CLINICAL REVIEW

Application Type	Supplemental NDA
Application Number(s)	022272, Supplement 27
Priority or Standard	Priority
Submit Date(s)	December 10, 2014
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Division / Office	Division of Anesthesia, Analgesia, and Addiction Products/ODE II
Reviewer Name(s)	CDR Javier A. Muñiz, MD
Review Completion Date	May 15, 2015
Established Name	OxyContin
(Proposed) Trade Name	OxyContin
Therapeutic Class	Opioid analgesic
Applicant	Purdue Pharma.
Formulation(s)	Controlled-release oxycodone
Dosing Regimen	Twice daily
Indication(s)	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.
Intended Population(s)	(b) (4) years old and older.

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Purdue Pharma L.P. (hereby known as Purdue) 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.

I recommend the approval of this supplemental NDA, with the amended labeling recommended by the review team. This review will not address the pediatric exclusivity determination although it will discuss, when appropriate, how the submitted studies complied with the Pediatric Written Request agreement.

1.2 Risk Benefit Assessment

Purdue did not request a change to the current approved indication for OxyContin (oxycodone hydrochloride extended-release tablets), which is 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. However, Purdue is requesting to extend this indication to (b) (4) Based on the data submitted, we recommend this indication to be approved for opioid-tolerant pediatric patients older than 11 years of age.

At this time we do not have any approved opioid medication for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for pediatric patients. These patients have immediate-release approved options that must be taken several times a day. The main benefit of approving this supplemental NDA is that it will provide these patients with a long-acting pain medication option that can be taken only twice a day.

On one hand, opioids fall into the most potent class of analgesics that treat malignant and nonmalignant types of chronic pain. However, the adverse event profile includes life-threatening respiratory depression along with sedation, nausea, vomiting, constipation, hypotension, and pruritus. The additional risk posed by opioids is the abuse potential related to this class of drugs.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

OxyContin is a member of the Extended-Release/Long-Acting (ER/LA) opioid analgesic Risk Evaluation and Mitigation Strategy (REMS). The central component of the ER/LA

opioid analgesics REMS is an education program for prescribers (e.g., physicians, nurse practitioners, physician assistants). Under the REMS, sponsors of ER/LA opioid analgesics are making education programs available to all DEA registered prescribers, including prescribers of ER/LA opioid analgesics. As expected, sponsors are meeting this obligation by providing educational grants to accredited CE providers who are offering training to prescribers at no or nominal cost. These CE activities cover the content and messages of a blueprint developed by Food and Drug Administration for this purpose.

No changes to the currently established Postmarket Risk Evaluation and Mitigation Strategies recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

No changes to the currently established Postmarket Requirements and Commitments recommended.

2 Introduction and Regulatory Background

2.1 Product Information

Oxycodone is semisynthetic drug with potent pain-relieving effects that is derived from thebaine, an alkaloid that occurs naturally in the opium poppy (*Papaver somniferum*). Oxycodone was first synthesized from in 1916 and was first used clinically the following year. It is an analgesic generally indicated for the relief of moderate to severe pain.

In general, it is thoughts that oxycodone has a similar mechanism of action as other opioids: it binds to specific receptors, inhibits adenylyl-cyclase and it hyperpolarizes neurons, thus decreasing neuronal excitability. More specifically, oxycodone has different degrees of affinity and agonist activity on mu, kappa and delta opioid receptors.

OxyContin is a modified-release formulation of oxycodone which was initially approved December 12, 1995 as 10 mg, 20 mg, and 40 mg tablets. An 80 mg tablet was approved in January 6, 1997, followed by a 160 mg tablet on March 15, 2000, and 15 mg, 30 mg and 60 mg tablets on September 18, 2006. The Sponsor ceased distribution of the 160 mg tablet in April of 2001. Out of concerns of growing numbers of reports of misuse, abuse, and addiction to OxyContin, the Food and Drug Administration worked with Purdue to strengthen the product's label and eventually re-formulate the product. The reformulation of OxyContin was intended to reduce the abuse liability of the product by making the modified-release characteristics more robust. In essence, the re-formulated tablet was designed to be more difficult to crush or dissolve, and more resistant to the extraction of oxycodone by chemical means. The re-formulated

OxyContin was approved in April 2010, and after a few months of overlap, the Sponsor ceased distribution of the non-abuse deterrent formulation of OxyContin later that year.

2.2 Tables of Currently Available Treatments for Proposed Indications

The table below summarizes the available US products with a chronic pain indication.

Drug	Formulation	Indication
Fentanyl	Extended-release fentanyl	Management of persistent, moderate to severe chronic pain in opioid-tolerant patients 2 years of age and older when a continuous, around-the-clock opioid analgesic is required for an extended period of time, and the patient cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids.
Single-entity hydrocodone	Extended-release hydrocodone	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
Combination hydrocodone-containing products	Hydrocodone-acetaminophen	Moderate to moderately severe pain
Hydromorphone	Immediate-release hydromorphone	Management of pain in patients where an opioid analgesic is appropriate
	Extended-release hydromorphone	Management of moderate to severe pain in opioid tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time
Methadone	Extended-release methadone	Management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time
Single-entity morphine sulfate	Immediate-release morphine sulfate	Relief of moderate to severe acute and chronic pain where the use of an opioid analgesic is appropriate
	Extended-release morphine sulfate	Management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time
Combination morphine-containing products	Morphine-naltrexone	For the treatment of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
Single-entity oxycodone products	Immediate-release oxycodone	Management of moderate to severe pain where the use of an opioid analgesic is appropriate
	Extended-release oxycodone	Management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time
Combination oxycodone-containing products	Oxycodone-naloxone	Relief of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
	Oxycodone-acetaminophen or oxycodone-aspirin	Moderate to moderately severe pain
Oxymorphone	Extended-release	Relief of moderate to severe pain in patients requiring

Drug	Formulation	Indication
	oxymorphone	continuous, around-the-clock opioid treatment for an extended period of time.
Tapentadol	Extended-release tapentadol	Management of moderate to severe chronic pain in adults when a continuous, around-the-clock analgesic is needed for an extended period of time

In response to public health needs and regulatory guidance, an increasing number of abuse deterrent formulations of some of the above drugs approved for chronic pain have been developed over the last few years and OxyContin is one of them. OxyContin and Nucynta ER (tapentadol) incorporate features making it difficult to crush, cut, or break the tablets. Opana ER (oxymorphone) was designed to cause a gel to form if the tablets are crushed. Different approaches to designing these abuse deterrent drugs also include the addition of novel excipients or other drugs. For example, Oxecta (oxycodone) contains sodium lauryl sulfate that makes snorting the drug unpleasant and an excipient that causes the tablet to turn into a gel if someone dissolves it in liquid. Embeda (morphine) uses naltrexone and Targiniq ER (oxycodone) uses naloxone to bind to opiate receptors, potentially eliminating euphoric effects if these drugs are intentionally misused. Although many of these medications have been approved for the management pain severe enough to require daily, around-the clock, long-term opioid treatment, none is approved for pediatric patients.

In addition to opioids, other pharmacological options available for the management of chronic pain severe to require around-the-clock treatment include nonsteroidal anti-inflammatory drugs (NSAIDS) such as celecoxib, naproxen and ibuprofen acetaminophen, and regional and local anesthetics such as lidocaine

2.3 Availability of Proposed Active Ingredient in the United States

Oxycodone is available in immediate or controlled-release formulations, and as single-entity or combination products as discussed in the previous section. Combination products may contain non-narcotic pain medications such as acetaminophen. One combination product contains the opioid agonist naxolone to deter tampering. Various generic oxycodone formulations have been approved. Liquid immediate-release formulations are marketed. Although parenteral formulations are in use in other countries, only oral formulations are approved in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Oxycodone and other mu opioid agonists are associated with well-known and potentially serious safety events including: respiratory depression (possibly leading to coma and death), withdrawal, physical dependence and abuse, and the risk of overdosage. Similar to other opioids, the OxyContin label contains a boxed warning which, in addition to the

above reactions, discusses events such as the risks of addiction, substance abuse and misuse, accidental exposure, and neonatal opioid withdrawal syndrome.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

This product has a long regulatory history related to pediatric studies. There have been three Pediatric Written Requests (PWRs), which I will briefly outline below.

PWR #1

The initial PWR for OxyContin was issued in November of 1998 and requested the following two studies:

> Study 1: Single-dose, cross-over study, evaluating the pharmacokinetics and safety of immediate- release (IR) and controlled-release oxycodone.
>
> Study 2: Multiple-dose study evaluating the steady state PK and PD (including pain intensity scores and rescue medication usage) of immediate- and controlled-release oxycodone in a parallel or cross-over design in opioid tolerant patients.

For both studies, the sponsor was asked to enroll pediatric patients between 5 and 16 years of age, stratified into two groups 1) 5 to 12 years old and 2) 12 to 16 years old. A sufficient number of pediatric patients were required for Study 1 to detect 30% or greater difference in AUC in each age group and at least 30 patients per age group were required for the multiple-dose study. The need for continuous opioid therapy was expected to be at least four days.

Following receipt of the PWR, the sponsor requested several modifications to the proposed studies including increasing the lower age limit to six years because Purdue expressed concern regarding the safe administration of oxycodone tablets to five-year-old children and children under 20 kg body weight. The sponsor also stated that they could face difficulties recruiting children this young.

PWR #2

In response to a new PPSR, after consulting with the Pediatric Committee and the Office Director, the Division of Anesthetic, Critical Care, and Addiction Drug Products, as it was known at the time, decided to issue an amended PWR that would extend the patient population age down to the newborn by using an age appropriate formulation. The submission deadline for the study reports was December 31, 2004.

Briefly, there were three studies required, summarized here:

Study 1: Pharmacokinetic study of an age-appropriate formulation of IR oxycodone in opioid-naïve patients from birth up to ≤ 4 years of age. Other features to include:

- Inpatient
- Open-label
- Dose-ranging
- Single- and multiple-dose
- Age strata: 0-30 days; 1 month to ≤ 6 months; 7 months to ≤ 4 years
- N = at least 60 total, approximately evenly distributed over the entire age range in each stratum and across both genders
- Endpoints: Age-appropriate pain intensity, rescue medication usage, safety data, pharmacokinetic parameters

Study 2: Efficacy, safety, and pharmacokinetic study of an age-appropriate formulation of IR oxycodone in opioid-naïve patients from 5 years up to ≤ 16 years of age (single- and multiple-dose). Other features to include:

- Inpatient
- Double-blind
- Placebo-controlled
- Dose-ranging
- Single- and multiple-dose
- Age strata: 5 years to ≤ 11 years; 12 years to ≤ 16 years
- N = at least 100 total, approximately evenly distributed over the entire age range in each stratum and across both genders
- Endpoints: Age-appropriate pain intensity, rescue medication usage, safety data, pharmacokinetic parameters

Study 3: Efficacy, safety, and pharmacokinetic study to determine a safe conversion from an immediate-release oxycodone to a controlled-release oxycodone formulation in opioid-tolerant patients from 6 years to ≤ 16 years of age. Patients should require a wide range of doses of opioid medications at screening. Verify the results of Study OC0602 (a pharmacokinetic study of OxyContin tablets in patients aged 6-12 years). Other features to include:

- Inpatient
- Open-label
- Multiple-dose
- Age strata: 6 years to ≤ 11 years; 12 years to ≤ 16 years
- N = at least 100 total (approximately 40 in the younger stratum and 60 in the older stratum), approximately evenly distributed over the entire age range in each stratum and across both genders
- Endpoints: Pharmacokinetic parameters from immediate- and controlled-release oxycodone formulations, pain intensity, rescue medication usage, conversion ratio from immediate- to controlled-release, safety data

PWR #3

With the reformulation of OxyContin, a third and final PWR was originally written in May, 2009 and the final and second amendment was agreed upon in November, 2011. This second amendment is the reason for this supplemental submission. I will briefly summarize the specific requests for these three studies below.

Study 1: Pharmacokinetic (PK) study of an age-appropriate formulation of oxycodone in opioid-naïve patients from birth up to < 4 years of age.

- Indication: Moderate to severe pain, on an age-appropriate pain scale, requiring treatment with an opioid analgesic.
- Number of patients: At least 60 patients, approximately evenly distributed over the entire age range in each stratum and across both genders.
- Design: In-patient, open-label, dose-ranging study evaluating the pharmacokinetics (using a population pharmacokinetic approach) of an age-appropriate formulation
- Endpoints:
    - Age-appropriate pain intensity, rescue medication usage, safety data (such as vital signs, oxygen saturation, somnolence, hypoventilation, and hypotension), and adverse events will be obtained.
    - Pharmacokinetic parameters such as T_{max}, $t_{1/2}$, C_{max}, AUC_{0-t}, AUC_{0-inf}, C_{ss} (steady state concentration with multiple dosing), Ke (elimination rate constant), apparent Vd (volume of distribution), and apparent oral CL (systemic clearance).

Study 2: Efficacy, safety, and pharmacokinetic study of an age-appropriate formulation of immediate-release (IR) oxycodone in opioid-naïve patients from 5 years up to ≤ 16 years of age.

- Indication: Moderate to severe pain, on an age-appropriate pain scale, requiring treatment with an opioid analgesic.
- Number of patients: Sufficient number of pediatric patients to demonstrate a clinically meaningful difference in pain intensity between active and comparator, approximately equally divided between the two treatment groups, evenly distributed over the entire age range in each stratum and across both genders in each treatment group.
- Design: Active or placebo-controlled, double-blind, dose-ranging, in-patient, superiority study evaluating the PK (using a population pharmacokinetic approach) of oxycodone after single and repeated dosing of an age-appropriate formulation.
- Endpoints:
    - Age-appropriate pain intensity, rescue medication usage, safety data (such as vital signs, oxygen saturation, somnolence,

hypoventilation, and hypotension), and adverse events will be obtained.
- Pharmacokinetic parameters such as T_{max}, $t_{1/2}$, C_{max}, AUC_{0-t}, AUC_{0-inf}, Css (steady state concentration with multiple dosing), Ke (elimination rate constant), apparent Vd (volume of distribution), and apparent oral CL (systemic clearance).

Study 3: Open-label, safety and pharmacokinetic study of an oxycodone extended-release tablet in opioid-tolerant patients from 6 years to ≤ 16 years of age.

- Indication: Moderate to severe pain requiring around-the-clock opioid therapy for an extended period of time.
- Number of patients: Enroll a sufficient number of pediatric patients treated with extended-release oxycodone to bring the total number of patients exposed to at least 260 (between Study 1, Study 2, and Study 3)
  - Approximately 40% of the pediatric patients must be in the age group 6-11 years old and 60% in the age group 12-16 years old.
  - Patients must be approximately evenly distributed over the entire age range in each stratum and across both genders.
- Design: Multiple-dose, open-label, safety, and PK study in a predominantly outpatient pediatric population that meets the criteria for chronic pain and the indications for oxycodone extended-release formulation use.
  - 80% of the data must be collected in an outpatient setting.
  - Half of the patients must be exposed to study drug for at least four weeks.
  - Selection of doses should be guided by the results of the completed pediatric studies.
  - For the PK component of the study, a population pharmacokinetic approach may be adopted.
- Endpoints: Safety data (such as vital signs, oxygen saturation, somnolence, hypoventilation, and hypotension), adverse events and extended-release oxycodone tablet PK profile.

