CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 022-272
Drug Name:	OxyContin (oxycodone hydrochloride) tablet
Indication(s):	Management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate
Applicant:	Purdue Pharma L.P.
Date(s):	Letter date: December 10, 2014, PDUFA date: June 8, 2015
Review Priority:	Priority
Biometrics Division:	II
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Keywords: NDA review, Pediatric Written Request (PWR), Clinical Studies

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1. EXECUTIVE SUMMARY

Purdue Pharma L.P. has submitted a supplemental NDA for OxyContin to apply for pediatric exclusivity and approval for updating the labeling to include the pediatric studies results in response to the Pediatric Written Request (PWR) #3, Amendment #2, issued on November 14, 2011. OxyContin is an extended-release (ER) oral formulation of oxycodone hydrochloride (HCl) and currently indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The applicant submitted three studies to fulfill the requirement of the PWR. This review focuses on the efficacy study (Study 2) requested by the PWR. Based on my review, the efficacy study was not prospectively designed or powered to demonstrate superiority over placebo, and as such could not provide evidence for efficacy with appropriate statistical significance for the proposed pediatric indication.

The submitted efficacy study (Study OXP3003) was a multicenter, double-blind, randomized, placebo-controlled, dose-ranging study designed to evaluate the pharmacokinetics, safety, and efficacy of Oxy Pediatric Liquid 1 mg/mL (oxycodone HCl oral solution) in patients aged 5 to 16 years old. Patients were opioid-naïve at study entry or pre-operatively and had moderate to severe pain requiring opioid analgesics for at least 2 days. At randomization, a total of 68 eligible patients were stratified into two groups (5 to < 12 years and 12 to ≤ 16 years) and randomly assigned in a 3:3:2 ratio to receive Oxy Pediatric Liquid 0.1 mg/kg, Oxy Pediatric Liquid 0.2 mg/kg, or placebo. Patients were administered Oxy Pediatric Liquid or placebo every 6 hours for a total of 4 to 5 doses. All patients were permitted to receive patient controlled analgesia (PCA) or oral morphine sulfate as supplemental pain medication. Efficacy assessments included supplemental pain medication usage and pain intensity. The study was powered for pharmacokinetics evaluation and adverse events detection.

Neither the protocol nor the Statistical Analysis Plan (SAP) clearly specified the primary or secondary efficacy endpoints for treatment comparisons. The study report presented analysis results for multiple variables evaluating pain scores and supplemental pain medication usage, respectively. A statistical test for dose response was performed on each of these efficacy variables using the Jonckheere-Terpstra approach. No adjustment for multiplicity was planned or performed. The full efficacy analysis population included the 65 patients who received at least one dose of study medication and had at least one subsequent efficacy evaluation. Efficacy outcomes were not collected for the discontinued patients after they stopped the randomized treatment pre-maturely. There was no imputation method proposed for missing efficacy assessments.

Dose response was not established with statistical significance at a one-sided level of 0.025 or two-sided level of 0.05 for most of the efficacy variables. Nevertheless, it was observed that all of these efficacy variables were numerically in favor of oxycodone against placebo. Patients randomized to placebo reported slightly higher pain on average and used more supplemental pain medications during the study.

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In summary, the efficacy study was not prospectively designed or powered to show superiority over placebo, and as such it could not provide evidence of efficacy with the usually required level of statistical significance.

2. INTRODUCTION

2.1 Overview

OxyContin is an extended-release (ER) oral formulation of oxycodone hydrochloride (HCl) and currently indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Purdue is submitting this efficacy supplemental NDA in support of updating the OxyContin labeling to include the pediatric study results in accordance with the November 14, 2011 Written Request (WR) #3, Amendment #2.

An initial PWR was issued in 1998. Thereafter, the division and the applicant have discussed revisions of the PWR on multiple occasions. The latest version was PWR #3, Amendment #2 issued in November 2011 for both NDA 020553 and NDA 022272, which requested the following three studies:

> Study 1: Pharmacokinetic (PK) study of an age-appropriate formulation of oxycodone in opioid-naïve patients from birth up to less than four years of age.
>
> Study 2: Efficacy, safety, and PK study of an age-appropriate formulation of immediate release (IR) oxycodone in opioid-naïve patients from five years up to no more than 16 years of age.
>
> Study 3: Open-label safety and PK study of an oxycodone controlled-release tablet in opioid tolerant patients from six years to no more than 16 years of age with moderate to severe pain requiring around-the-clock opioid therapy for an extended period of time.

The PWR specified that Study 2 should be active or placebo-controlled, double-blind, dose-ranging, in-patient, superiority study evaluating the pharmacokinetics (using a population pharmacokinetic approach) of oxycodone after single and repeated dosing (preferably at a steady state) of an age-appropriate population. This study should also include assessment of efficacy (i.e., pain intensity evaluations and rescue medication usage) and safety (i.e., adverse events). The study should enroll sufficient number of pediatric patients to demonstrate a clinically meaningful difference in pain intensity between active and comparator. The PWR further requested that confidence intervals and significance test for differences between treatment groups in pain scores and rescue medication use be computed, variability of patients within treatment groups be characterized.

In the advice letter dated May 14, 2010, the division stated that completed Study OXP1005 and Study OXP3003 may be used as Studies 1 and 2, respectively. The applicant subsequently completed Study OTR3001 to fulfill Study 3 requirements. Both Study OXP1005 and Study

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OTR3001 were open-label studies. Study OXP3003 was a randomized, double-blind, placebo-controlled dose-ranging study. This statistical review focuses on Study OXP3003.

This review mainly evaluates whether the updated labeling was supported by the study data.

2.2 Data Sources

The efficacy data submitted for Study OXP3003 can be found at \\Cdsesub1\evsprod\NDA022272\0224\m5\datasets\oxp3003.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The applicant submitted study SDTM tabulation datasets and AdaM analysis datasets in CDISC format. The datasets and define files were of acceptable quality, and were sufficient for validating study results.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study OXP3003 was a multicenter, double-blind, randomized, placebo-controlled, dose-ranging study designed to evaluate the pharmacokinetics, safety, and efficacy of Oxy Pediatric Liquid 1 mg/mL (oxycodone HCl oral solution) in patients aged 5 to 16 years old. Patients were opioid-naïve at study entry or pre-operatively and had moderate to severe pain requiring opioid analgesics for at least 2 days. The primary objectives of this study stated in the protocol were to characterize in-patients the pharmacokinetics and safety of Oxy Pediatric Liquid 1 mg/mL. The secondary objective was to assess the efficacy of Oxy Pediatric Liquid 1 mg/mL compared with placebo. The study started enrollment in January 2003 and completed in April 2004.

The protocol stated that sufficient number of patients would be enrolled to achieve 100 PK evaluable patients with approximately equal number of patients in the 5 to <12 year old age group and 12 to ≤16 year old age group. At randomization, eligible patients were stratified into the two age groups and randomly assigned in a 3:3:2 ratio to receive 0.1 mg/kg Oxy Pediatric Liquid, 0.2 mg/kg Oxy Pediatric Liquid, or placebo. Patients were administered Oxy Pediatric Liquid or placebo every 6 hours for a total of 4 to 5 doses. In the case of post-operative patients, study treatment could begin when the patients were ready to take oral medication. Dosing was based on the weight of the patients in this study. 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 the double-blind treatment.

