Thirteen subjects enrolled, with 2 subjects discontinuing after completing the first period. Subject 4 received only OxyContin®, and subject 5 only received IR oxycodone.
[c]Ratio (%) (test/reference) of least squares means (ANOVA) derived from logarithmic-transformed values of AUCt and AUC.
[d]Ninety-percent confidence interval (CI) around the least squares means ratio.
Cross-references: Table 14.4.5; Appendix 16.2.6.1.

TABLE 2C.

Subject Incidence and Number of Adverse Events by Treatment

	Period 1		Period 2		Combined Periods	
	IR Oxy-codone (N = 7)	OxyContin® (N = 6)	IR Oxy-codone (N = 5)	OxyContin® (N = 6)	IR Oxy-codone (N = 12)	OxyContin® (N = 12)
No. (%) of subjects	4 (57)	3 (50)	1 (20)	4 (67)	5 (42)	7 (58)
No. of AEs	7	5	2	6	9	11

AE = adverse event.
Cross-references: Table 14.3.1.1; Appendix 16.2.7.1.

TABLE 2D.

Adverse Events That Occurred in 1 or More Subjects, by Decreasing Frequency

	Number (%) of Subjects					
	Period 1		Period 2		Combined Periods	
Adverse Event	IR Oxy-codone (N = 7)	OxyContin® (N = 6)	IR Oxy-codone (N= 5)	OxyContin® (N = 6)	IR Oxy-codone (N = 12)	OxyContin® (N = 12)
Fever	2 (29)	2 (33)	1 (20)	2 (33)	3 (25)	4 (33)
Constipation	0	1 (17)	1 (20)	0	1 (8)	1 (8)
Vomiting	2 (29)	0	0	1 (17)	2 (17)	1 (8)
Vaginitis	1 (14)	0	0	1 (17)	1 (8)	1 (8)
Pruritus	0	1 (17)	0	1 (17)	0	2 (17)
Hypotension	1 (14)	0	0	0	1 (8)	0
Nausea	0	1 (17)	0	0	0	1 (8)
Electrolyte abnormality	0	0	0	1 (17)	0	1 (8)
Epistaxis	1 (14)	0	0	0	1 (8)	0

Cross-references: Table 14.3.1.1; Appendix 16.2.7.1.

Table 3 Relative Bioavailability of Oxycodone: Summary of Point Estimates of PK Metrics and 90% Confidence Intervals of Original OxyContin Tablet (OC) and IR Oxycodone Solution - Study OC94-0101

PK Metric	Geometric Mean		Ratio (%)	(90% CI)
	OC (Test) 10 mg	IR (Reference) Solution (10 mg/10 mL)	Test / Reference	
AUC0-36hr (ng.hr/mL)	111.7	109.3	102.7	(97.7 – 107.9)
AUCinf (ng.hr/mL)	113.4	109.3	104.3	(99.2 – 109.6)
Cmax (ng/mL)	9.2	26.0	35.1	(30.8 – 40.1)
Tmax (hr)[a]	2.3	0.8	NA	NA

Source: CSR OC94-0101, Table 3.4.2
[a] Arithmetic mean; NA = Not Applicable.

Table 4 Relative Bioavailability of Oxycodone: Summary of Point Estimates of PK Metrics and 90% Confidence Intervals of Immediate Release Oxycodone Tablet (IR) and IR Oxycodone Solution - Study OC94-0101

PK Metric	Geometric Mean		Ratio (%)	(90% CI)
	IR (Test) 2 x 5 mg	IR (Reference) Solution (10 mg/10 mL)	Test / Reference	
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AUCinf (ng.hr/mL)	111.9	109.3	103.0	(98.0 – 108.3)
Cmax (ng/mL)	29.0	26.0	111.5	(97.8 – 127.0)
Tmax (hr)[a]	0.8	0.8	NA	NA

Source: CSR OC94-0101, Table 3.4.2
[a] Arithmetic mean; NA = Not Applicable.

Conclusions:

Following oral administration in the fasted state, the OC 10 mg tablet was equally bioavailable to IR oxycodone 2x5 tablets and to IR oxycodone 10 mL oral solution with respect to the extent but not the rate of absorption. The Cmax of the controlled-release tablet was approximately one-third that observed with the IR products. All three treatments were well tolerated. There were no unexpected or clinically relevant safety findings. Overall, the safety profile of all was typical of that expected from oxycodone administration to healthy adult subjects. None of the adverse experiences were serious or severe. Dizziness or nausea was reported more frequently in the IR oxycodone tablets and solution than the controlled-release original OxyContin.

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/s/

SRIKANTH C NALLANI
02/04/2015

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02/04/2015