As per the last Written Request, adverse events monitoring for all three studies must include a minimum of respiratory compromise, hypotension, and appropriate clinical laboratory assessments. It also stipulates that all studies must be submitted to the Agency no later than (b) (4)

2.6 Other Relevant Background Information

In 2010, a scientific workshop was sponsored by the Food and Drug Administration. The participants developed a consensus on aspects of pediatric analgesic clinical trial design. This consensus was published in the American Academy of Pediatrics in an

article titled “Pediatric Analgesic Clinical Trial Designs, Measures, and Extrapolation: Report of an FDA Scientific Workshop” by Berde CB *et al*.

The studies submitted with this application were designed and conducted from the late 1990s through the year 2014. This article (Berde *et al*.) will guide us in the design of future analgesic trials in children. Also, understanding the core principles of the consensus summarized in the article can help us understand the strengths and limitations of the studies submitted with this application.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This supplemental NDA was submitted in Electronic Common Technical Document (eCTD) format. All sections/modules were completed appropriately. The submission was reasonably well-organized and paginated to allow for an acceptable review.

3.2 Compliance with Good Clinical Practices

Three study sites (one site encompassed 2 studies) were inspected by the Division of Scientific Investigations (DSI) and a report was sent to our division on April 30, 2015. These sites were identified for Good Clinical Practices (GCP) audit based on relative importance of the study to the NDA and on large site (in terms of number of subjects) enrollment. No special concerns were identified for protocol violations, AEs or investigator’s conflict of interest.

In the 3 audited studies combined, 283 subjects were treated at 157 study-sites, of whom case records for 84 subjects (30% of 283) were reviewed at audit of four study-sites (2.5% of 157), including detailed review for 47 subjects (17% of 283). Overall, the data from these sites were considered reliable. The preliminary outcome of these inspections is shown on the table below. Most of the text below was summarized from the DSI report.

Table 1. Clinical Sites Investigated

Clinical Investigator (CI)	Study, Site, Enrollment	Inspection Outcome
Peter Szmuk, M.D. University of Texas-Southwestern 1935 Medical District Drive Dallas, Texas	Study OTR3001 Site 1863A 15 subjects	April 7-17, 2015 Pending, preliminary VAI
Andrea L. D. Orsey, M.D. Connecticut Children's Medical Center 282 Washington Street Hartford, Connecticut	Study OTR3001 Site 1360A 17 subjects	March 11-24, 2015 Pending, preliminary VAI
Gregory B. Hammer, M.D. Stanford Medical Center 300 Pasteur Drive, H3580 Stanford, California	Study OXP3003 Site 0033A 26 subjects	April 9-17, 2015 Pending, preliminary VAI
	Study OXP1005 Site 0033A 26 subjects	

Pending = preliminary results based on communication with field investigator
VAI = voluntary action indicated (minor GCP violations)
(Source: DSI report, page 7)

3.2.1 Site 1863A (Study OTR3001)

Fifteen subjects were screened, 15 were enrolled, and 11 completed the study. Records were reviewed in detail for 10 subjects. The following deficiencies were observed for this site:

- For one subject (9001), the initially adequate Informed Consent (IC) was not supplemented by a re-signed copy of the IC document (ICD) upon availability of a modified version of the ICD.
- For each subject, selected medical information redacted for subject identity was sent to the sponsor for eligibility adjudication, and if accepted by the sponsor, the screening assessment for that subject was formally completed and the subject was enrolled into the study. Although this is not inconsistent with GCP, this screening practice was cited for not consulting the IRB about sharing selected subject information with the sponsor, even if the information shared had been adequately redacted to protect subject confidentiality.

- Subject eligibility worksheets (including laboratory worksheets) were not signed by the study staff during screening (signed later) for 10 of the 15 enrolled subjects. The CI review and confirmation of subject eligibility was consistently not documented on the worksheets (or elsewhere) for 11 of the 15 enrolled subjects.
- A serious adverse event (SAE) of sustained migraine in Subject 9006 was not reported to the sponsor until six days later. The protocol specifies SAE reporting within 24 hours.
- A case of febrile neutropenia with back pain requiring hospitalization was not immediately recognized as serious and was not reported to sponsor as SAE until one month later. As stated previously, the protocol specifies SAE reporting within 24 hours.
- Laboratory tests were not always obtained according to the study protocol:
    - No urinalysis for Subjects 9011, 9012, 9013, and 9014.
    - No electrolytes for Subject 9009.
- Physical examination findings during screening for Subject 9015 were not adequately documented, to include no documentation of Tanner Stage of Development Score and inadequate documentation for the examination of the eyes, abdomen, and lymph nodes.
- Insomnia and lip numbness reported by Subject 9003 at Visit 2 were not reported to the sponsor, and not documented in the study records as AEs.
- Vincristine chemotherapy administered to Subject 9010 was not reported as a concomitant medication.

Additionally, it was noted that paper records were not "optimally organized" to facilitate review, minor inconsistencies in pain scoring, vital signs taken outside the protocol-specified window, calcium levels were not corrected for albumin, poor collection of patient diaries, and poor clarification of discrepancies on these diaries. The DSI investigator stated that all verbal or cited deficiencies appear minor and unlikely to be significant. "The data from this study side appear reliable."

3.2.2 Site 1360A (Study OTR3001)

Twenty-one subjects were screened, 17 were enrolled, and 16 completed the study. Records were reviewed for all subjects, including detailed review for all enrolled subjects. The following deficiencies were observed.

- Although all doses were verifiable and accurate as specified in the study protocol, dose calculations were not shown on dose calculation worksheets.
- OxyContin was used as supplemental medication, prior to a protocol amendment which permitted its use as such on 2 subjects.
- A copy (not the original) of the informed consent form (IC) was only available for 1 subject.

Additionally, staff who were not qualified to do so, documented adverse events, there were incomplete drug accountability logs, and there were study notes about the ICs written by staff who did not participated in obtaining ICs. Overall, the DSI inspector noted, the deficiencies "reflected poor recordkeeping of otherwise adequate study conduct, including adequate informed consent, AE reporting, and drug accountability. The data from this study site was deemed reliable.

3.2.3 Site 0033A

3.2.3.1 Study OXP3003

Twenty-seven subjects were screened, 26 were enrolled, and 24 completed the study. Records were reviewed for all enrolled subjects, including a detailed review for 10 subjects completing study. The following deficiencies were observed.

- One subject (26006) was enrolled under the minimum protocol-specified weight.
- For the first 9 of the 15 months of the study, the temperature logs for the freezer were not conducted. The DSI inspector commented that "inadequate freezer temperature log may indicate more than inadequate recordkeeping and may include inadequate PK blood sample handling and storage for much of the study period (nine of 15 months). A comparison of the PK data from this CI site with those from other CI sites may be helpful in evaluating the reliability of the PK data from this CI site".
- The IC document for one subject was the IC for another study (OXP1005).
- Assent was not obtained for a 7-year old subject.
- For some subjects, outdated ICs were used.
- WhiteOut was "occasionally" used to correct study records, making it difficult to track interpret, or otherwise audit the correction.

There were differences between the Sponsor and the CI regarding the use of propofol and within 24 hours of expected study enrollment. These differences were based on whether or not propofol is a CYP3A4 inhibitor, which will be discussed further on the next section. "Overall, the study conduct appears to be GCP-compliant, including for IC, AE reporting, and drug accountability." The data from this study site was deemed reliable by the DSI inspector.

3.2.3.2 Study OXP1005

Twenty-nine subjects were screened, 26 were enrolled, and 23 completed the study. Records were reviewed for all enrolled subjects, including detailed review for 10 subjects completing study. The following deficiencies were observed.

- Although the protocol specified a gestational age > 36 weeks for a child who was less than one year of age to be enrolled, 1 subject (34015) born at 29 weeks gestation was enrolled at age of six months.

- As discussed on the site investigation for Study OXP3003, the temperature log for the freezer in which PK blood samples were stored did not include the first nine of the total 15 months of storage.
- Some concomitant medications (fentanyl, acetaminophen, potassium chloride, milrinone, and sodium bicarbonate) for Subject 34001 were not reported on the NDA, apparently due to the Sponsor's mishandling of 2 pages of the case report form.
- WhiteOut was "occasionally" used to correct study records, making it difficult to track interpret, or otherwise audit the correction.
- Just like in Study OXP3003, there were disagreements between the Sponsor and the CI at this site. In this study, the disagreements stem from the enrollment of some (unidentified) subjects without the Sponsor's written concurrence for potentially exclusionary conditions. The CI's position is that the sponsor's concurrence was not necessary, and documented as part of study records that the following conditions (sponsor's concerns) were clearly not protocol deviations as applicable to each subject at time of enrollment:
    - Clinically significant hepatic dysfunction, as evidenced by bilirubin > 18mg/dl, aspartate aminotransferase (AST) >100 IU/L, and/or alanine aminotransferase (ALT) > 80 IU/L

      CI response: Transiently elevated bilirubin and/or liver enzymes, typical following cardiac surgery, do not indicate clinically significant hepatic dysfunction in the subjects enrolled.

      Reviewer's comment: Although elevated transaminases are not necessarily specific to hepatic dysfunction, the Sponsor explicitly specified cutoffs values for AST and ALT. However, this is unlikely to significantly impact the reliability of the data.
    - Receipt of propofol within 24 hours of expected enrollment, in deviation of the study protocol which specifies the receipt of a CYP3A4 inhibitor as an exclusion criterion.

      CI response: Propofol was not on the list of protocol-prohibited drugs, and is not commonly thought of as a CYP3A4 inhibitor.

      Reviewer's comment: After a quick review of the literature, it appears that that propofol inhibits CYP3A4 in vitro and in vivo. However, it may not have been absolutely clear at the time the OXP3003 and OXP1005 were done and it was not listed on the protocol-specified prohibited drugs. The use of propofol is unlikely to significantly impact the reliability of the data.
    - Insertion of a Blalock-Taussig (BT) shunt within 30 days of expected enrollment, in deviation of the study protocol which specifies subject exclusion for insertion of any intra-cardiac or intracranial experimental device within 30 days of expected enrollment.

      CI response: The BT shunt is a small synthetic tube inserted during the Blalock surgical procedure. Neither the Blalock procedure nor the BT shunt is experimental.

The DSI inspector commented that "these sponsor-identified concerns do not appear to be true protocol deviations, as discussed by the CI at inspection and documented as part of study records". However, it should be noted that this site provided a significant proportion of patients for both, Study OXP3003 and OXP1005. Because of this, the lack of refrigeration logs for 9 out of 15 months could potentially have a significant impact if it is determined that improper handling of the blood samples could have affected the PK analysis for the test drug by the Clinical Pharmacology reviewer.

In summary, for all 4 study-sites audited, the observed GCP deficiencies were minor, and all were isolated and/or otherwise unlikely to be significant. Study conduct appeared adequate at all three CI sites inspected, as did IRB oversight and sponsor monitoring of CI's study conduct. At the time of this writing, these findings are preliminary.

3.3 Financial Disclosures

No financial arrangements were identified that would affect the approvability of this application.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new data was submitted with this supplemental application.

4.2 Clinical Microbiology

No new data was submitted with this supplemental application.

4.3 Preclinical Pharmacology/Toxicology

No new data was submitted with this supplemental application.

4.4 Clinical Pharmacology

Oxycodone is a full opioid agonist. It is relatively selective for the mu receptor, although it can bind to other opioid receptors at higher doses. The principal therapeutic action of oxycodone is analgesia. Clinically, oxycodone's dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression.

A detailed discussion of this application's clinical pharmacology analysis is contained in the review by Dr. Srikanth Nallani, clinical pharmacology reviewer.

The majority of the text below comes from OxyContin's latest approved label.

4.4.1 Mechanism of Action

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

4.4.2 Pharmacodynamics (Source: OxyContin label)

A single-dose, double-blind, placebo-and dose-controlled study was conducted using OxyContin (10, 20, and 30 mg) in an analgesic pain model involving 182 patients with moderate to severe pain. OxyContin doses of 20 mg and 30 mg produced statistically significant pain reduction compared to placebo.

4.4.2.1 Effects on the Central Nervous System

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in CO_2 tension and to electrical stimulation.

Oxycodone depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

4.4.2.2 Effects on the Gastrointestinal Tract and Other Smooth Muscle

Oxycodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

4.4.2.3 Effects on the Cardiovascular System

Oxycodone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

4.4.2.4 Effects on the Endocrine System

Opioids inhibit the secretion of ACTH, cortisol, testosterone, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

4.4.2.5 Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in in vitro and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

4.4.2.6 Concentration–Efficacy Relationships

Studies in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects, such as pupillary constriction, sedation, overall subjective “drug effect”, analgesia and feelings of relaxation. The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of oxycodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance.

4.4.2.7 Concentration –Adverse Reaction Relationships

There is a relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related side effects.

4.4.3 Pharmacokinetics (Source: OxyContin label))

The activity of OxyContin is primarily due to the parent drug oxycodone. OxyContin is designed to provide delivery of oxycodone over 12 hours. Cutting, breaking, chewing, crushing or dissolving OxyContin impairs the controlled-release delivery mechanism and results in the rapid release and absorption of a potentially fatal dose of oxycodone.

Oxycodone release from OxyContin is pH independent. The oral bioavailability of oxycodone is 60% to 87%. The relative oral bioavailability of oxycodone from OxyContin to that from immediate-release oral dosage forms is 100%. Upon repeated dosing with OxyContin in healthy subjects in pharmacokinetic studies, steady-state levels were achieved within 24-36 hours. Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The apparent elimination half-life (t½) of oxycodone following the administration of OxyContin was 4.5 hours compared to 3.2 hours for immediate-release oxycodone.

4.4.3.1 Absorption

About 60% to 87% of an oral dose of oxycodone reaches the central compartment in comparison to a parenteral dose. This high oral bioavailability is due to low pre-systemic and/or first-pass metabolism.

4.4.3.2 Plasma Oxycodone Concentration over Time

Dose proportionality has been established for OxyContin 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg tablet strengths for both peak plasma concentrations (Cmax) and extent of absorption (AUC) (see table below). Given the short elimination t½ of oxycodone, steady-state plasma concentrations of oxycodone are achieved within 24-36 hours of initiation of dosing with OxyContin. In a study comparing 10 mg of OXYCONTIN every 12 hours to 5 mg of immediate-release oxycodone every 6 hours, the two treatments were found to be equivalent for AUC and C_{max}, and similar for C_{min} (trough) concentrations.

4.4.3.3 Food Effects

Food has no significant effect on the extent of absorption of oxycodone from OxyContin.