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Efficacy assessments included supplemental pain medication usage and pain intensity. Pain intensity (i.e., pain right now) was measured using the Faces Pain Scale-Revised (FPS-R) prior to and 1 hour after each dose, with additional recordings at 0.5, 1, 2, and 3 hours after the first dose. These pain intensities were recorded as scheduled pain assessments. Additionally, unscheduled pain intensity scores were recorded based an 11-point Numeric Rating Scale when nurse-administered PCA was given. All doses of PCA morphine and other supplemental pain medications were to be recorded in the case report form.

According to the applicant, the study was powered for PK evaluation and adverse events detection instead of efficacy demonstration.

3.2.2 Statistical Methodologies

Neither the protocol nor the Statistical Analysis Plan (SAP) clearly specified the primary or secondary efficacy endpoints for treatment comparisons. The study report presented analysis results for multiple variables evaluating pain scores and supplemental pain medication usage, respectively. A statistical test for dose response was performed on each of these efficacy variables using the Jonckheere-Terpstra approach. No adjustment for multiplicity was planned or performed. The full efficacy analysis population included the 65 patients who received at least one dose of study medication and had at least one subsequent efficacy evaluation. Efficacy outcomes were not collected for the discontinued patients after they stopped the randomized treatment pre-maturely. There was no imputation method proposed for missing efficacy assessments.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The protocol stated that sufficient number of patients would be enrolled to achieve 100 PK evaluable patients. However, according to the applicant, Study OXP3003 was terminated early due to reasons unrelated to safety and efficacy. A total of 68 patients were randomized. Three patients discontinued the study early prior to receiving the study treatments. The full analysis population included 65 patients, 19 receiving placebo, 24 receiving Oxy Pediatric Liquid 0.1 mg/kg, and 22 receiving Oxy Pediatric Liquid 0.2 mg/kg (Table 1). Overall, approximately 17% of the patients discontinued the double-blind period early. The primary reason for discontinuation was subject's choice. The discontinuation rate of the Oxy Pediatric Liquid 0.2 mg/kg group was the lowest among the three treatment groups while the other two treatment groups had similar discontinuation rates. The dropout pattern was similar between the two age groups.

The demographic and baseline characteristics were comparable across treatment groups (Table 2). About 40% of the patients were less than 12 years old. The majority of the patients were female (63%). The median pre-dose pain score of the patients randomized to Oxy Pediatric Liquid 0.2 mg/kg was 2.5, notably lower than those of the other two groups. The median pre-

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dose pain scores of the patients randomized to placebo and Oxy Pediatric Liquid 0.1 mg/kg were both 4.

Table 1: Subject Disposition

Age Group	Placebo	0.1 mg/kg	0.2 mg/kg	Total
All patients	**N=19**	**N=24**	**N=22**	**N=65**
Completed, n (%)	15 (79)	18 (75)	21 (95	54 (83)
Discontinued, n(%)	4 (21)	6 (25)	1(5)	11 (17)
Adverse event	1 (5)	1 (4)	0	2 (3)
Subject's choice	3 (16)	3 (13)	1 (5)	7 (11)
Administrative	0	2 (8)	0	2 (3)
Age group: 5 to <12 years	**N=7**	**N=10**	**N=9**	**N=26**
Completed, n (%)	6 (86)	7 (70)	9 (100)	22 (85)
Discontinued, n(%)	1 (14)	3 (30)	0	4 (15)
Adverse event	0	1 (10)	0	1 (4)
Subject's choice	1 (14)	1 (10)	0	2 (8)
Administrative	0	1 (10)	0	1 (4)
Age group: 12 to ≤16 years	**N=12**	**N=14**	**N=13**	**N=39**
Completed, n (%)	9 (75)	11 (79)	12 (92)	32 (82)
Discontinued, n(%)	3 (25)	3 (21)	1 (8)	7 (18)
Adverse event	1 (8)	0	0	1 (3)
Subject's choice	2 (17)	2 (14)	1 (8)	5 (13)
Administrative	0	1 (7)	0	1 (3)

Source: Clinical study report, Table 14.1.1

Table 2: Summary of Demographics and Baseline Characteristics

	Placebo (N=19)	0.1 mg/kg (N=24)	0.2 mg/kg (N=22)	Total (N=65)
Mean age (SD)	12 (3)	11 (3)	11 (4)	11 (3)
Age group, n (%)				
5 to <12 years	7 (37)	10 (42)	9 (41)	26 (40)
12 to ≤16 years	12 (63)	14 (58)	13 (59)	39 (60)
Gender, n (%)				
Male	7 (37)	9 (37)	8 (36)	24 (37)
Female	12 (63)	15 (63)	14 (64)	41 (63)
Race, n (%)				
White	16 (84)	16 (67)	16 (73)	48 (74)
Black	1 (5)	3 (12)	1 (4)	5 (8)
Asian	1 (5)	1 (4)	0	2 (3)
Other	1 (5)	4 (17)	5 (23)	10 (15)
Weight (kg)				
Mean (SD)	43 (14)	43 (19)	44 (23)	44 (19)
Baseline pain intensity*				
Mean (SD)	3.5 (2.6)	3.3 (2.8)	2.8 (2.5)	3.2 (2.6)
Median	4	4	2.5	3.5
(Min, Max)	(0, 9)	(0, 10)	(0, 8)	(0, 10)

Source: Clinical study report, Table 14.1.3; SD: standard deviation
*: derived using the pre-dose FPS-R pain scores from the ADXP dataset.

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3.2.4 Results and Conclusions

The applicant provided a table of summary of efficacy results with p-values from the Jonckheere-Terpstra test for non-increasing dose response (Table 3). Confidence intervals for the treatment differences were not submitted. I was able to reproduce these results and noted that the p-values provided in the table are all one-sided.

Denote T1, T2, and T3 as the median of an efficacy variable for placebo, Oxy Pediatric Liquid 0.1 mg/kg, and Oxy Pediatric Liquid 0.2 mg/kg, respectively. The null hypothesis $T1=T2=T3$ was tested against the alternative of non-increasing order, that is, $T1 \geq T2 \geq T3$, with at least one strict inequality. The applicant compared the left-tail p-value from the Jonckheere-Terpstra test to the significance level of 0.05 to determine if there was a statistically significant dose response for each efficacy variable and thus claimed that most of the efficacy variables demonstrated dose response with statistical significance. In particular, the applicant claimed that "During the 6 hour interval following first dose, pain scores were statistically significantly lower in the active treatment groups compared to the placebo group (p=.034)" in Section 14 of the labeling.

To be comparable to a hypothesis testing based on a two-sided significance level of 0.05, which is the usual standard for efficacy comparisons, a statistical test based on a one-sided p-value should be compared to the threshold of 0.025. Thus, only the tests for dose responses in total PCA morphine usage excluding the first dosing interval and the maximum overall pain score reached nominal significance at the level of 0.025. However, since there was no multiplicity adjustment, the overall type-I error was not controlled and it is difficult to interpret these p-values. Nevertheless, all the analyses results were numerically in favor of oxycodone in comparison to placebo. Overall, placebo patients reported higher pain scores and used more supplemental pain medications than the two active treatment groups.

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Table 3: Summary of Efficacy Analysis Results

	Dose Interval	Placebo Mean (SD)	0.1 mg/kg Mean (SD)	0.2 mg/kg Mean (SD)	*P* value
PCA Morphine	0 - <6 hours	0.19 (0.15)	0.11 (0.11)	0.11 (0.10)	.083
	Overall, excl 0-<6 hours	0.58 (0.52)	0.25 (0.27)	0.27 (0.30)	.017
	Overall, incl 0-<6 hours	0.69 (0.64)	0.34 (0.35)	0.37 (0.38)	.047
Total Opioid	0 - <6 hours	0.20 (0.16)	0.11 (0.11)	0.12 (0.10)	.096
	Overall, excl 0-<6 hours	0.60 (0.52)	0.27 (0.28)	0.33 (0.35)	.040
	Overall, incl 0-<6 hours	0.71 (0.64)	0.35 (0.36)	0.44 (0.44)	.077
Acetaminophen	0 - <6 hours	0.26 (1.13)	0	0	.096
	Overall, excl 0-<6 hours	5.25 (10.94)	1.44 (3.71)	0.47 (2.14)	.032
	Overall, incl 0-<6 hours	4.68 (10.34)	1.32 (3.57)	0.45 (2.09)	.039
Pain Score	Mean, 0-<6 hours	4.1 (1.37)	3.3 (2.07)	3.1 (2.50)	.034
	Max, 0-<6 hours	6.8 (2.12)	4.8 (2.79)	5.4 (3.05)	.047
	1 hr post dose, excl 0-<6	3.5 (1.30)	2.8 (2.07)	2.8 (2.67)	.038
	1 hr post dose, incl 0-<6	3.9 (1.28)	2.9 (2.02)	3.0 (2.54)	.031
	6 hrs post dose, excl 0-<6	3.5 (1.35)	3.0 (2.27)	3.2 (2.87)	.195
	6 hrs post dose, incl 0-<6	4.2 (1.54)	2.9 (2.23)	3.2 (2.81)	.033
	Mean, Overall	4.1 (1.09)	3.2 (2.00)	3.2 (2.50)	.030
	Max, Overall	7.5 (2.01)	6.0 (2.63)	5.7 (2.97)	.018

*Based on Jonckheere-Terpstra test. Smaller p-values are evidence in favor of nonincreasing dose response.

Source: Clinical Study Report, Table 11; SD: standard deviation

The average pain score and total supplemental opioid usage are depicted by dose intervals for each treatment group in Figures 1 and 2, respectively. For all treatment groups, the average pain was not high at baseline and well-controlled during the study (Figure 1). Since all patients were on supplemental PCA throughout the study, it might cause difficulties to show analgesic dose response among treatments. Figure 1 shows that the separations among the pain curves for the treatments are small. In contrast, there is notable separation of the curve for the total supplemental opioid usage of the placebo patients from those of the oxycodone treated patients (Figure 2). Placebo-treated patients requested more supplemental opioids than oxycodone-treated patients throughout all dosing intervals. The two oxycodone-treated groups were similar in terms of pain scores and supplemental opioid usage. The total supplemental opioids usage included both PCA and non-PCA opioids usage. PCA morphine was the primary supplemental pain medication during the treatment period. Separate illustrations of PCA, non-PCA opioid and acetaminophen usages are further provided in the Appendix Figures 1, 2 and 3.

The pain scores analyzed were the average of the scheduled pain assessments and those recorded before each PCA administration during the corresponding dose interval. Analyses utilizing only scheduled pain scores produced similar results. The mean scores of scheduled and unscheduled pain assessments are depicted for each treatment by dose intervals in the Appendix Figures 4 and 5, respectively. Only several patients in each treatment group had unscheduled pain scores.

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Figure 1: **Pain Assessments by Dose Interval**

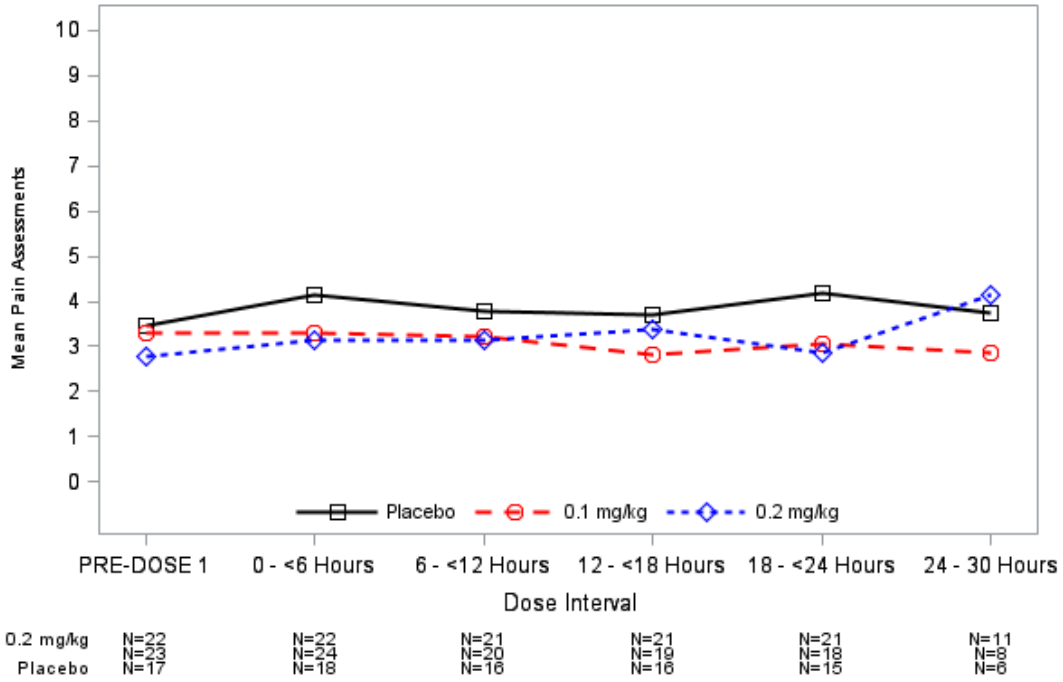
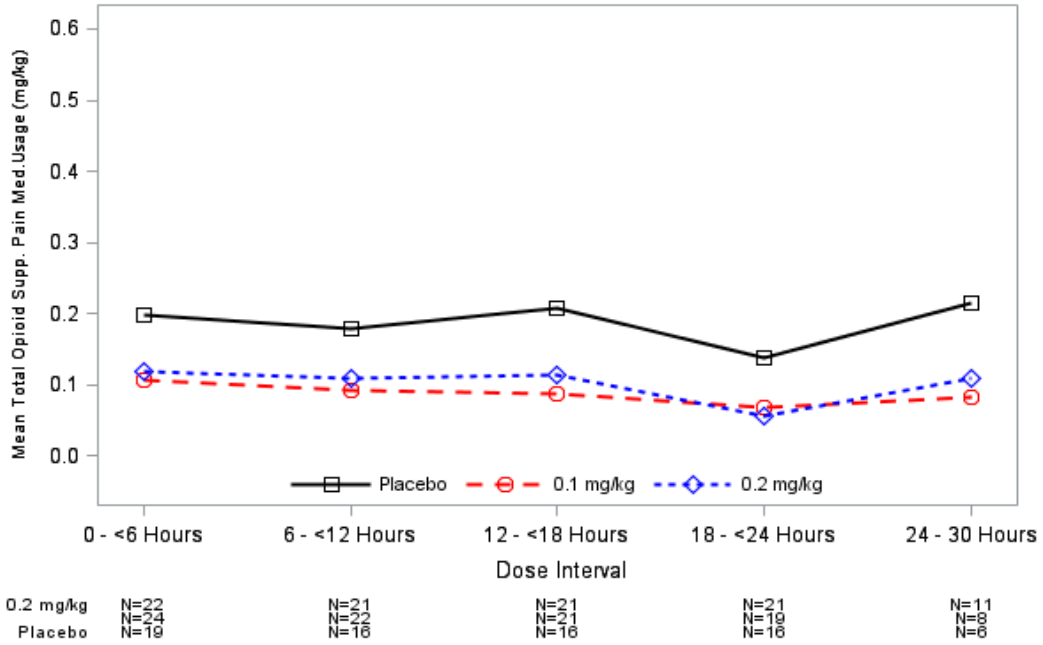