4.4.3.4 Distribution

Following intravenous administration, the steady-state volume of distribution (Vss) for oxycodone was 2.6 L/kg. Oxycodone binding to plasma protein at 37°C and a pH of 7.4 was about 45%. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen, and brain. Oxycodone has been found in breast milk.

4.4.3.5 Metabolism

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 Ndemethylation to noroxycodone is the primary

metabolic pathway of oxycodone with a lower contribution from CYP2D6 mediated O-demethylation to oxymorphone. Therefore, the formation of these and related metabolites can, in theory, be affected by other drugs.

Noroxycodone exhibits very weak anti-nociceptive potency compared to oxycodone, however, it undergoes further oxidation to produce noroxymorphone, which is active at opioid receptors. Although noroxymorphone is an active metabolite and present at relatively high concentrations in circulation, it does not appear to cross the blood-brain barrier to a significant extent. Oxymorphone is present in the plasma only at low concentrations and undergoes further metabolism to form its glucuronide and noroxymorphone. Oxymorphone has been shown to be active and possessing analgesic activity but its contribution to analgesia following oxycodone administration is thought to be clinically insignificant. Other metabolites (α-and ß-oxycodol, noroxycodol and oxymorphol) may be present at very low concentrations and demonstrate limited penetration into the brain as compared to oxycodone. The enzymes responsible for ketoreduction and glucuronidation pathways in oxycodone metabolism have not been established.

4.4.3.6 Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free and conjugated oxycodone 8.9%, free noroxycodone 23%, free oxymorphone less than 1%, conjugated oxymorphone 10%, free and conjugated noroxymorphone 14%, reduced free and conjugated metabolites up to 18%. The total plasma clearance was approximately 1.4 L/min in adults.

4.4.3.7 Specific Populations

4.4.3.7.1 Geriatric Use

The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects (age 21-45).

4.4.3.7.2 Gender

Across individual pharmacokinetic studies, average plasma oxycodone concentrations for female subjects were up to 25% higher than for male subjects on a body weight-adjusted basis. The reason for this difference is unknown.

4.4.3.7.3 Renal Impairment

Data from a pharmacokinetic study involving 13 patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) showed peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, and AUC values for oxycodone, noroxycodone, and oxymorphone 60%, 50%, and 40% higher than normal

subjects, respectively. This was accompanied by an increase in sedation but not by differences in respiratory rate, pupillary constriction, or several other measures of drug effect. There was an increase in mean elimination t½ for oxycodone of 1 hour.

4.4.3.7.4 Hepatic Impairment

Data from a study involving 24 patients with mild to moderate hepatic dysfunction show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, than healthy subjects. AUC values are 95% and 65% higher, respectively. Oxymorphone peak plasma concentrations and AUC values are lower by 30% and 40%. These differences are accompanied by increases in some, but not other, drug effects. The mean elimination t½ for oxycodone increased by 2.3 hours.

4.4.3.7.5 Drug-Drug Interactions

4.4.3.7.5.1 CYP3A4 Inhibitors

CYP3A4 is the major enzyme involved in noroxycodone formation. Co-administration of OXYCONTIN (10 mg single dose) and the CYP3A4 inhibitor ketoconazole (200 mg BID) increased oxycodone AUC and Cmax by 170% and 100%, respectively.

4.4.3.7.5.2 CYP3A4 Inducers

A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, decreased oxycodone AUC and Cmax values by 86% and 63%, respectively.

4.4.3.7.5.3 CYP2D6 Inhibitors

Oxycodone is metabolized in part to oxymorphone via CYP2D6. While this pathway may be blocked by a variety of drugs such as certain cardiovascular drugs (e.g., quinidine) and antidepressants (e.g., fluoxetine), such blockade has not been shown to be of clinical significance with OXYCONTIN.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

This supplemental application is supported by three principal studies, as required by the Written Request, (OXP3003, OTR3001, and OXP1005).

Table 2. Written Request-Required Studies

Study ID/ Design	Age and Characteristics of Study Population	Study and Control Drugs Dose Regimen	Number of Patients/Arm	Efficacy endpoints	Principal Results
ORT3001 Open-label multiple dose Inpatient and outpatient Duration of treatment was up to 4 weeks	Opioid-tolerant children 6 to 16 years old with moderate to severe malignant or nonmalignant pain	Controlled-release oxycodone HCl (ORF: OxyContin) tablets, q12h	155 patients	-Supplemental pain medication usage - "pain right now" scores -Parent/Caregiver-Assessed Global Impression of Change (PGIC) -Functional Disability Inventory (FDI)	Pain control with oxycodone was "good": Mean pain-right-now scores (VAS) in the older group decreased from 44.58 at baseline to 35.58 (morning) and 35.30 (evening) at Week 4. Among younger patients, scores (FPS-R) decreased from 4.44 at baseline to 3.13 (morning) and 3.42 (evening) at Week 4. Overall, few (16.1%) patients needed to increase dose. Supplemental pain medication (opioid) was administered to 73.5% and (non-opioid) to 59.4% of patients. Use of supplemental short-term opioid medications and non-opioid supplemental pain medications was approximately the same in the 2 age groups.
OXP3003 Double-blind, placebo-controlled, multiple dose. All patients were in-patients. Duration of treatment was up to 2 days.	Patients 5 to ≤ 16 years of age who were opioid-naïve at study entry or preoperatively (for surgical patients) and who were anticipated to have moderate to severe pain requiring opioid analgesia for ≥2 days	Oxycodone HCl oral solution (1 mg/mL); q6h for 18 - 24 hrs (4-5 doses): 0.1 mg/kg 0.2 mg/kg Matching oral placebo; q6h for 18 - 24 hrs (4-5 doses)	24 patients - 0.10 mg/kg 22 patients - 0.20 mg/kg (*Total = 46 pts treated with oxycodone*); *19 patients received placebo.*	-Supplemental pain medication usage (PCA morphine, total opioid, acetaminophen) - "pain-right- now" scores	Patients in active treatment arms used significantly less PCA morphine (P = 0.047) and acetaminophen (P = 0.039) and across all doses reported significantly lower mean pain scores (P = 0.030) compared with the placebo group. Total opioid pain medication usage followed a similar pattern to that of PCA morphine.

Study ID/ Design	Age and Characteristics of Study Population	Study and Control Drugs Dose Regimen	Number of Patients/Arm	Efficacy endpoints	Principal Results
OXP1005 Multicenter, open-label, group-sequential, dose-ranging, phase 1 PK and safety study.	Hospitalized, postsurgical pediatric patients from birth to 4 years of age who were opioid-naïve at study entry or preoperatively (for surgical patients) with moderate to severe pain requiring opioid analgesia for ≥2 days	Oxycodone HCl oral solution (1 mg/mL) to be given q6 hours for 7 doses: -0.05 mg/kg -0.1 mg/kg -0.2 mg/kg	60 patients total: - 26 patients on the 0.05 mg/kg dose -17 patients on the 0.1 mg/kg dose -17 patients on the 0.2 mg/kg dose	-Supplemental pain medication usage (PCA morphine, total opioid, acetaminophen) - "pain-right- now" scores	Supplemental pain medication use and pain intensity scores were similar across the 3 dosing groups at all dosing intervals. Means for supplemental medication use for the 0.05, 0.10 and 0.20 mg/kg dose groups respectively were 0.09, 0.18, & 0.25 for PCA morphine; 0.14, 0.20, & 0.25 for total opioids; and 28.42, 23.49, & 32.08 for acetaminophen. The dose-response relationship with respect to mean and maximum pain scores at first dose interval (P = .927 and P = .968, respectively) and at all dose intervals (P = .948 and P = .971, respectively) were not statistically or clinically significant.

(Source: Derived from Table 1, pages 12-15, of the Summary of Clinical Efficacy.)

In addition to the required studies summarized above, the following four studies were submitted in support of the supplemental application. Three are pharmacokinetic studies (OXP3004, OTR1020, and OC96-0602) and the last one (OTR3002), was conducted for the purpose of collecting long-term safety data.

Table 3. Additional Studies in Support of the Application

Trial ID	Trial Design; Control Type	# 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
OC96-0602	Open-label, randomized, 2-way crossover, phase 1 PK study in patients 5 to 12 years	n=13/11: Period 1: OxyIR: n=7 OC: n=6 Period 2: OxyIR: n=5 OC: n=6	Hospitalized, postsurgical pediatric pts (5 to 12 y) receiving opioids	7M/6F mean, 9.6 y (6-12 y) 5/8/0/0	Up to 2 d	Original OxyContin tablet: 10 mg PO Oxycodone immediate release: 5 mg PO
OXP3004 (terminated early for administrative reasons)	Multicenter, open-label, phase 3, opioid conversion study	Conversion phase with Oxy IR: n=10/7 Long-term phase with OxyContin: n=7/6	Hospitalized (at entry) pediatric pts With moderate-to severe chronic pain	Conversion Phase: 6M/4F 12 y (7-16 y) (7/2/0/1) Long-term Phase: 5M/2F 12 y (7-16 y) (6/0/0/1)	Conversion Phase: Up to 3 d Long-term Phase: Up to 3 mo	Immediate release oxycodone (OxyIR): 5 mg capsules OXYCONTIN (original formulation): 10 mg tablets
OTR3002	Multicenter, open-label, long-term extension to Study OTR3001	Enrolled: n=23 Completed: n=21	Opioid-tolerant pediatric in-or outpts with moderate to severe, malignant or nonmalignant pain	10M/13F 12 y (6-16y) (16/7/0/0)	Up to 6 mo	OXYCONTIN (reformulated tablet): 20 to 240 mg total daily dose
OTR1020	Open-label, single or multiple dose, group sequential, ascending dose regimen	Planned: n=36 Safety population n=30 Completed n=28	Hospitalized, postsurgical pediatric pts with moderate-to severe pain	13M/17F 13 y (9-16y) (25/4/0/1)	0 to 24-h (single dose) 0 to 72-h (5 doses) tx period Follow-up for 7-10 d beginning 24 h after last dose	OXYCONTIN (reformulated tablet) 10, 15, 20 mg

(Source: Derived from Table 1, pages 12-15, of the Summary of Clinical Efficacy.)

5.2 Review Strategy

As previously discussed, this application consists of 3 principal studies, as requested by the Pediatric Written Request: OXP1005 or Written Request Study #1, OXP3003 or Written Request Study #2, and OTR3001 or Written Request Study #3. These will be described extensively below. The additional four studies (OXP3004, OTR1020, OC96-0602, and OTR3002) will be outlined and key findings will be highlighted.

Although Purdue has submitted OXP3003 and OTR3001 with the intent to support the OxyContin's efficacy, OTR3001 is an open-label study and cannot, by design, formally support efficacy. Only study OXP3003 will be reviewed for efficacy although it suffers from some design weaknesses.

I should be noted that, if Purdue was asked to do these studies under today's standards (summarized in the Berde *et al*. article) the Food and Drug Administration would require these studies to evaluate the safety, dose response profile, and the pharmacokinetic profile of the drug on this population and then extrapolate efficacy for patients as young as 2 years of age.

All seven studies submitted will be evaluated in regards to major safety findings, such as deaths and nonfatal serious adverse events. The principal studies (OXP3003, OTR3001, and OXP1005) will be analyzed to evaluate the general safety of the study drug (common adverse events, laboratory findings, etc.) and specific supporting studies will be discussed if thought to contribute unique findings or perspectives.

Finally, I will examine the Postmarketing pediatric data for OxyContin from approval in 1995 through June, 2014.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study OXP3003

The following summary of the design of Study OXP3003 was derived from the revised protocol incorporating Amendment 2, dated August 12, 2002.

Title: 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) versus Placebo in the Treatment of Acute Moderate to Severe Pain.

5.3.1.1 Dates Conducted:

Study Start Date: January 31, 2003
Study End Date: April 3, 2004

5.3.1.2 Objectives:

The primary objectives were:

- To characterize the pharmacokinetics (using a population PK approach) of Oxy Pediatric Liquid (1 mg/mL) after the first dose and after repeated dosing in pediatric patients 5 to ≤16 years of age.
- To evaluate the safety of Oxy Pediatric Liquid (1 mg/mL) in pediatric patients 5 to ≤16 years of age.

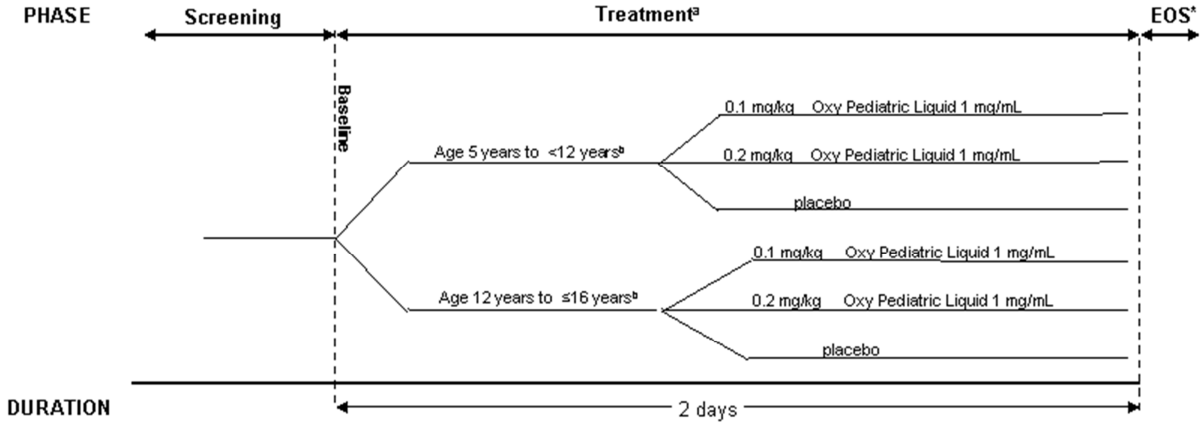
The secondary objective was:

- To characterize efficacy of Oxy Pediatric Liquid (1mg/mL), based on supplemental analgesic requirements and pain scores in pediatric patients 5 to ≤16 years of age.

5.3.1.3 Study Design

Study OXP3003 was a multicenter, double blind, randomized, placebo-controlled, dose-ranging study using Oxy Pediatric Liquid 1mg/mL and placebo, in children 5 to ≤16 years of age, who were receiving morphine as standard supplemental pain medication. The study was stratified into two age groups (5 years to <12 years and 12 years to ≤16 years). Patients were randomized to receive treatment with 0.1 mg/kg Oxy Pediatric Liquid, 0.2 mg/kg Oxy Pediatric Liquid or placebo q6 hours for 18 to 24 hours (4 to 5 doses) and they were randomization on a 3:3:2 ratio. All patients were allowed to receive PCA or oral morphine sulfate (if the intravenous route stopped functioning) as supplemental pain medication during double blind treatment. Patients needed to be able to take morphine in order to be eligible to participate in the study.