Figure 2: **Total Supplemental Opioids by Dose Interval**



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3.3 Evaluation of Safety

The evaluation of the safety data was conducted by the clinical reviewer, Dr. Javier Muniz. Please refer to Dr. Muniz's review for detailed information regarding the adverse event profile.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The applicant presented subgroup summaries for Study OXP3003 in the Summary of Clinical Efficacy (Module 2.7.3) within this submission. I also conducted subgroup descriptive statistics and produced some plots (see below) for visual comparisons by dose intervals. Findings from the subgroup analyses were generally consistent with those observed in the overall population.

4.1 Gender, Age and Race

Subgroup analyses for race were not conducted since the majority of patients were White (74%). The average pain and average total supplemental opioids usage of each treatment group by dose intervals are depicted by age groups in Figures 3 and 4, respectively. It appears the differences between placebo- and active-treated groups are more apparent in the elder group, especially for the supplemental opioids usage. The subgroup plots by gender for pain scores and supplemental opioids usage are provided in Figures 5 and 6, respectively. The separation of the pain curves seems more evident for male patients, which may primarily due to the difference observed at baseline. The treatment effect on supplemental opioids usage in male was rather similar to that in female patients.

Figure 3: Pain Assessments by Age Group

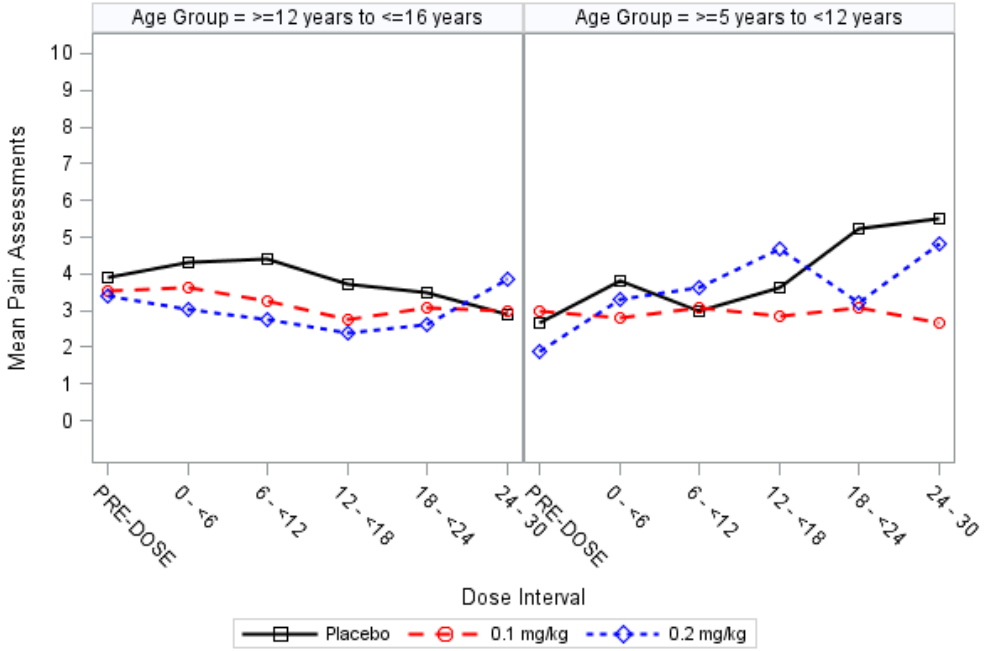

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Figure 4: Total Supplemental Opioids by Age Group