Figure 1. OXP3003 Study Schematic



*EOS= End of Study
(Source: OXP3003 Study Report, Figure 1, page 23)

5.3.1.4 Population

In this study, children 5 to ≤16 years of age who are opioid naïve at study entry or pre-operatively (for surgical patients) were enrolled. The protocol stated that sufficient number of patients were to be enrolled to achieve at least 100 PK evaluable patients, with approximately equal number of patients in the 5 to <12 year old age group and in the 12 to ≤16 year old age group, aiming to enroll an equal number of males and females.

5.3.1.5 Inclusion Criteria

Patients were to have met all of the following criteria:

- Male or female patients 5 to ≤16 years of age.
- Anticipated to have moderate to severe pain requiring conversion to treatment with an oral opioid analgesic for 2 or more days.
- Inpatient at the time of enrollment.
- Weight must be ≥15 kg at the time of study entry. Children less than 15 kg will be evaluated on a case-by-case basis by the Sponsor to determine eligibility based on their requirement for opioid therapy.
- Patients of child bearing potential must have a negative urine pregnancy test and must be using an acceptable form of birth control. If the patient is post-operative, the pre-operative pregnancy test will suffice. Acceptable forms of birth control including but not limited to the following: abstinence, birth control pills, intra-uterine device, depot and implant preparations.
- Sufficiently alert to communicate and perform study related procedures.
- Written informed consent from parent or legal guardian and child assent if appropriate in accordance with local regulations and the policies of the Investigator's IRB/IEC.
- Postoperative surgical patients receiving intravenous PCA for pain control will be eligible for inclusion.

5.3.1.6 Exclusion Criteria:

Patients were to have been excluded if any of the following applied:

- American Society of Anesthesiologists Physical Status ≥4 (severe, life threatening disease). Exception: Patients with cancer who would otherwise meet this criterion may be enrolled.
- Unable to take clear liquids.
- History of sleep apnea.
- Cystic Fibrosis.
- Malabsorption syndromes.
- Sickle Cell Anemia.
- Allergy to oxycodone.
- Unable to take morphine.

- Current oxycodone therapy (within 72 hours of study entry).
- Known clinically significant renal or hepatic disease or dysfunction.
- Receiving clonidine or dexmedotomidine for sedation/analgesia.
- Requiring mechanical ventilation.
- Anticipated need for or currently taking NSAIDs or acetaminophen (paracetamol) other than for pyrexia.
- Patients who have received an investigational drug within 30 days of screening and who meet all other criteria will be evaluated on a case-by-case basis by the investigator and sponsor to determine study eligibility.
- Family members of employees of Purdue Pharma L.P. or the clinical investigative site staff.
- Patients who, in the opinion of the investigative staff, are not well suited for the study.
- Patients contra-indicated for the use of opioids.
- Nonsurgical patients who have taken opioids within 30 days prior to study entry.

5.3.1.7 Withdrawal/Discontinuation Criteria

Patients were supposed to be discontinued or be withdrawn from the study under any of the following circumstances:

- Patient cannot tolerate the study medication.
- Patient or their parent (s)/legal guardian request withdrawal from the trial.
- In the investigator's opinion it is in the patient's best interest to discontinue.
- Patient continues to have pain despite maximum PCA dosing.

In addition to recording the reason for discontinuation on the CRF, all end-of-study assessments (physical examination, vital signs, pulse oximetry, somnolence evaluation, pain scores and safety laboratory tests) were to be performed at the time of discontinuation.

If a patient was discontinued due to an adverse event, an additional blood sample for PK analysis was to be collected at the time of discontinuation. Patients who were discharged from the hospital prior to completing the study could have PK samples collected at home.

A patient was considered as completing the study if all scheduled doses of study drug had been administered and if the patient was followed until the last scheduled PK blood draw, which was 4 – 8 hours after the last dose.

5.3.1.8 Study Methods

5.3.1.8.1 Schedule of Visits and Procedures

Table 4. Summary of Schedule of Visits and Procedures. Study OXP3003

		Study Period			
	Pre-Study Screening	Baseline Day 1 Pre-Dose	Day 1	Day 2	End of Study
Informed consent	X				
Demographics		X			
Inclusion/Exclusion	X				
Medical history		X			
Prior medications		X[1]			
Physical examination		X			X
Tanner staging		X			
Laboratory tests		X			X
Pregnancy Test[2]		X			
Vital signs, Hemoglobin-Oxygen Saturation and Somnolence[3]		X	X	X	X
Study Drug			X[4]	X[4]	
PK blood samples			X	X	X
Pain score[3]		X	X	X	X
Supplemental pain medication[5]			X	X	X
Drug accountability			X	X	X
Adverse events		X	X	X	X
Concomitant medications		X	X	X	X

(Source: Protocol OXP3003, Table 9.4.1A, page 20)
[1]All medications taken within the past 7 days will be recorded. All opioid medications taken within 30 days prior to study drug administration will also be recorded.
[2]Urine pregnancy test will be performed on all patients of childbearing potential. If patient is post-operative and a pre-operative pregnancy test was performed then the pre-operative pregnancy test will suffice.
[3]Vital signs, Hemoglobin-Oxygen Saturation, Somnolence score and Pain Scores will be obtained as follows:
• At baseline (before administration of study medication)
• After the first dose: At 0.5h, 1.0h, 2.0h and 3.0h post dose.
• Subsequent doses of study drug: immediately prior to each dose and one hour after each dose
• At the end of study
[4]Oxy Pediatric Liquid or placebo will be administered q6 hours as per randomization code
[5]Supplemental Pain Medication:
• All patients will be allowed to receive PCA morphine as supplemental pain medication during double blind treatment. Patients will be allowed to receive oral morphine only if patient no longer has intravenous access.
• If a patient is unable to take morphine then they are not elig ble to participate in this study.

5.3.1.8.1.1 Screening and Baseline

Screening was to be performed any time up to 14 days prior to study drug administration. Baseline procedures included medical history and physical examination, collecting medication history during the 7 days prior to study drug dosing, vital signs, hemoglobin-oxygen saturation, somnolence score, pain score, laboratory tests, and opioid medication history during the 30 days prior to study drug dosing will also be collected. Safety laboratory tests were to be performed by a local laboratory.

5.3.1.8.1.2 Study Drug Dosing

For post-operative patients, study drug dosing could begin as soon as the patient was ready to take clear oral liquid. Patients were to be randomized (double-blind) to receive oral Oxy Pediatric Liquid 0.1 mg/kg, 0.2 mg/kg or placebo every 6 hours for up to 48 hours. Patients could receive PCA with morphine sulfate 15 mcg/kg/dose with an 8-minute lockout, maximum 6 doses/hour or oral morphine sulfate (0.1 – 0.3 mg/kg q2h), if the intravenous stops functioning. If a patient continued to have pain despite maximum PCA dosing, the investigator was expected to re-assess the patient and consider increasing the maximum dose of supplemental pain or withdraw the patient from the study.

5.3.1.8.1.3 Blood Collections for Pharmacokinetic Analyses

The protocol called for a maximum of 8 blood samples (when feasible) of 1 ml each to be collected over the entire study period to assess for oxycodone and oxycodone-metabolites concentration as well as for morphine concentration. Blood samples were to be collected in accordance with the time windows specified in the table below and the sites were to select a convenient sampling time within each specified time window for PK sample collection. However, at least a one-hour interval between each sample collection was necessary.

Table 5. Schedule for PK Sample Collection. Study OXP3003

Time	Dose	Study Drug	PK Samples[1]		
			No of Samples	Time Windows Post Dose	Actual Time Since First Dose
0h	1	Oxy Pediatric Liquid or Placebo q6h	3	0.5h < 2h	0.5h < 2h
				2h < 4h	2h < 4h
				4h - 6h	4h - 6h
6h	2	Oxy Pediatric Liquid or Placebo q6h	1	2h - 4h	8h - 10h
12h	3	Oxy Pediatric Liquid or Placebo q6h	1	2h - 4h	14h - 16h
18h	4	Oxy Pediatric Liquid or	3 (PK samples	0h < 2h	18h < 20h
				2h < 4h	20h < 22h

Time	Dose	Study Drug	PK Samples[1]		
			No of Samples	Time Windows Post Dose	Actual Time Since First Dose
		Placebo q6h	only if this is the last dose)	4h - 8h	22h - 26h
24h	5	Oxy Pediatric Liquid or Placebo q6h	3	0h < 2h	24h < 26h
				2h < 4h	26h < 28h
				4h - 8h	28h - 32h

(Source: Protocol OXP3003, Table 9.4.1B, page 23)
[1]If the study staff has prior knowledge of early discharge from hospital or discontinuation from study before administration of a dose then that dose will be considered the last dose and reasonable effort will be made to collect all PK samples in accordance with the time windows provided for the last dose. There must at least a one-hour interval between each sample.

5.3.1.8.1.4 End of Study

End of study procedures (i.e., physical examination, vital signs, hemoglobinoxygen saturation, somnolence assessment, pain score, supplemental pain medication usage and safety laboratory tests) were to be performed after the last PK blood sample or at the time of discontinuation.

5.3.1.8.2 Study Variables Assessed

5.3.1.8.2.1 Efficacy Variables

All doses of PCA morphine were to be recorded by total amount of morphine (mg) administered in one-hour period, number of doses in one-hour period, and route of administration on the case report form. All other supplemental pain medications were to be recorded by exact clock time for each dose, dose in milligrams, and route of administration on the case report form.

Pain scores (pain right now) were to be obtained using The Faces Pain Scale – Revised (FPS-R). The FPS-R consists of six facial expressions. Each face is 25 x 35 mm with 13 mm between faces. Patients were to be asked to point to the face that reflects his or her pain. The end points were 0 = no pain and 10 = very much pain.

- At baseline (before administration of study medication).
- After the first dose: At 0.5h, 1.0h, 2.0h and 3.0h post dose.
- Subsequently pain scores were to be obtained immediately prior to each dose and one hour after each dose.
- Pain scores were also to be obtained at the end of study.
- Routine Children's Center nursing practice was to continue throughout the study.
- Routine nursing pain scores were to be obtained every 4 hours or obtained more often, if pain was uncontrolled.

5.3.1.8.2.2 Pharmacokinetic Metrics

A population PK modeling approach was planned to be applied to oxycodone and metabolites, in addition to morphine concentrations.

5.3.1.8.2.3 Safety Assessments

Safety assessments will consist of vital signs (including temperature, heart rate, blood pressure and respiratory rate), hemoglobin-oxygen saturation (measured by pulse oximetry), somnolence, physical examination, clinical laboratory tests and reports of adverse experiences.

The protocol called for the investigator to utilize ICH E2A definitions for adverse events (AEs) and serious adverse events (SAEs) during the conduct of the study. All AEs occurring during the course of the study regardless of causality was to be collected in the case report form along with a description of the event, date of onset, date of resolution (or that the event is continuing), action taken, severity/seriousness, outcome, and, the Investigator's assessment of relationship to study medication. A cluster of symptoms that resulted from a single diagnosis was to be reported as a single AE (eg, fever, elevated WBC, cough, abnormal chest x-ray, etc. could all be reported as "pneumonia.") All SAEs were to be reported to the Sponsor via fax within 24 hours of the Investigator's knowledge. The fax was expected to be followed by a completed Serious Adverse Event Data Form.

5.3.1.8.2.4 Laboratory Measurements

Safety laboratory tests were to be obtained as shown in the Summary of Schedule of Visits and Procedures.

For patients of childbearing potential, a urine pregnancy test was to be taken at baseline unless performed pre-operatively.

5.3.1.8.2.5 Vital Sign Measurements

Vital signs were to be obtained as shown in the Summary of Schedule of Visits and Procedures.

5.3.1.8.2.6 Somnolence

The University of Michigan Sedation Scale (categorical scale 0=awake to 4=unarousable to stimuli) was to be used to assess somnolence as shown in the Summary of Schedule of Visits and Procedures.

5.3.1.8.2.7 Hemoglobin-Oxygen Saturation

During treatment with study medication, hemoglobin-oxygen saturation was to be measured as shown in the Summary of Schedule of Visits and Procedures.

5.3.1.8.3 Analysis Plan

Analysis of the study variables was to be done mainly using descriptive statistics. Inference was to be conducted on efficacy variables and selected safety variables (somnolence, respiratory rate and hemoglobin oxygen saturation derived variables) using Jonckheere-Terpstra test and confidence intervals. P-values and confidence intervals were only to be presented for the first dose interval and for the overall summary block excluding the first dose interval. Data summaries were to be performed overall and by age-group. In the summaries by age group instead of presenting a column for p-values, a total column (across all treatment groups) was to be presented.

If the end of study visit was missing but there was data for an unplanned visit after the last intake of study medication, then the unplanned visit data should have been used as the end of study visit, provided that the visit was performed within seven days of the last intake of study drug. No covariates were to be used in the analyses. Missing prior/concomitant/past medication dates were to be imputed in order to assign a medication to dose intervals. No other imputation of missing data was to be done. No adjustments for multiplicity were to be performed in this study.

It is important to note that no primary or secondary endpoints were specified in the protocol.

5.3.1.9 Treatments

5.3.1.9.1 Treatments Administered

All patients were to receive morphine sulfate as standard supplemental pain medication. The protocol called for the study medication to be administered to patients orally using Amber Oral Dosing Syringes (provided by the Sponsor). Patients will be administered Oxy Pediatric Liquid or placebo orally every 6 hours for a total of 4 to 5 doses. In the case of post-operative patients, study treatment was to commence when the patients were ready to take oral liquids.

Dosing was based on the weight of the patient. The three treatment groups were

- Oxy Pediatric Liquid 0.1 mg/kg
- Oxy Pediatric Liquid 0.2 mg/kg
- Placebo

In order to maintain the blind, total volume dispensed by the pharmacist should have matched the total volume that would be dispensed at the highest dose (i.e., 0.2mg/kg).

Randomization was to be carried out as discussed in Section 5.3.1.3.

5.3.1.9.2 Blinding

Except in case of emergency, all personnel, including the investigators, site personnel (with the exception of the pharmacist and a pharmacy monitor), the clinical monitors, and the Purdue Pharma and/or designee monitoring staff were to be blinded to the randomization codes until the completion of the study and the final data.

5.3.1.9.3 Concomitant Therapy

All medications taken by the patient 7 days prior to study entry were to be recorded in the case report form, including name of the drug and duration of treatment. Opioid medication history during the 30 days prior to study drug dosing was also to be collected.

Patients, who had received oxycodone therapy within 72 hours of study entry, were not eligible to participate in this study. Continuous infusion morphine or other opioid must have been discontinued at least 2 hours prior to administration of the study drug. Epidurals were to be discontinued at least 4 hours before administration of study drug.

The following medications were not permitted 24 hours prior to study drug administration through the end of the study: clonidine hydrochloride for sedation/analgesia, oral trovafloxacin, CYP2D6 inhibitors (such as nefazodone, fluphenazine, thioridazine, or cimetidine), and CYP3A inhibitors (such as the azole antifungals, clarithromycin, erythromycin, or grapefruit juice).