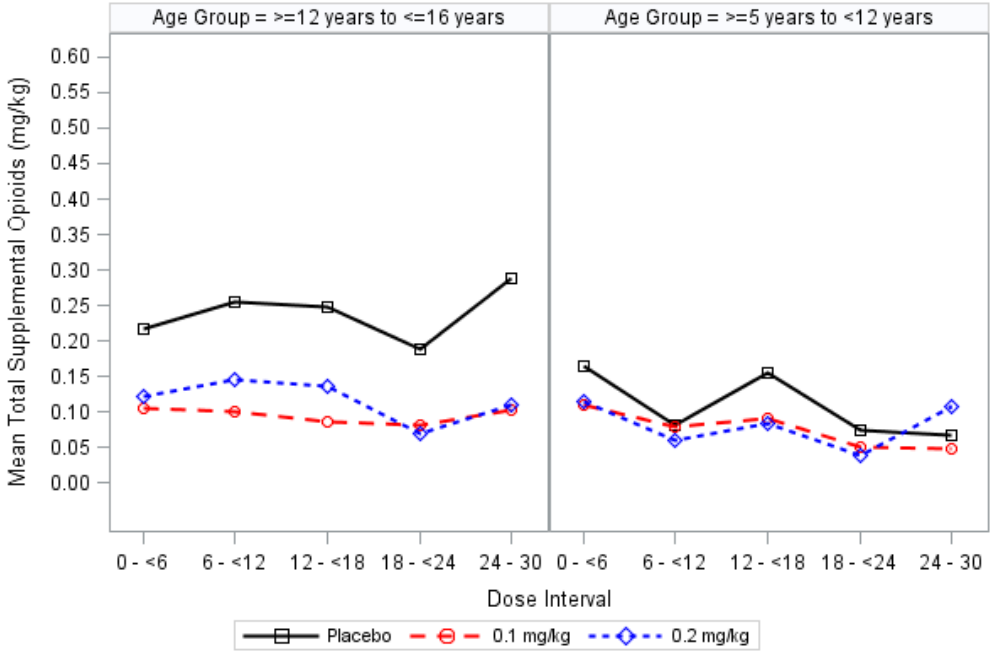

Figure 5: Pain Assessments by Gender

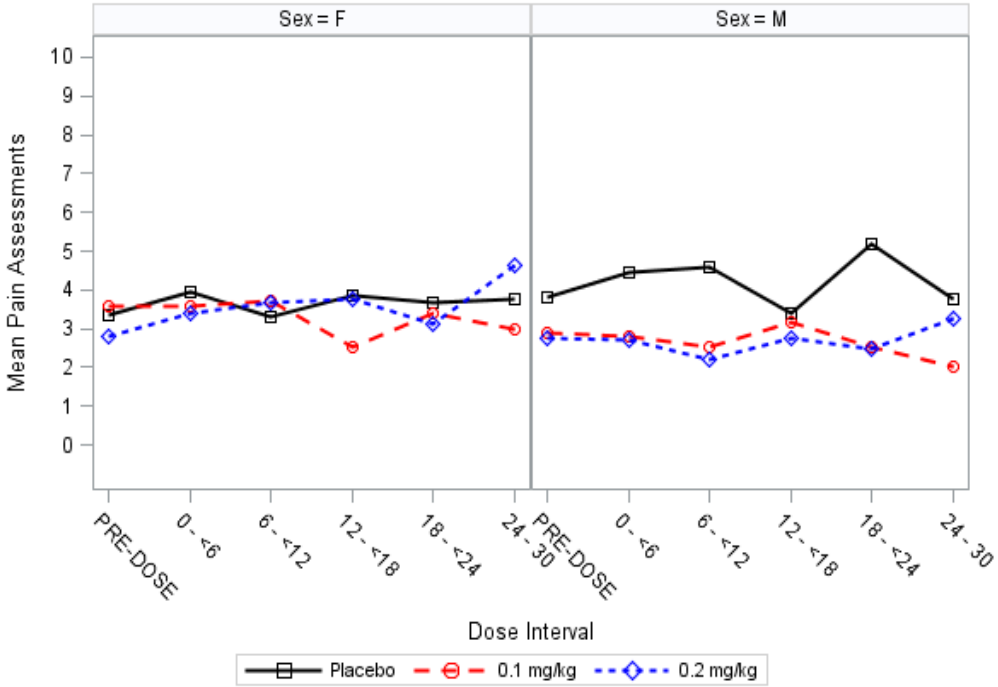

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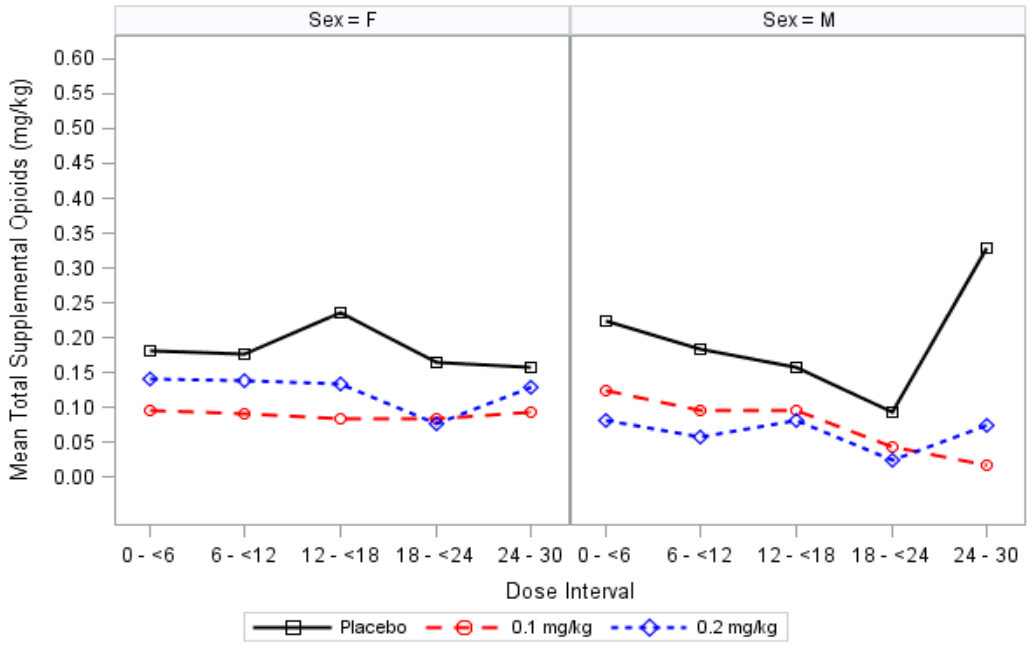
Figure 6: Total Supplemental Opioids by Gender



4.2 Other Special/Subgroup Populations

No other subgroup summaries were performed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Some statistical issues in the applicant's efficacy analyses were identified.

Firstly, neither the protocol nor the SAP clearly specified the primary or secondary efficacy endpoints and there was no multiplicity adjustment for the multiple tests conducted for multiple endpoints. Efficacy was evaluated by testing dose response for pain intensity and supplemental pain medication usage. Efficacy variables analyzed included, but not limited to, pain intensity and total amount of supplemental pain medications in the first dose interval, overall including the first dose interval, and overall excluding the first dose interval. In the absence of an appropriate multiplicity adjustment approach, the overall Type I error was not controlled and it is difficult to interpret the p-values. This may not be a concern when all the tests reached statistical significance favoring the active drug. However, most of the tests for the efficacy variables did not reach significance at the one-sided level of 0.025 or two-sided level of 0.05. The applicant incorrectly claimed that most of the tests reached significance by inappropriately comparing one-sided p-values to the usual threshold of 0.05, which is for two-sided tests.

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Secondly, neither efficacy outcomes were collected nor imputation methods were implemented for the missing data from the patients who stopped the randomized treatment pre-maturely. The applicant's efficacy analyses were based on available data only, which might be biased, especially for the total amount of supplemental pain medications usage. In the in-patient setting with 2-day treatment duration, it would have been sensible to continue to collect the efficacy outcomes off treatment from those discontinued patients.

Lastly, the study was powered for PK and adverse events detection instead of efficacy evaluation, which might be the main reason why most of the efficacy variables did not reach statistical significance. Furthermore, the applicant applied the Jonckheere-Terpstra approach for testing a monotonic dose response among placebo, oxycodone 0.1 mg/kg, and oxycodone 0.2 mg/kg. The Jonckheere-Terpstra approach is a valid test in this setting. However, the efficiency is not at its maximum when both active doses are superior to placebo but no difference between the two doses of oxycodone, which appeared to be the case observed in this study.

5.2 Collective Evidence

Dose response was not established with appropriate statistical significance for most of the efficacy variables assessing pain intensity or supplemental pain medication use. Nevertheless, it was observed that the results of the efficacy variables were all numerically in favor of oxycodone. Patients randomized to placebo reported slightly higher pain intensity on average and used more supplemental pain medications during the study. Overall, the observed data suggest that the two oxycodone doses may be efficacious for the desired indication in pediatric population. However, the study did not provide evidence of efficacy with the usually required level of statistical significance.

5.3 Conclusions and Recommendations

Study OXP3003 was the efficacy study conducted to fulfill the requirement of Study 2 specified in the PWR. However, the study was not powered for demonstrating efficacy. The efficacy results were only numerically in favor of oxycodone against placebo with respect to management of pain and reduction of usage of supplemental pain medication. Thus, the study did not meet the usual standard for providing substantial evidence of efficacy.