5.3.1.10 OXP3003 Results

Study OXP3003 was terminated early due to “administrative reasons”, which are not clearly explained by Purdue, although they do specify it was not due to safety reasons.

5.3.1.10.1 Study Population

5.3.1.10.1.1 Patient Demographics

The table below, derived from Table 8 of the study’s report, is a summary of the demographic and baseline characteristics of the safety population by treatment group.

Table 6. Safety Population Demographic and Baseline Characteristics. Study OXP3003

Characteristics	Placebo (n = 19)	Oxy Pediatric Liquid 1mg/ml 0.1 mg/kg (n = 24)	Oxy Pediatric Liquid 1mg/ml 0.2 mg/kg (n = 22)	Total (N = 65)
Age (y)				
Mean (SD)	12.1 (2.94)	11.0 (3.43)	11.3 (3.90)	11.4 (3.44)
Median	13.0	12.0	12.5	12.0
Min, Max	5, 16	5, 16	5, 16	5, 16
Age Group, n (%)				
5 y to < 12 y	7 (36.8)	10 (41.7)	9 (40.9)	26 (40.0)
12 y to ≤16 y	12 (63.2)	14 (58.3)	13 (59.1)	39 (60.0)
Sex, n (%)				
Male	7 (36.8)	9 (37.5)	8 (36.4)	24 (36.9)
Female	12 (63.2)	15 (62.5)	14 (63.6)	41 (63.1)
Race, n (%)				
White	16 (84.2)	16 (66.7)	16 (72.7)	48 (73.8)
Black	1 (5.3)	3 (12.5)	1 (4.5)	5 (7.7)
Asian	1 (5.3)	1 (4.2)	0	2 (3.1)
Other	1 (5.3)	4 (16.7)	5 (22.7)	10 (15.4)
Tanner Puberty Staging, n (%)				
Stage 1	6 (31.6)	7 (29.2)	7 (31.8)	20 (30.8)
Stage 2	3 (15.8)	7 (29.2)	4 (18.2)	14 (21.5)
Stage 3	5 (26.3)	3 (12.5)	5 (22.7)	13 (20.0)
Stage 4	4 (21.1)	5 (20.8)	5 (22.7)	14 (21.5)
Stage 5	1 (5.3)	2 (8.3)	1 (4.5)	4 (6.2)
Weight (kg)				
Mean (SD)	43.44 (14.034)	43.28 (19.119)	44.35 (22.655)	43.69 (18.852)
Median	45.00	43.10	42.25	43.60
Min, Max	14.5, 62.0	16.8, 80.4	14.3, 101.0	14.3, 101.0
Height (cm)				
N	18	20	20	58
Mean (SD)	147.6 (21.82)	149.3 (25.22)	141.4 (32.06)	146.0 (26.62)
Median	155.0	155.5	152.0	154.0
Min, Max	91, 168	107, 196	44, 173	44, 196

5.3.1.10.1.2 Baseline Medical Conditions

The table below summarizes the medical history conditions for 10% or more of patients in the overall safety population.

Table 7. Baseline Medical Conditions Occurring in ≥ 10% of Patients. Study OXP3003

System Organ Class Preferred Term	Placebo (N=19) n (%)	Oxy Pediatric Liquid 1mg/mL 0.1mg/kg (N=24) n (%)	 0.2mg/kg (N=22) n (%)	Total (N=65) n (%)
Blood and lymphatic system disorders	**4 (21.1)**	**3 (12.5)**	**1 (4.5)**	**8 (12.3)**
Anaemia	2 (10.5)	3 (12.5)	0	5 (7.7)
Cardiac disorders	**6 (31.6)**	**10 (41.7)**	**6 (27.3)**	**22 (33.8)**
Pulmonary valve stenosis	1 (5.3)	3 (12.5)	1 (4.5)	5 (7.7)
Congenital, familial and genetic disorders	**8 (42.1)**	**13 (54.2)**	**12 (54.5)**	**33 (50.8)**
Arnold-Chiari malformation	2 (10.5)	0	0	2 (3.1)
Atrial septal defect	0	4 (16.7)	4 (18.2)	8 (12.3)
Ventricular septal defect	1 (5.3)	2 (8.3)	3 (13.6)	6 (9.2)
Gastrointestinal disorders	**6 (31.6)**	**4 (16.7)**	**5 (22.7)**	**15 (23.1)**
Constipation	2 (10.5)	1 (4.2)	2 (9.1)	5 (7.7)
Nausea	3 (15.8)	1 (4.2)	2 (9.1)	6 (9.2)
Vomiting	2 (10.5)	1 (4.2)	0	3 (4.6)
General disorders and administration site	**4 (21.1)**	**6 (25.0)**	**6 (27.3)**	**16 (24.6)**
Pyrexia	3 (15.8)	1 (4.2)	25 (19.5)	5 (7.7)
Injury, Poisoning And Procedural Complications	**13 (68.4)**	**12 (50.0)**	**14 (63.6)**	**39 (60.0)**
Postoperative fever	1 (5.3)	6 (25.0)	4 (18.2)	11 (16.9)
Procedural nausea	4 (21.1)	3 (12.5)	3 (13.6)	10 (15.4)
Procedural pain	8 (42.1)	9 (37.5)	11 (50.0)	28 (43.1)
Investigations	**5 (26.3)**	**6 (25.0)**	**4 (18.2)**	**15 (23.1)**
Catheterisation cardiac	2 (10.5)	2 (8.3)	1 (4.5)	5 (7.7)
Urine output decreased	2 (10.5)	1 (4.2)	0	3 (4.6)
Musculoskeletal and connective tissue disorders	**7 (36.8)**	**4 (16.7)**	**10 (45.5)**	**21 (32.3)**
Kyphosis	2 (10.5)	0	0	2 (3.1)
Muscle Spasms	1 (5.3)	0	3 (13.6)	4 (6.2)
Scoliosis	5 (26.3)	4 (16.7)	6 (27.3)	15 (23.1)
Nervous system disorders	**4 (21.1)**	**6 (25.0)**	**3 (13.6)**	**13 (20.0)**
Syringomyelia	2 (10.5)	1 (4.2)	0	3 (4.6)
Respiratory, thoracic and mediastinal disorders	**3 (15.8)**	**9 (37.5)**	**9 (40.9)**	**21 (32.3)**
Asthma	1 (5.3)	1 (4.2)	3 (13.6)	5 (7.7)
Atelectasis	0	3 (12.5)	4 (18.2)	7 (10.8)
Skin and subcutaneous tissue disorders	**3 (15.8)**	**3 (12.5)**	**3 (13.6)**	**9 (13.8)**
Pruritus	2 (10.5)	1 (4.2)	3 (13.6)	6 (9.2)
Surgical and medical procedures	**18 (94.7)**	**23 (95.8)**	**23 (95.8)**	**63 (96.9)**
Atrial septal defect repair	1 (5.3)	7 (29.2)	3 (13.6)	11 (16.9)
Bone graft	2 (10.5)	0	0	2 (3.1)

System Organ Class Preferred Term	Placebo (N=19) n (%)	Oxy Pediatric Liquid 1mg/mL 0.1mg/kg (N=24) n (%)	 0.2mg/kg (N=22) n (%)	Total (N=65) n (%)
Cardiac operation	3 (15.8)	3 (12.5)	2 (9.1)	8 (12.3)
Pulmonary valve replacement	0	3 (12.5)	1 (4.5)	4 (6.2)
Scoliosis surgery	2 (10.5)	2 (8.3)	0	4 (6.2)
Spinal fusion surgery	4 (21.1)	5 (20.8)	7 (31.8)	16 (24.6)
Ventricular septal defect repair	2 (10.5)	1 (4.2)	2 (9.1)	5 (7.7)
Vascular disorders	**5 (26.3)**	**5 (20.8)**	**2 (9.1)**	**12 (18.5)**
Hypertension	4 (21.1)	1 (4.2)	0	5 (7.7)

(Source: OXP3003's report, page 55, Table 10)

The most commonly reported medical history conditions (those reported in over 20% of patients) by MedDRA preferred term were procedural pain (43.1%), nausea (38.7%), spinal fusion surgery (26.5%), and scoliosis (23.9%). For in the 6 to less than 12 year group, the most commonly reported medical history conditions were constipation (55.6%), spinal fusion surgery (24.6%), and scoliosis (23.1). In terms of the MedDRA system organ class (SOC), the highest percentage of patients had "Surgical and medical procedures" (96.9%), "Injury, poisoning and procedural complitations" (60%), and "Congenital, familial, and genetic disorders" (50.8%).

5.3.1.10.1.3 Concomitant Therapies

The following table summarizes the concomitant therapies taken by patients.

Table 8. Concomitant Therapies. Study OXP3003

Anatomic Class Pharmacologic Class Pharmacologic Sub-class	Placebo (n = 19)	Oxy Pediatric Liquid 1mg/ml 0.1 mg/kg (n = 24)	 0.2 mg/kg (n = 22)	Total (N = 65)
Nervous System	19 (100.0)	24 (100.0)	22 (100.0)	65 (100.0)
Analgesics	19 (100.0)	24 (100.0)	22 (100.0)	65 (100.0)
Opioids	19 (100.0)	24 (100.0)	22 (100.0)	65 (100.0)
Fentanyl	18 (94.7)	21 (87.5)	20 (90.9)	59 (90.8)
Hydromorphone HCl	0	4 (16.7)	2 (9.1)	6 (9.2)
Morphine	16 (84.2)	19 (79.2)	13 (59.1)	48 (73.8)
Morphine sulfate	4 (21.1)	3 (12.5)	7 (31.8)	14 (21.5)
Nalbuphine	0	0	1 (4.5)	1 (1.5)
Nalbuphine hydrochloride	1 (5.3)	0	0	1 (1.5)
Oxycodone	1 (5.3)	0	0	1 (1.5)
Oxycodone hydrochloride	1 (5.3)	0	0	1 (1.5)
Panadeine Co	1 (5.3)	1 (4.2)	1 (4.5)	3 (4.6)
Pethidine hydrochloride	1 (5.3)	0	1 (4.5)	2 (3.1)
Vicodin	1 (5.3)	2 (8.3)	2 (9.1)	5 (7.7)
Other analgesics and antipyretics	14 (73.7)	17 (70.8)	16 (72.7)	47 (72.3)
Acetylsalicylic acid	0	2 (8.3)	2 (9.1)	4 (6.2)
Paracetamol (APAP)	14 (73.7)	14 (58.3)	15 (68.2)	43 (66.2)
Propacetamol hydrochloride	0	1 (4.2)	0	1 (1.5)

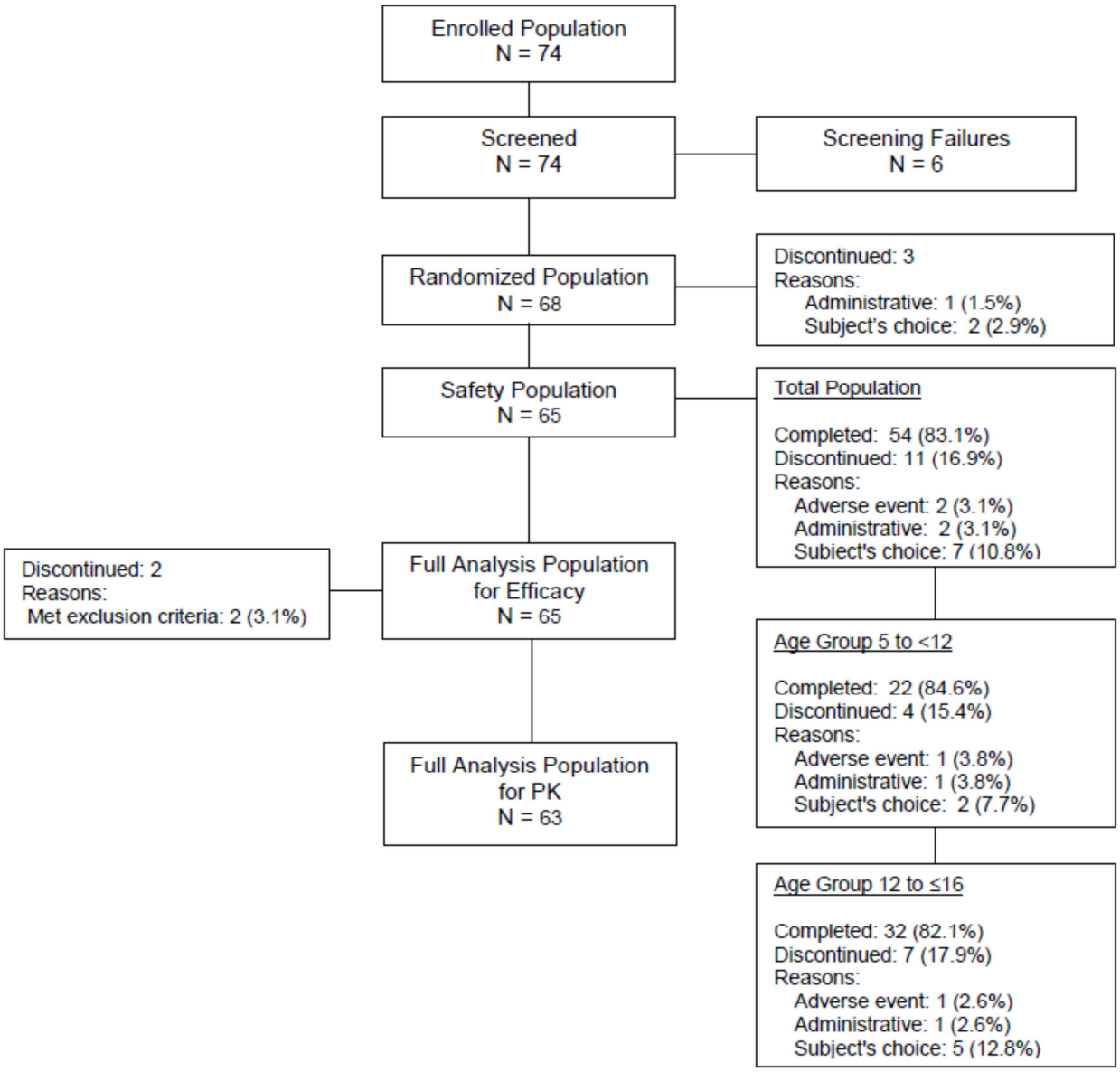
(Source: OXP3003's report, Table 9, page 54)

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

5.3.1.10.1.4 Patient disposition

Seventy-four patients were enrolled into the study, with 6 failing screening procedures and 68 finally being randomized. Of the 68 randomized subjects 1 subject (1.5%) did not complete the study due to administrative reason and 2 subjects (2.9%) did not complete the study due to "subject's choice". Patient disposition is summarized in the figure below.

Figure 2. Summary of Patient Disposition. Study OXP3003.



(Source: OXP3003's report, Figure 2, page 50)

Eleven patients in the safety population also discontinued due to "subject's choice. One patient from the Oxy Pediatric Liquid 0.1 mg/kg treatment group discontinued due to AEs. There were no AEs that led to discontinuation in the Oxy Pediatric Liquid 0.2 mg/kg treatment group.

The following table, derived from Study OXP3003's report (Table 7, page 51), presents the disposition of patients in the safety population by age group and the reasons for discontinuation.

Table 9. Patient Disposition and Reasons for Discontinuation by Age Group: Safety Population. Study OXP3003

Age Group	Placebo (n = 19)	Oxy Pediatric Liquid 1mg/ml 0.1 mg/kg (n = 24)	Oxy Pediatric Liquid 1mg/ml 0.2 mg/kg (n = 22)	Total (N = 65)
All Patients				
Completed, n (%)	15 (78.9)	18 (75.0)	21 (95.5)	54 (83.1)
Discontinued, n (%)	4 (21.1)	6 (25.0)	1 (4.5)	11 (16.9)
Adverse event	1[a] (5.3)	1 (4.2)	0	2 (3.1)
Subject's choice	3 (15.8)	3 (12.5)	1 (4.5)	7 (10.8)
Administrative	0	2 (8.3)	0	2 (3.1)
Age Group: 5 to <12 years	**n = 7**	**n = 10**	**n = 9**	**N = 26**
Completed, n (%)	6 (85.7)	7 (70.0)	9 (100.0)	22 (84.6)
Discontinued, n (%)	1 (14.3)	3 (30.0)	0	4 (15.4)
Adverse event	0	1 (10.0)	0	1 (3.8)
Subject's choice	1 (14.3)	1 (10.0)	0	2 (7.7)
Administrative	0	1 (10.0)	0	1 (3.8)
Age Group: 12 years to ≤ 16	**n = 12**	**n = 14**	**n = 13**	**N = 39**
Completed, n (%)	9 (75.0)	11 (78.6)	12 (92.3)	32 (82.1)
Discontinued, n (%)	3 (25.0)	3 (21.4)	1 (7.7)	7 (17.9)
Adverse event	1 (8.3)	0	0	1 (2.6)
Subject's choice	2 (16.7)	2 (14.3)	1 (7.7)	5 (12.8)
Administrative	0	1 (7.1)	0	1 (2.6)

[a] Patient experienced a pretreatment-emergent AE (vomiting) before placebo administration.

5.3.1.10.2 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. The following table summarizes the extent of exposure for Study OXP3003.

Table 10. Summary of Extent of Exposure Oxy Pediatric Liquid: Safety Population. Study OXP 3003.

Extent of Exposure (Doses) All Patients	Placebo (N=19) n (%)	Oxy Pediatric Liquid 1mg/mL		Total (N = 65) n (%)
		0.1 mg/kg (N = 24) n (%)	0.2 mg/kg (N = 22) n (%)	
≥1	19 (100.0)	24 (100.0)	22 (100.0)	65 (100.0)
≥2	16 (84.2)	22 (91.7)	21 (95.5)	59 (90.8)
≥3	16 (84.2)	21 (87.5)	21 (95.5)	58 (89.2)
≥4	16 (84.2)	19 (79.2)	21 (95.5)	56 (86.2)
≥5	6 (31.6)	8 (33.3)	11 (50.0)	25 (38.5)
Number of Doses				
Mean (SD)	3.8 (1.34)	3.9 (1.18)	4.4 (0.90)	4.0 (1.15)
Median	4.0	4.0	4.5	4.0
Min, Max	1, 5	1, 5	1, 5	1, 5
Time from First to Last Dose (hours)				
Mean (SD)	17.4 (8.28)	17.7 (7.17)	20.5 (5.61)	18.6 (7.08)
Median	18.0	18.0	21.5	18.0
Min, Max	0, 25	0, 25	0, 25	0, 25

(Source: Study OXP3003's report. Table 14.1.4.1, page 164)

5.3.1.10.3 Protocol Deviations

As per Study OXP3003's report, "there were no major protocol deviations identified and no exclusions were made in efficacy analyses due to protocol deviations". However, there were 43 subjects with "minor" protocol deviations: 1 subject met exclusion criteria and the rest were using prohibited medications. Also, there were 36 subjects with at least one study procedure deviation, most of them being deviations from scheduled time of assessment of one of the study variables (e.g., the University of Michigan Sedation Scale) or deviations in the timing of the collection of vital signs.

5.3.1.10.4 Summary of Study Findings

In Study OXP3003, patients in the active treatment arms used significantly less PCA morphine (P = 0.047) and acetaminophen (P =0.039) according to the Sponsor. This appears to be the case across all doses, with reported significantly lower mean pain scores (P = 0.030) compared against the placebo group. Additionally, the total use of opioid pain medications followed a similar pattern to that of PCA morphine. The following table, derived from the study's report (Table 11, page 56) summarizes the efficacy results.

Table 11. Sponsor's Summary of Efficacy Results. Study OXP3003*

	Dose Interval	Placebo Mean (SD)	0.1 mg/kg Mean (SD)	0.2 mg/kg Mean (SD)	Nominal *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.
** One-tailed p-value. Please see efficacy discussion in Section 6 for further details

During the study, there were no patient deaths. Four patients (1 patient in the placebo group) had SAEs but recovered from the events. The majority of the treatment emergent adverse events (TEAEs) appear to be similar to TEAEs expected with the use of opioid analgesics. Most of these AEs were mild to moderate in intensity.

Clinical laboratory tests and vital sign assessments did not uncover any unexpected safety concern. There were two AEs due to increased blood pressure, neither of which resulted in study discontinuation or dose change. Study OXP3003 was not powered to identify significant differences in clinical laboratory evaluations and vital sign measurements between the age groups. There was no significant difference in mean respiratory rate, the degree of hemoglobinoxygen saturation, or somnolence scores between the dose groups.

In summary, Oxy Pediatric Liquid (1 mg/mL) appears to be effective and relatively safe, the Sponsor contends, when 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.

5.3.2 Study OTR3001

The following summary of the design of Study OTR3001 was derived from the revised protocol incorporating Amendment 6, dated February 12, 2014.

Title: 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.

5.3.2.1 Dates Conducted:

Study Start Date: 28 Feb 2011
Study End Date: 29 Jul 2014

5.3.2.2 Objectives:

The primary objective was:

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

The secondary objective was:

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

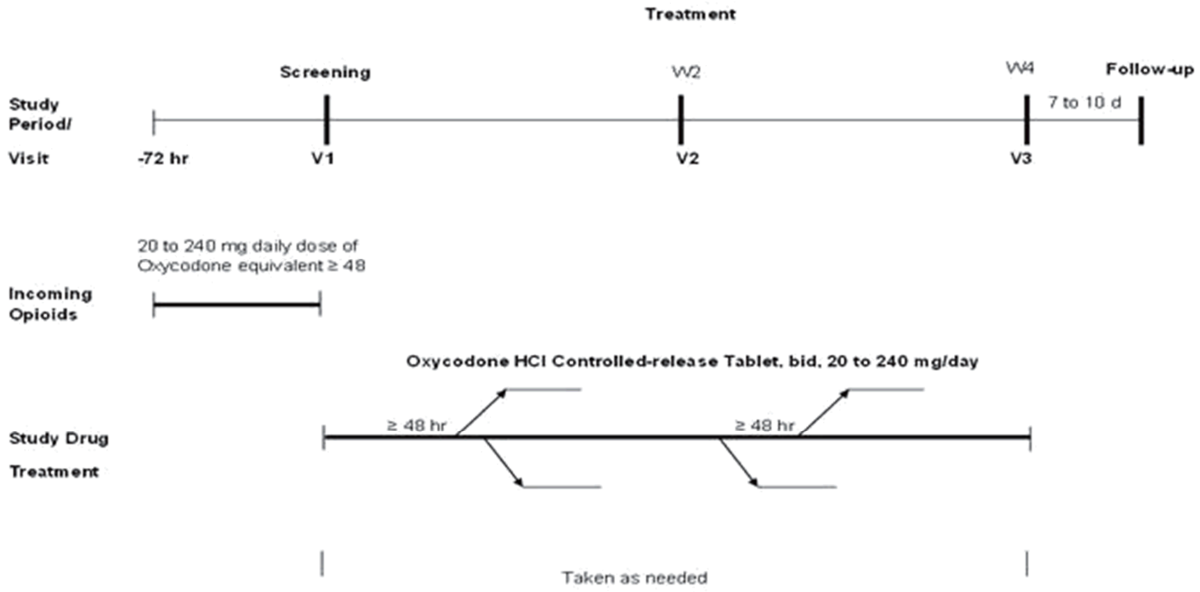
5.3.2.3 Study Design

Study OTR3001 was a phase 3, multicenter, open-label clinical trial in 155 opioid tolerant pediatric patients. The study sought to provide safety data on OxyContin when used for an extended period of time in pediatric patients with moderate to severe pain requiring around-the-clock opioid therapy.

Patients must have been opioid tolerant. This is defined by the protocol as “having been treated with opioids for at least the 5 consecutive days prior to dosing and with at least 20 mg of oxycodone daily and no more than 240 mg daily during at least the last 48 hours before the start of study drug dosing”. Patients could have been outpatients or inpatients at the time of enrollment. Inpatients were to continue in the study upon hospital discharge.

As per the protocol, the study was to include a 0-72 hour screening period, a treatment period of up to 4 weeks which included a total of up to 3 clinic visits/evaluations, and a follow-up period. Patients were to have a visit or evaluation at week 2 (visit 2) and week 4 (visit 3) or at early discontinuation from the study. Phone calls were to be made to the parent/caregiver every 48 hours for outpatients to assess the safety of the patient and efficacy of OxyContin. Unscheduled visits could occur at any time to assess safety, for drug resupply following a dose titration, or for other reasons. All patients were to have a follow-up phone call or visit 7 to 10 days after their last dose of the test article for a safety follow-up evaluation.

Figure 3. OTR3001 Study Schematic



Abbreviations: bid=twice daily; HCl = hydrochloride; Hr = hour; V = visit; W = week
Note: Upward and downward arrows indicate an up- and down-titration of the study drug, respectively.
(Source: OTR3001 Study Report, Figure 1, page 24)

5.3.2.3.1 Protocol Amendments

There were 6 protocol amendments and 4 administrative letters.

- Amendment 1 – dated 27-Jan-2011
  - Added the collection of sparse PK sampling.
  - Added additional somnolence assessments for uptitration for additional safety measures.
  - Added additional conversion factors for fentanyl.
  - Added a phone call to occur every 48 hours for outpatients to collect safety information.
  - Added more detailed study drug dosing procedures clarifying how the study drug should be administered.

  - Added more detailed study drug dosing procedures clarifying how the study drug should be administered.
  - Added and revised additional inclusion and exclusion criteria: Clarified definition of opioid tolerant patient; postoperative patients cannot be enrolled until at least 120 hours after surgery; exclusion criteria regarding CYP3A4 inhibitors and the use of epidurals prior to study drug administration were clarified to make less stringent.
  - Revised laboratory requirements for day 1; clarified that local laboratory may be used for eligibility.
  - Added oxycodone as a prohibited supplemental analgesic medication since it would interfere with the analysis of study drug.
  - Increased the sample size to 135 patients in order to meet current minimum requirements for the number of pediatric patients to be exposed to study drug.
  - Changed opioid experienced to opioid tolerant throughout the protocol.
- Amendment 2 – 24-Jan-2012
  - The increase in the number of patients from 135 to 154 was made to account for the total number of patients required to be exposed to oxycodone for the evaluation of the safety of oxycodone in children, including all studies in our program; the original number was based on the number of patients in the safety database and included the 19 patients who received placebo in the OXP3003 study.
  - Sample size calculations were amended to reflect the increase in number of patients.
  - For those patients who had undergone surgery, the postoperative criterion of waiting at least 120 hours from surgery to the start of study drug dosing was revised to at least 5 days; patients can receive the first dose of study drug on the 5th day post-surgery as long as the opioid-tolerant criteria (treated with opioids for at least 5 consecutive days prior to dosing and with at least 20 mg daily of oxycodone or the equivalent during at least the last 48 hours prior to the start of the study drug dosing) had been met.
  - Based on spontaneous post-marketing reports, including reports of intestinal obstruction and exacerbation of diverticulitis, warnings and precautions were added to the package insert in October 2011 advising physicians to use caution when prescribing OxyContin to patients who had underlying gastrointestinal disorder predisposing them to obstruction. In order to ensure adherence with the guidelines added to the package insert, similar language was included in the exclusion criteria of the protocol such that patients who were predisposed to these types of conditions were not enrolled in the study.
  - Due to the long half-life of methadone, if a patient was taking this medication prior to enrolling into the study, a washout period of at least 4 days was needed prior to the patient starting study drug.

  - Since tramadol is a medication commonly used ex-US, a conversion factor was added to convert the incoming dose of tramadol to oxycodone.
  - The protocol previously allowed for a serum or urine pregnancy test to be conducted for all patients at visit 3. Recruitment of a urine pregnancy test, without the option of a serum pregnancy test, was added to visit 3 for patients who completed the OTR3001 study and were being screened to participate in the OTR3002 extension study. This requirement was added so patients could rollover into OTR3002 immediately without waiting for results of a serum pregnancy test.
  - Section 5.2 of the protocol was updated to reflect the most current ICH/GCP guidelines (these guidelines were already distributed to sites in the form of an administrative letter).
  - The screening window was changed from up to 48 hours to up to 72 hours prior to Day 1 to allow adequate time for availability of laboratory results for review at the time that dosing initiation was planned.
  - Values used to define ranges of bilirubin displayed in listings and ranges of AST and ALT displayed in tables and listings were modified to be more inclusive and provide information on more patients with potentially clinically significant liver function test abnormalities.
  - Specified the volume (2 mL) of the tubes used for PK sampling.
- Amendment 3 – 11-Jun-2012
  - If a patient had difficulty getting to the site for a study visit, these visits might be conducted at a patient's home if the principal investigator deemed this to be appropriate based on the patient's medical status.
- Amendment 4 – 23-Jan-2014
  - A population PK analysis was conducted to determine whether additional PK samples would be required from the remaining patients to be enrolled into OTR3001. For this analysis, the final population PK data set included 255 pediatric patients with ages ranging from newborn to 16 years and weights from 2.4 to 112kg. There were 99 patients included from OTR3001.
  - The major conclusions of these analyses were:
    - The simulation based model evaluation shows a predictive ability for both pediatric and multiple dose adult oxycodone PK.
    - The results of this analysis demonstrated that exposures (Area under the curve at steady state [AUCss], maximum concentration in the dosing interval [Cmax], minimum concentration in the dosing interval [Cmin]) in 2 pediatric subgroups (ages >6 to <12 and ages ≥ 12 to ≤ 16 years) were similar by graphical comparison when the exposure was calculated both at the time of first dose and time of last dose.
    - At a weight-based oxycodone dose of 0.2 mg/kg, expected adult (age >16 years) exposure (AUCss) under the model was similar to

pediatric (age 6 to 16 years) AUCss, with pediatric patients doses as in the clinical study.
    - Based on these results, as described above, the decision was made to discontinue further collection of PK samples for this study; therefore, the PK sampling requirement was removed from the protocol.
- Amendment 5 – 12-Feb-2014
    - Based on these results, as described above, the decision was made to discontinue further collection of PK samples for this study; therefore, the PK sampling requirement was removed from the protocol. It is unclear why this needed to be reiterated from Amendment 4, dated Jan 2014.