5.4 Labeling Recommendations

The applicant submitted the following wording to add to the clinical study section of the label for review:

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Pediatric clinical studies

(b) (4)

I have the following recommendations to the applicant:

Paragraph 4: replace (b) (4) ".

Paragraph 4: delete the sentence " (b) (4) "

Paragraph 4: Revised the last two sentences to be (b) (4) "

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Appendix

Figure 1: PCA Morphine Usage by Dose Interval

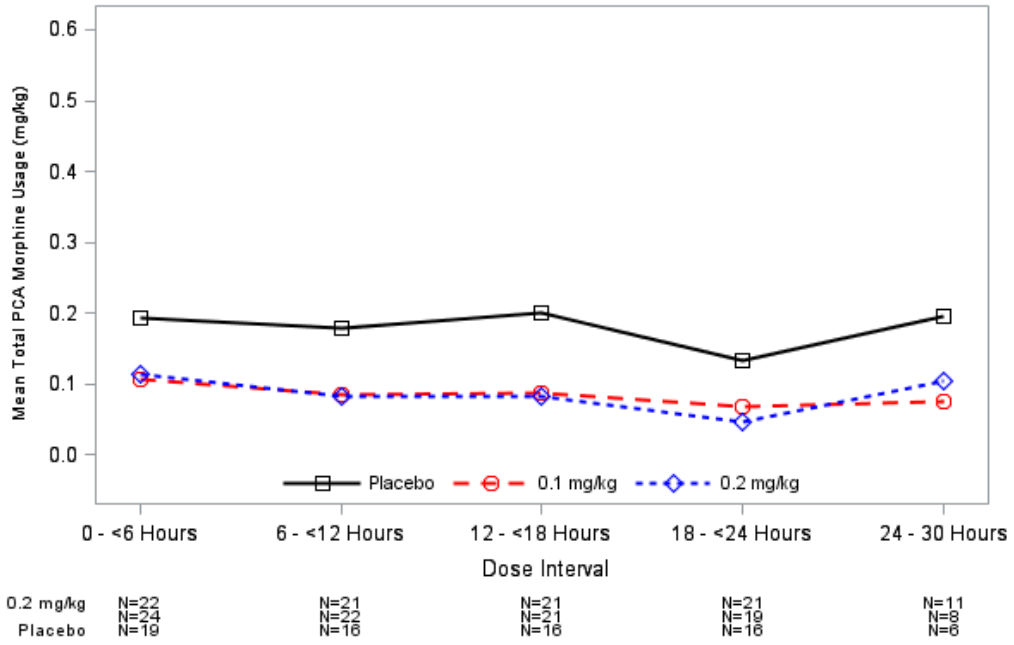

Figure 2: Total Non-PCA Morphine Usage by Dose Interval

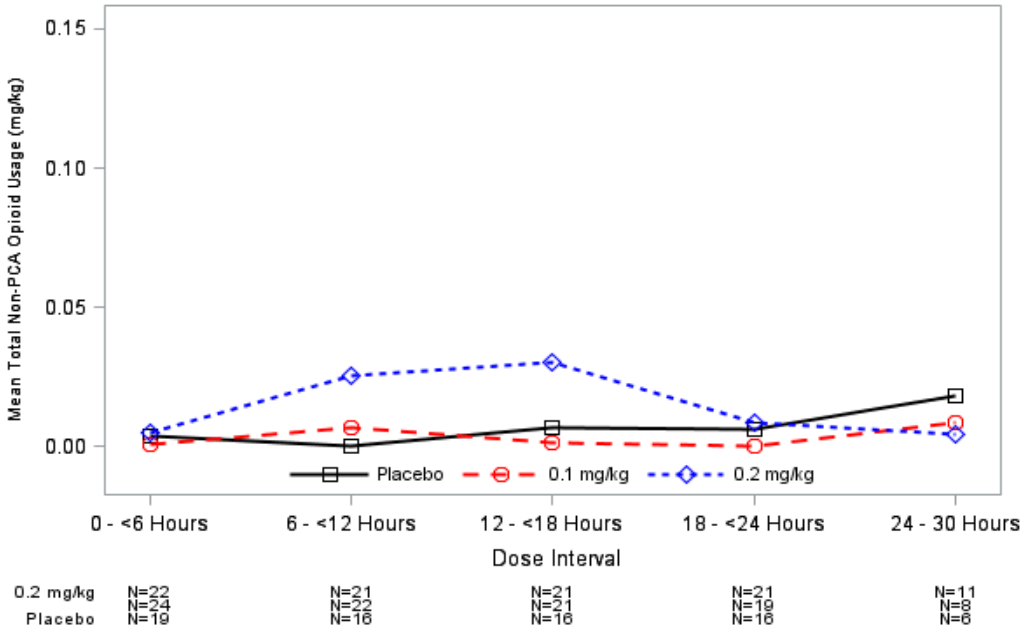

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Figure 3: Total Acetaminophen Usage by Dose Interval