5.3.2.4 Population

The study population was to include children 6 to ≤16 years of age who were opioid-tolerant patients, mainly outpatients, with treatment durations of 2 to 4 weeks, and with chronic or persistent pain.

5.3.2.5 Inclusion Criteria

Patients were to have met all of the following criteria:

- Male or female patients 6 to ≤16 years of age who were expected to require ongoing around-the-clock opioid treatment equivalent to at least 20 mg daily dose of oxycodone for at least 2 weeks for management of moderate to severe (based on the investigator's judgment) malignant or nonmalignant pain.
- Patients must have been be opioid tolerant, that is, they must have been treated with opioids for at least the 5 consecutive days prior to dosing and with at least 20 mg daily of oxycodone or the equivalent during at least the last 48 hours prior to the start of study drug dosing and have tolerated the therapy, as demonstrated at the start of study drug dosing by:
    a. A normal respiratory rate for age,
    b. Pulse oximetry (SpO2) ≥ 92% on room air,
    c. No significant (grade 3 or 4) opioid-induced somnolence based on the University of Michigan Sedation Scale (UMSS) and the investigator's judgment.
- Patients who were using transdermal fentanyl should have been on the patch for at least 3 days before removing the patch and OxyContin treatment could only be initiated at least 18 hours following the patch's removal.
- Patients could not require more than a 240 mg total daily dose of OxyContin.
- Patients must have been willing and able to swallow the OxyContin tablets whole.
- Patients must have been able to understand and complete the age appropriate scale to rate pain intensity.
- Patients must have had a parent/caregiver who could perform study assessments, including the assessment of UMSS, Functional Disability Inventory

(FDI), and Parent/Caregiver-Assessed Global Impression of Change (PGIC); and record the assessment scores, each dose of OxyContin, and each dose of supplemental pain medication.
- Female patients of childbearing age must have had a negative pregnancy test within 24 hours prior to study drug administration and be nonlactating.
- Female patients who were sexually active must have been using an acceptable method of birth control.

5.3.2.6 Exclusion Criteria:

Patients were to have been excluded if any of the following applied:
- Allergy to oxycodone or other opioids
- Patients who had surgery within 5 days prior to Day 1 (day of first dose of study drug).
- Patients who had received epidural opioids < 2 hours prior to the first dose of study drug or who had received epidural morphine < 12 hours prior to the first dose of study drug.
- Patients who were taking moderate to strong CYP3A4 inhibitors if the dose had not been stable for at least 1 month.
- Patients who are taking moderate to strong CYP3A4 inhibitors will be excluded if the dose has been stable for at least 1 month but the adjusted starting dose determined for OxyContin is less than 20mg daily.
- Patients for whom it is anticipated that therapy with a moderate to strong CYP3A4 inhibitor will be initiated during the study, after the screening visit.
- Patients who, in the investigator's opinion, have an underlying gastrointestinal condition or other disorder that may predispose them to obstruction.
- Patients who were cyanotic postoperatively.
- History of sleep apnea within the past year.
- History of cystic fibrosis.
- History of malabsorption syndrome.
- Paralytic ileus.
- Require mechanical ventilation.
- Patients who were being maintained on methadone for pain.
- Patients who had a life expectancy of less than 2 weeks.
- Patients who had an abnormality on vital signs, physical examination, or laboratory testing significant enough that the investigator deems the patient is not appropriate for the study.
- Patients who had hepatic impairment as evidenced by serum alanine amino transferase (ALT) or serum aspartate amino transferase (AST) > 5 times the upper limit of normal (ULN) for age.
- Patients who had evidence of impaired renal function (serum creatinine > 2 times the upper limit of normal [ULN] for age).
- Patients who had any planned surgery during the course of the study, with the exception of the placement of central or peripheral venous access devices.

- Patients taking an investigational medication/therapy at the start of screening or during the study.

5.3.2.7 Withdrawal/Discontinuation Criteria

Patients were to be discontinued or be withdrawn from the study under any of the following circumstances:

- If they no longer required a minimum of 20 mg of OxyContin daily or required more than 240 mg OxyContin daily (not including any supplemental opioid pain medication).
- If a safe and effective dose of OxyContin could not be achieved.
- If, in the opinion of the investigator, they no longer required OxyContin for pain control.
- Informed consent withdrawal.
- Patient cannot tolerate the study medication (AEs or SAEs leading to discontinuation).
- Patient or their parent (s)/legal guardian request withdrawal from the trial (subject's choice).
- In the investigator's opinion it is in the patient's best interest to discontinue.
- Lack of therapeutic effect.
- Confirmed or suspected diversion.
- If, in the opinion of the investigator or the sponsor, it was in the patient's best interest to discontinue.
- Administrative reasons/loss to follow up.

A patient was considered as completing the study if the patient had completed at least 2 weeks of study drug dosing and did not need additional treatment with opioid medication for pain relief (OxyContin was not required any longer) per the investigator's clinical judgment or if the patient had completed the entire 4 weeks of study drug dosing.

5.3.2.8 Study Methods

5.3.2.8.1 Schedule of Visits and Procedures

Table 12. Summary of Schedule of Visits and Procedures. Study OTR3001

	Screen (up to 72 hrs prior to or on day 1)	Treatment Period				Follow-up 7 to 10 days[a]
		Day 1, Day 2, every 48 h thereafter[a]	Week 2 (±3 days)	Unscheduled[b]	Week 4/early discontinuation (±3 days)	
Visit	**1**	**Phone**	**2**	**Visit**	**3**	**Phone/Visit**
Study Center Procedures						
Informed consent/assent	X					
Demography	X					
Medical history	X					
Complete physical examination	X				X	
Tanner staging	X					
Vital signs[c]	X		X	X[c]	X	
Pulse oximetry (SpO_2)[c]	X			X[c]		
Laboratory tests	X				X	
Pregnancy test[d]	X				X	
Bowel prep	X					
Confirm inclusion/exclusion criteria	X					
Record prior opioid treatment	X					
Assess current opioid requirement	X	X	X	X	X	
Record concomitant medications and therapies	X		X	X	X	X
Parent/caregiver and patient instructions/ reminders[e]	X	X	X	X	X	
Diary distribution/collection	X		X		X	
Study drug administration[f]	X→	→	→	→	→X	
Dispense/return study drug, assess compliance	X		X	(X)	X	
Assess abuse and diversion			X	X	X	
Adverse events	X[g]	X	X	X	X	X
Review supplemental pain medication use		X	X	X	X	
Review diary		X	X	X	X	
Final disposition					X	
Parent/caregiver assessments						
Study drug administration	X→	→	→	→	→X	
Record study drug, supplemental analgesic use and pain right now FPS-R[h] score in Diary	X→	→	→	→	→X	
Somnolence (UMSS)[i]	X[i]			X[i]		
FDI	X		X			
PGIC					X	
Patient assessments						
Pain right now (FPS-R or 100-mm VAS)[j]	X[j]→	→	→	→	→X[j]	

Source: Protocol OTR3001, pages 25-27.

Note: If patient is an inpatient, assessments assigned to the parent/caregiver will be done by study center staff. X→X indicates assessment to be performed or study drug to be administered between visits during the indicated period. (X) indicates procedures performed as necessary (drug dispensation at an unscheduled visit).

[a] For outpatients, study center will call parent/caregiver every 48 hours from the afternoon of day 2 (if the call is to occur on a weekend or holiday, the call can be made on the next business day) and 7 to 10 days after the last on-study visit to assess patient's status. In addition, the study center will contact the parent/caregiver in the evening on day 1 and in the afternoon on day 2 and in the evening and the next afternoon after any up-titration. Unscheduled calls may be made at any time by the parent/caregiver to discuss safety, dose level, or other concerns.

[b] Unscheduled visits should occur as necessary for dose changes or other reasons. Any procedures should be performed as needed.

[c] Vital signs (blood pressure, respiratory rate, heart rate, and temperature), weight (pre-dose and visit 3 only), height (pre-dose only) and pulse oximetry (SpO_2) will be collected within 2 hours prior to the first dose of oxycodone HCl CR tablets and every 30 minutes for 90 minutes after the first dose for all patients and after the first increased dose of any up-titration for inpatients and patients receiving the first increased dose at study center. For inpatients, vital signs and pulse oximetry (SpO_2) should be assessed by medical staff at 3 and 4 hours post-dose and then every 4 hours for 48 hours after the first dose of oxycodone HCl CR tablets and after the first increased dose of any up-titration.
[d] Serum pregnancy test at screening (or urine if serum is not practical) and serum or urine pregnancy test at visit 3/early discontinuation (a urine pregnancy test, not a serum pregnancy test, must be performed at Visit 3 for any patient being screened to participate in the OTR3002 extension study*); for female patients of childbearing potential only. If a patient had a pregnancy test performed preoperatively within 24 hours of the surgery and the surgery is within 5 days of the first dose, a second pregnancy test performed prior to the first oral dose of oxycodone HCl CR is not required.
[e] Including training in use of Diary, assessment and recording of pain scores (FPS-R and 100-mm VAS), UMSS, and FDI; administration of oxycodone HCl CR tablets and supplemental pain medication; recording of each dose of oxycodone HCl CR tablets, supplemental pain medication, and when to contact the study center.
[f] Oxycodone HCl CR tablets will be administered every 12 hours (± 1 hour), twice daily. Every attempt should be made to maintain an every-12-hour dosing schedule, including waking the patient if asleep. Oxycodone HCl CR tablets will be administered by study center staff for the first dose on day 1 for all patients and for all subsequent doses for inpatients and for patients receiving the first increased dose at the study center for any up-titration. Oxycodone HCl CR tablets will be administered by parent/caregiver for the second dose and all subsequent doses for outpatients.
[g] AEs are collected beginning from the time informed consent is signed.
[h] FPS-R is completed for patients aged 6 to < 12 years only.
[i] UMSS will be assessed before dose 1, post-dose 1 on day 1 (at the end of the 90-minute observation period), and just prior to the first increased dose for each up-titration of oxycodone HCl CR tablets unless the patient is asleep; in such case, UMSS will be assessed when the patient awakens. In addition, for each up-titration, UMSS will be assessed approximately 24 and 48 hours after the first increased dose.
[j] Pain right now measured on the FPS-R will be assessed by patients aged 6 to < 12 years and recorded in the Diary by parents/caregivers before the first dose and 90 minutes post-dose on day 1 and, thereafter, during AM and PM approximately at the time of each dosing (morning and evening dose) of oxycodone HCl CR tablet throughout study treatment. Pain right now measured on the 100-mm VAS will be assessed by patients aged ≥ 12 to ≤ 16 years before the first dose and 90 minutes post-dose on day 1 and, thereafter, during AM and PM approximately at the time of each dosing (morning and evening dose) of oxycodone HCl CR tablet throughout study treatment.
*OTR3002 is an extension study to OTR3001 entitled "An Open-label, Extension Study to Assess the Long-Term Safety of Twice Daily Oxycodone Hydrochloride Controlled-release Tablets in Opioid Experienced Children Who Completed the OTR3001 Study." Patients must have completed 4 weeks of treatment in OTR3001 and, in the opinion of the investigator, demonstrated a clinical benefit from and tolerated study drug treatment.

5.3.2.8.1.1 Screening and Baseline

Screening procedures were scheduled to be performed at visit 1. After written informed consent was obtained, patients had a complete evaluation for study eligibility. The patients' analgesic medication use was recorded. Only patients who met the study entry criteria, including those for laboratory values, were eligible to receive the study drug. Patients were to be opioid tolerant (as previously defined). Patients who were currently using transdermal fentanyl could only to be initiated at least 18 hours following the removal of the transdermal fentanyl patch.

5.3.2.8.1.2 Treatment Period

Eligible patients were to immediately begin treatment with OxyContin tablets with the exception of postoperative patients, who could not be dosed with the study drug until at least 5 days after surgery. These individuals were to receive a 20- to 240-mg total daily dose of OxyContin tablets administered in divided doses q12h (± 1 hour). Upward or downward dose titration was allowed to be performed until the most effective and safe dose was established. Dose titrations could occur at any time during the study and not just at scheduled visits. Upward titration could only occur after 48 hours of study drug treatment at a particular dose (considering the time required to reach steady-state oxycodone plasma concentrations). Supplemental pain medication was permitted during the study as deemed appropriate by the investigator.

For outpatients, the patient's parent/ caregiver was instructed to contact the investigator if the patient required an amount of supplemental opioid pain medication that could justified a dose increase or if the caregiver believed the patient's pain was not

adequately controlled or had any tolerability or safety concerns. The investigator was to evaluate the information provided for consideration of a change in OxyContin tablet dose to achieve adequate pain control or for tolerability or safety purposes.

Patients were to have a visit or evaluation at week 2 (visit 2) and week 4 (visit 3) or at early discontinuation from the study. Study visits were allowed at a patient's home if deemed appropriate by the investigator, based on the medical status of the patient. Phone calls were made to the parent/ caregiver every 48 hours for outpatients to assess the safety and efficacy of OxyContin. Unscheduled visits could have occurred at any time to assess safety, for drug resupply following a dose titration, or for any other reasons.

5.3.2.8.1.3 Follow up Period

All patients had a follow-up phone call or visit 7 to 10 days after their last dose of OxyContin tablets for a safety follow-up evaluation.

5.3.2.9 Treatments

5.3.2.9.1 Treatments Administered

As previously discussed, eligible patients were to immediately begin treatment with OxyContin tablets with the exception of postoperative patients, who could not be dosed with the study drug until at least 5 days post-surgery. These individuals were to receive a 20- to 240-mg total daily dose of OxyContin tablets administered in divided doses q12h (± 1 hour) for a minimum of 2 weeks and up to 4 weeks. Upward and downward titration as well as asymmetric dossing was permitted, as long as the study drug was administered twice daily.

5.3.2.9.1.1 Converting from Other Opioids

The investigators used the following sponsor-provided table to convert other opioid medications to oral OxyContin.

Table 13. Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Daily Dose of Oral OxyContin. Study OTR3001

	Oral Prior Opioid	Parenteral Prior Opioid
Oxycodone	1	--
Codeine	0.15	--
Fentanyl	--	0
Hydrocodone	0.9	--
Hydromorphone	4	20
Levorphanol	7.5	15
Meperidine	0.1	0.4
Morphine	0.5	3
Tramadol	0.17	0.2

*To be used only for conversion to oral oxycodone. For patients receiving high-dose parenteral opioids, a more conservative conversion is warranted. For example, for high-dose parenteral morphine, use 1.5 instead of 3 as a multiplication factor. The formula for conversion of prior opioids to the daily dose of oral oxycodone is mg/day prior opioid x factor = mg/day oral. (Source: OTR3001 Study Report, page 33, Table 1.)