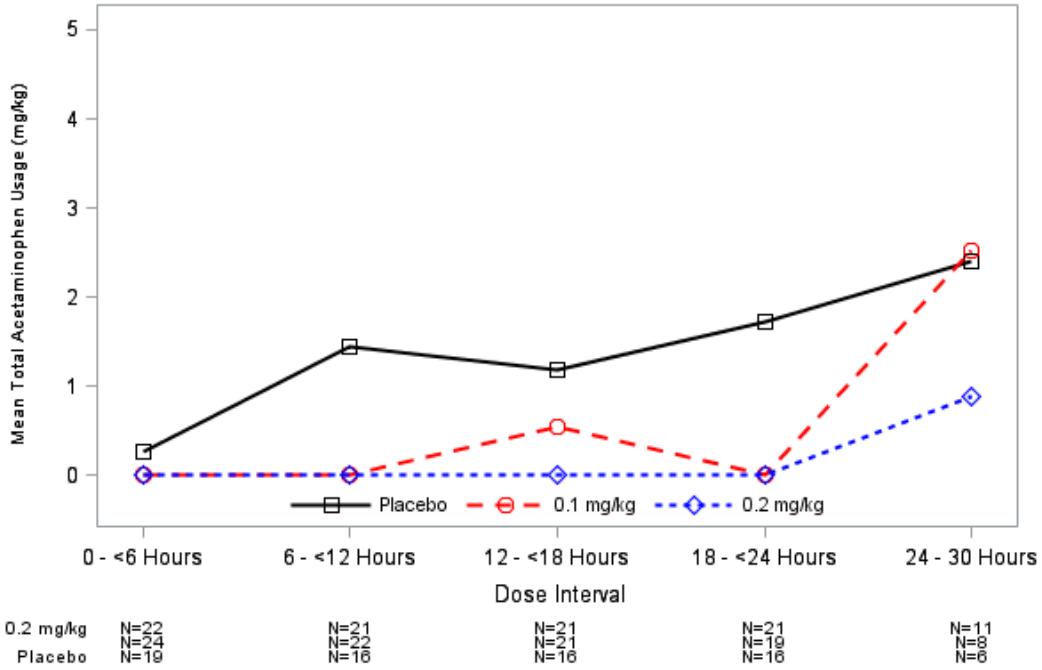
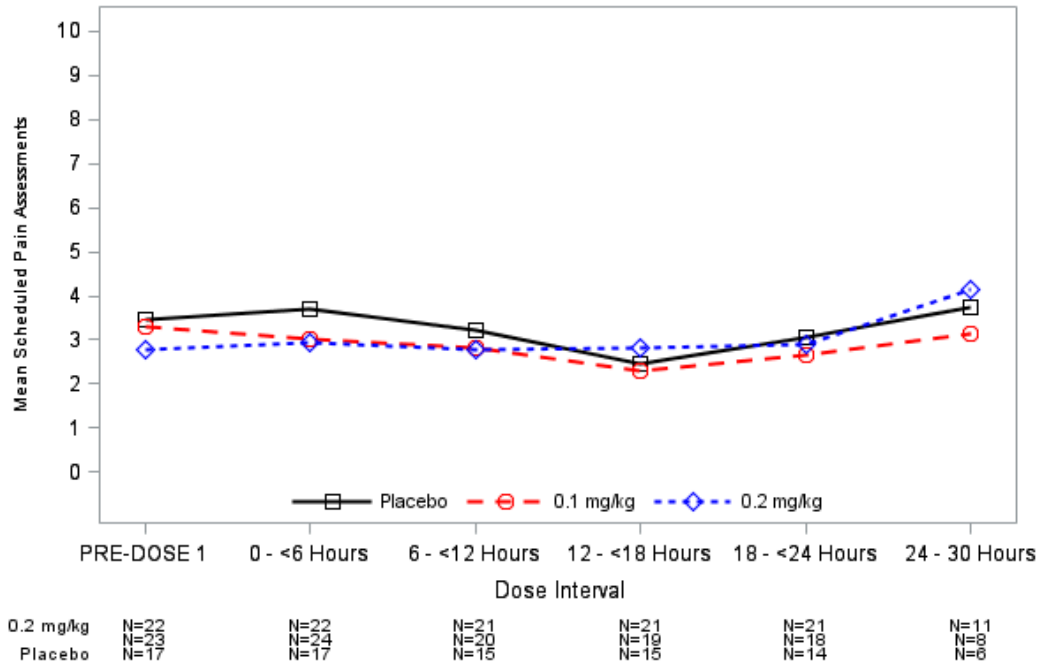
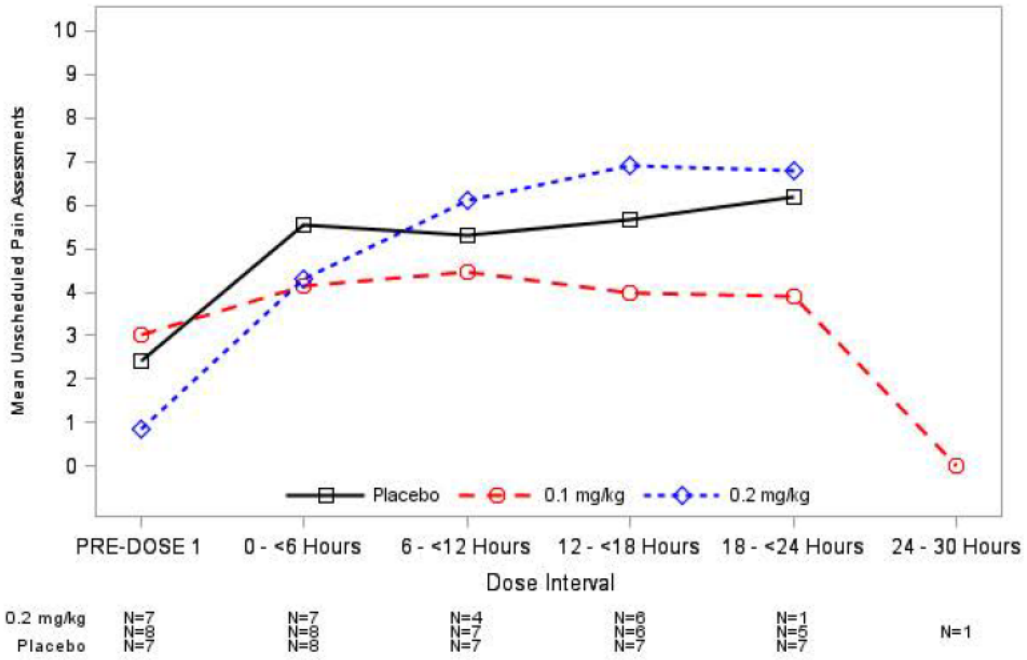


Figure 4: Scheduled Pain Assessments by Dose Interval



Reference ID: 3749626

Figure 5: Unscheduled Pain Assessments by Dose Interval



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/s/

FENG LI
05/07/2015

FREDA COONER
05/07/2015
I concur

STATISTICS FILING REVIEW

NDA Number: 22272/027 **eCTD Sequence #: 0224**	**Applicant: Purdue Pharma L.P.**	**Stamp Date: Dec 10, 2014**
Drug Name: OxyContin® **(oxycodone hydrochloride)** **Tablets, extended-release**	**BLA Type: 505(A) NDA** **Pediatric Efficacy** **Supplement (Priority)**	**Indication: Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate**

On **initial** overview of the Supplemental NDA application for RTF:

	Content Parameter for RTF	Yes	No	NA	Comments
1	Electronic Submission: Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	X			Some subgroup analyses were not conducted; however, sufficient rationale was provided.
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

THE STATISTICAL SECTION OF THE APPLICATION IS FILEABLE

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	Not present
Appropriate references for novel statistical methodology (if present) are included.			X	Not present
Safety data organized to permit analyses across clinical trials in the NDA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

Reference ID: 3695897

STATISTICS FILING REVIEW

Background

Purdue is submitting this efficacy supplemental NDA in support of updating the OxyContin® labeling to include the pediatric study results in accordance with the November 14, 2011 Written Request (WR) #3, Amendment #2. Purdue is requesting six months of pediatric exclusivity be recognized (b) (4).

OxyContin is an extended-release (ER) oral formulation of oxycodone hydrochloride (HCL), currently indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. It was originally approved for a similar indication by the FDA on December 12, 1995. A newly reformulated OxyContin ("ORF") tablet with abuse-deterrent properties was approved by the FDA on April 5, 2010 and is marketed in approximately 60 countries.

The FDA issued formal WR for OxyContin pediatric studies dated November 4, 1998 (WR #1), December 31, 2001 (WR #2), May 13, 2009 (WR #3), November 18, 2010 (WR #3, Amendment #1), and November 14, 2011 (WR #3, Amendment #2) responding to the sponsor's Proposed Pediatric Study Requests (PPSRs) dated August 28, 1998, February 2, 2001, December 18, 2008, June 4, 2010, and September 21, 2011, respectively.

The final WR (WR #3, Amendment #2) requested the following three studies:

Study 1: Pharmacokinetic (PK) study of an age-appropriate formulation of oxycodone in opioid-naïve patients from birth up to less than four years of age.

Study 2: Efficacy, safety, and PK study of an age-appropriate formulation of immediate-release (IR) oxycodone in opioid-naïve patients from five years up to no more than 16 years of age.

Study 3: Open-label safety and PK study of an oxycodone controlled-release tablet in opioid-tolerant patients from six years to no more than 16 years of age with moderate to severe pain requiring around-the-clock opioid therapy for an extended period of time.

Per FDA's General Advice letter, dated May 14, 2010, the previously completed Studies OXP1005 and OXP3003 met the requirements for Studies 1 and 2, respectively. Purdue subsequently completed Study OTR3001 to fulfill Study 3 requirements.

Purdue also conducted three retrospective cohort epidemiologic studies of extended-release oxycodone HCL use in pediatric patients in order to better understand and assess the real-word use of OxyContin tablets in pediatric patients of no more than 16 years of age. Data were obtained from electronic medical records and insurance claims in usual-care settings of regular in- and out-patient clinical practice.

The tabulation data in the CDISC-SDTM format and the analysis datasets in ADaM format for all the studies, as well as the study reports for this submission have been submitted in electronic Common Technical Document (eCTD) format to the EDR at: \\CDSESUB1\evsprod\NDA 022272\0224.

Reference ID: 3695897

STATISTICS FILING REVIEW

Overview of studies

Study OXP 1005 (N = 60) was an open-label study designed to evaluate the safety, PK, and efficacy of oxycodone HCL oral solution (1 mg/mL) in opioid-naïve inpatients aged from birth to no more than four years. At baseline, patients were stratified into three age groups (birth to 30 days, 31 days to no more than six months, seven months to no more than four years). The patients received oxycodone HCL oral solution (0.05, 0.1, or 0.2 mg/kg) every six hours (q6h) for up to two days (up to seven doses) in group-sequential ascending doses. Supplemental pain medication was permitted.

Study OXP3003 (N = 65) was a double-blind, placebo-controlled study designed to evaluate the safety, PK, and efficacy of oxycodone HCL oral solution (1 mg/mL) in opioid-naïve inpatients five to no more than 16 years of age. At randomization, patients were stratified into two age groups (five to no more than 11 and 12 to no more than 16 years) and randomly assigned in a 3:3:2 ratio to receive 0.1 mg/kg oxycodone HCL oral solution, 0.2 mg/kg oxycodone HCL oral solution, or placebo. Doses were administered q6h for up to two days. Supplemental pain medication was permitted.

Study OTR3001 (N = 155) was an open-label study designed to evaluate the safety, PK, and efficacy of OxyContin in opioid-tolerant pediatric patients, aged six to no more than 16 years, who were either outpatients or inpatients at the time of enrollment. Inpatients continued in the study upon hospital discharge. The trial consisted of a 72-hour screening period, an open-label treatment period of up to four weeks, and a 7- to 10-day follow-up period. Patients must have been treated with opioids for at least five days before study entry (no less than 20 mg/day of oxycodone or equivalent for the last 48 hours before the first dose of OxyContin). The patient's current daily dose of opioid analgesia was then converted to an appropriate dose of OxyContin given every 12 hours (q12h). Dose adjustments were permitted as necessary. Supplemental pain medication was permitted. Written Request #3, Amendment #2 specified that the patients in Study 3 should be separated into two age groups, with approximately 40% of the patients in the younger group (six to no more than 11 years) and 60% in the older group (12 to no more than 16 years) and with patients approximately evenly distributed over the entire age range and across sexes.

Supplemental pain medication usage was an efficacy endpoint in all studies. Pain intensity was evaluated in Study OXP3003 (all patients) and in Study OTR3001 (patients aged six to 12 years) using the Faces Pain Scale-Revised (FPS-R). Additional efficacy endpoints evaluated in Study OTR3001 only were the Functional Disability Inventory (FDI) and the Parent/Caregiver Global Impression of Change (PGIC).

Efficacy was a secondary endpoint in each of the three WR studies, and two were open-label. Most of the efficacy data were summarized using descriptive statistics. Due to the differences in study designs, populations, and formulations, no pooling of efficacy data across studies was performed by the sponsor. The sponsor reported that patients in Study OXP3003 treated with 0.1 and 0.2 mg/kg used less supplemental pain medication compared with patients treated with placebo. The difference in mean values for the entire treatment period was reportedly statistically significant for patient-controlled analgesia (PCA) morphine (0.69, 0.34, and 0.37 mg/kg, for the placebo, 0.1 mg/kg, and 0.2 mg/kg group, respectively; $p = 0.047$) and acetaminophen (4.68, 1.32, and 0.45 mg/kg, respectively; $p = 0.039$), and numerically greater for total opioids (0.71, 0.35, and 0.44 mg/kg, respectively; $p = 0.077$). The primary statistical review will focus on Study OXP3003.

Reference ID: 3695897

The three WR studies mentioned above are summarized in the table below:

Trial ID (Status)	Trial Design; Control Type	Number of Study Centers (Locations)	# Patients by Arm; Entered/ Completed	Indication Studied	Sex (M/F) Median age (Range) Race (W/B/A/O)	Duration	Study and Control Drugs Dose, Route, Regimen	Frequency of Dosing
OXP1005 (completed) Written Request Study 1	Multicenter, open-label, group-sequential, dose-ranging, phase 1 study	26 (US, Canada, Finland, the Netherlands, Scotland, England)	n=60/50: 0.05 mg/kg: n=26/21 0.1 mg/kg: n=17/15 0.2 mg/kg: n=17/14	Hospitalized, postsurgical, opioid-naïve pediatric pts (birth to 4 y) with moderate to severe pain	29M/31F 165.5 d (1-1763 d) (42/2/2/14)	Up to 2 d	Oxycodone HCL oral solution (1 mg/mL): 0.05 mg/kg 0.1 mg/kg 0.2 mg/kg	q6h for 7 doses
OXP3003 (completed) Written Request Study 2	Multicenter, randomized (3:3:2 ratio), double-blind, placebo-controlled, phase 3 study	30 (US, Canada, England, Finland, the Netherlands)	n=74/54: 0.1 mg/kg: n=24/18 0.2 mg/kg: n=22/21 Placebo: n=19/15	Hospitalized, opioid-naïve pediatric pts (5 to 16 y) with moderate to severe pain	Safety Pop: 24M/41F 12 y (5-16 y) 48/5/2/10	Up to 2 d	Oxycodone HCL oral solution (1 mg/mL): 0.1 mg/kg 0.2 mg/kg Matching oral placebo	q6h for 4-5 doses
OTR3001 (completed) Written Request Study 3	Multicenter, open-label, phase 3 study	44 (US, Israel, Greece, Guatemala, Hungary, New Zealand, Spain, UK)	Planned: n=154 Treated: n=155 Completed: n=122	Opioid-tolerant pediatric in- or outpatients (6 to 16 y) with moderate to severe, malignant or nonmalignant pain	66M/89F 14.0 y (6-16 y) (108/38/1/8)	Up to 4-wk tx period 7- to 10-d follow-up period	ORF: 20 to 240 mg total daily dose	q12h

Source: Module 2.7.4, Table 1
Number of enrolled patients does not include screening failures.
A = Asian; B = black; d = days; F = female; HCL = hydrochloride; M = male; O = other; ORF = reformulated tablet of OxyContin (extended-release oxycodone); pt = patient; q = every; tx = treatment; UK = United Kingdom; US = United States; W = white; y = years.

Reference ID: 3695897

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/s/

FREDA COONER
02/02/2015

THOMAS J PERMUTT
02/02/2015
I concur.