On page 32 for the CRF, there is a field to input concomitant medications. In addition, there is a follow up question: "Was this medication used to calculate Incoming Oxycodone Equivalent Dose?" and two fields are available "Yes" and "No". This input (which eventually gets stored in the SUPPCM dataset), plus information regarding the dose, route, and frequency gets checked against the conversion factor (summarized in the table above and stored in the UOPIOID dataset) and a conversion to an OxyContin dose is given, with an option to confirm or override it. Because the experience gained with this conversion may be potentially useful to for labeling and thus, to clinicians, I have made a table of the most common medications converted to OxyContin on the table below. However, it should be noted that more than one medication may have been used to calculate the OxyContin converted dose for any given patient, up-titrations and down-titrations were permitted as discussed, some of these opioids could be continued in addition to the test drug, and that the final OxyContin converted dose could have been overridden by the investigator.

Table 14. Frequency of Individual Opioid Medications Utilized for Dose Conversion to OxyContin

Opioid medication	Number of times used for conversion
OXYCODONE	194
MORPHINE	35
HYDROMORPHONE	47
HYDROCODONE	21
CODEINE	5
TRAMADOL	3

(Resourse: Reviewer-constructed utilizing JMP 11.)

5.3.2.9.1.2 Converting from Transdermal Fentanyl to Oral Oxycodone

Eighteen hours from the time of the transdermal patch removal must have passed prior to starting oral OxyContin. Approximately 10mg q12 hours of OxyContin was initially substituted for each 25 mcg/h of transdermal fentanyl patch, although because of limited experience with this conversion, patients were closely monitored during the conversion period.

In the actual study, only one patient was converted to from fentanyl transdermal patch although he was started on the minimum dose permitted by the protocol. I have been unable to determine the process utilized for selecting this specific dose for this patient.

5.3.2.9.2 Concomitant Therapy

All medications (prescribed and over-the-counter) taken by the patient 30 days prior to study entry were to be recorded in the case report form.

Supplemental opioid and non-opioid pain medication were permitted during the study. Non-opioid medication used specifically for pain, "including nonsteroidal anti-inflammatory drugs and gabapentin and other neuropathic pain medications, if taken on a stable regular schedule for at least 2 weeks prior to the screening visit, could be continued during the study, but could not be started for pain control during the study". However, the dose of these supplemental non-opioid pain medications could be reduced for safety reasons. Any changes to the patient's concomitant medications and therapies were recorded supposed to be recorded.

Patients taking moderate to strong CYP3A4 inhibitors were to be excluded from participation in the study if the dose had not been stable for at least 30 days or if the dose had been stable for at least 1 month but the adjusted starting dose determined for OxyContin was less than 10 mg (total daily dose of 20 mg). Therefore, patients for

whom it was anticipated that therapy with a moderate to strong CYP3A4 inhibitor would be initiated during the study were also to be excluded.

5.3.2.10 Drug Accountability

A record of the date and amount of study drug dispensed to each patient was to have been available for inspection at any time. The assigned clinical research associate (CRA) was expected to review these documents with regard to all other study conduct documents at each visit to the study center. The investigator/ designee was required to maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which was required to be given to the sponsor (or clinical supplies designee) at the end of the study. At the conclusion of the study and as appropriate during the course of the study, the clinical supply handling was to be documented in the Site Operations Manual or appropriate Study Plan.

Clinical Supplies Product Complaints (CSPCs) of study drug(s) consisted of any issues involving:

- Supply quality, quantity, and packaging.
- Supply shipping
- Supply storage
- Suspected or known theft or diversion by a non-patient
- Suspected or known theft or diversion by a patient.
    - Site personnel evaluated the clinical supplies dispensed/used/by each patient at each visit, and upon patient completion or discontinuation of the patient for any reason. The investigator was to record in the patient's source documents his/her evaluation of any incidents meeting the following thresholds:
        - Study drugs - For oral dosage forms, 10% or more in excess of the maximum prescribed dose of dispensed drug was used or unaccounted for.
        - Study drugs or any other substance - If diversion or theft was suspected, regardless of the amount of the substance involved.

Any patient involved in suspected or known theft or diversion was to be discontinued from the study. The reason for discontinuation was to be recorded as confirmed or suspected diversion. If theft or significant loss of controlled substances occurred in US clinical sites, the investigator was to notify the Filed Division Office of the Drug Enforcement Administration (DEA) within 1 business day of the discovery.

5.3.2.11 OTR3001 Results

5.3.2.11.1 Study Population

5.3.2.11.1.1 Patient Demographics

The table below, derived from Table 11 of the study's report, is a summary of the demographic and baseline characteristics of the safety population by treatment group.

Table 15. Demographic and Baseline Characteristics: Safety Population. Study OTR3001

Characteristics	Age Group		
	6 to < 12 Years (N=27)	≥ 12 to ≤ 16 Years (N=128)	Total (N = 155)
Age (y)			
N	27	128	155
Mean (SD)	9.6 (1.65)	14.5 (1.34)	13.7 (2.33)
Median	10.0	15.0	14.0
Min, Max	6, 11	12, 16	6, 16
Sex, n (%)			
Male	13 (48.1)	53 (41.4)	66 (42.6)
Female	14 (51.9)	75 (58.6)	89 (57.4)
Race, n (%)			
White	20 (74.1)	88 (68.8)	108 (69.7)
Black	7 (25.9)	31 (24.2)	38 (24.5)
Asian	0	1 (0.8)	1 (0.6)
Other	0	8 (6.3)	8 (5.2)
Ethnicity, n (%)			
Latino or Hispanic	2 (7.4)	16 (12.5)	18 (11.6)
Not Latino	25 (92.6)	112 (87.5)	137 (88.4)
Tanner Puberty Staging, n (%)			
Stage 1	14 (51.9)	6 (4.7)	20 (12.9)
Stage 2	10 (37.0)	3 (2.3)	13 (8.4)
Stage 3	2 (7.4)	24 (18.8)	26 (16.8)
Stage 4	1 (3.7)	61 (47.7)	62 (40.0)
Stage 5	0	34 (26.6)	34 (21.9)
Screen Weight (kg)			
N	25	128	153
Mean (SD)	38.72 (10.055)	63.21 (18.474)	59.21 (19.587)
Median	39.90	60.00	56.20

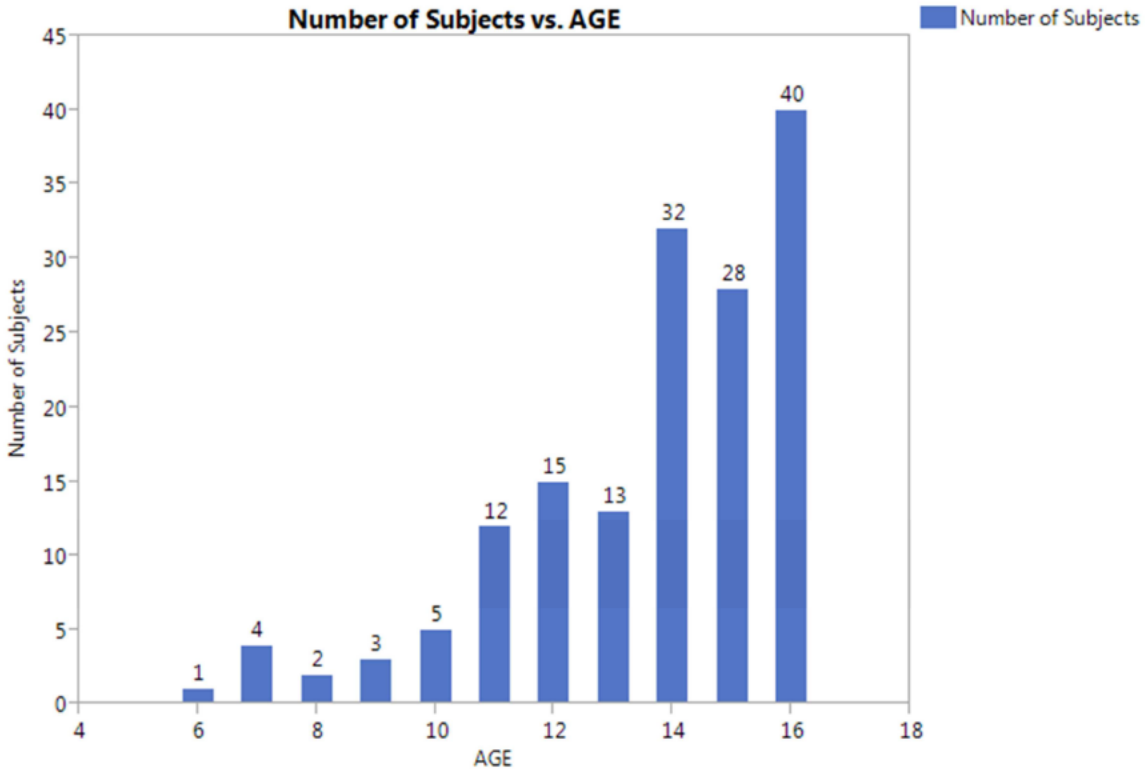
Characteristics	Age Group		Total (N = 155)
	6 to < 12 Years (N=27)	≥ 12 to ≤ 16 Years (N=128)	
Min, Max	24.5, 65.0	26.0, 124.6	24.5, 124.6
Missing	2	0	2
Height (cm)			
N	24	128	152
Mean (SD)	141.71 (13.034)	165.30 (10.241)	161.58 (13.733)
Median	145.60	165.05	162.60
Min, Max	119.0, 158.0	136.0, 190.5	119.0, 190.5
Missing	3	0	3
Body Mass Index (kg/m^2)			
N	24	128	152
Mean (SD)	19.08 (2.775)	22.92 (5.639)	22.32 (5.468)
Median	18.57	21.92	21.21
Min, Max	14.2, 27.1	12.2, 44.7	12.2, 44.7
Missing	3	0	3

5.3.2.11.1.1 Other Demographic Considerations

The PWR stipulated that for this study, approximately 40% of the pediatric patients must have been in the age group 6-11 years old and 60% in the age group 12-16 years old. Additionally, it specified that patients must have been evenly distributed (approximately) over the entire age range in each stratum and across both genders.

As seen in the table in the previous section, in the younger age group there were 13 (48.1%) males and 14 (51.9%) females. In the older cohort the gender differences were higher; 53 (41.4%) males and 75 (57.4%) females. Overall there were 66 (42.6%) males and 89 (57.4%) females. Although not ideal, gender differences across both age groups were acceptable. However, the requirement for patients to be evenly distributed over the entire age range was not acceptable. The following reviewer-constructed figure below illustrates the significant age distribution differences.

Figure 4. Age Distribution Breakdown, Study OTR3001 (N=155)



Of the 155 patients in the safety population, only 27 or 17.4% were in the 6 to less than 12 years age group, far from the 40% expectation for this age group. Additionally, as the figure above shows, the age distribution is not evenly distributed within each age bracket. The 6 to less than 12 years cohort is highly represented by subjects who are 10 to 11 years old. (b) (4) Only one 6-year-old child, four were 7 years-old (one of them only presented for the screening visit, was dispensed study drug, but never returned- giving us no information about the safety of the study drug), two age 8 years old, and only three 9 year-olds were studied. (b) (4) Similarly, in the 12 to 16 age bracket, children in the older spectrum of the range (ages 14 through 16) are overwhelmingly represented (78%) – clearly missing the PWR-specified requirement described above.

5.3.2.11.1.2 Baseline Medical Conditions

The table below summarizes the medical history conditions for 5% or more of patients in the overall safety population.

Table 16. Baseline Medical Conditions Occurring in ≥ 5% of Patients. Study OTR3001.

System Organ Class Preferred Term	Age Group 6 to <12 Years (N=27) n (%)	Age Group ≥12 to ≤16 Years (N=128) n (%)	Total (N=155) n (%)
Any medical diagnosis/surgical procedure	**27 (100.0)**	**127 (99.2)**	**154 (99.4)**
Blood and lymphatic system disorders	**9 (33.3)**	**26 (20.3)**	**35 (22.6)**
Anaemia	6 (22.2)	13 (10.2)	19 (12.3)
Thrombocytopenia	2 (7.4)	4 (3.1)	6 (3.9)
Congenital, familial and genetic disorders	**6 (22.2)**	**26 (20.3)**	**32 (20.6)**
Sickle cell anaemia	4 (14.8)	10 (7.8)	14 (9.0)
Pectus excavatum	1 (3.7)	9 (7)	10 (6.5)
Eye disorders	**4 (14.8)**	**5 (3.9)**	**9 (5.8)**
Dry eye	2 (7.4)	0	2 (1.3)
Gastrointestinal disorders	**6 (9.2)**	**143**	**89 (57.4)**
Constipation	17 (63.0)	72 (56.3)	67 (43.2)
Nausea	13 (48.1)	47 (36.7)	60 (38.7)
Vomiting	4 (14.8)	19 (14.8)	23 (14.8)
Gastrooesophageal reflux disease	3 (11.1)	10 (7.8)	13 (8.4)
Abdominal pain	2 (7.4)	10 (7.8)	12 (7.7)
Diarrhoea	3 (11.1)	5 (3.9)	8 (5.2)
Flatulence	2 (7.4)	0	2 (1.3)
Stomatitis	2 (7.4)	0	2 (1.3)
General disorders and administration site	**11 (40.7)**	**40 (31.3)**	**51 (32.9)**
Pyrexia	6 (22.2)	25 (19.5)	31 (20.0)
Pain	1 (3.7)	8 (6.3)	9 (5.8)
Mucosal inflammation	2 (7.4)	4 (3.1)	6 (3.9)
Immune system disorders	**10 (37)**	**18 (14.1)**	**28 (18.1)**
Seasonal allergy	7 (25.9)	8 (6.3)	15 (9.7)
Drug hypersensitivity	2 (7.4)	3 (2.3)	5 (3.2)
Infections and infestations	**9 (33.3)**	**30 (23.4)**	**39 (25.2)**
Pneumonia	4 (14.8)	1 (0.8)	5 (3.2)
Injury, Poisoning And Procedural Complications	**5 (18.5)**	**44 (34.4)**	**49 (31.6)**
Procedural nausea	1 (3.7)	7 (5.5)	8 (5.2)
Procedural pain	0	7 (5.5)	7 (4.5)
Investigations	**14 (51.9)**	**33 (25.8)**	**47 (30.3)**
Biopsy	2 (7.4)	5 (3.9)	7 (4.5)
Biopsy bone marrow	2 (7.4)	2 (1.6)	4 (2.6)
Haemoglobin decreased	3 (11.1)	1 (0.8)	4 (2.6)
Blood phosphorus decreased	2 (7.4)	1 (0.8)	3 (1.9)
Haematocrit decreased	2 (7.4)	1 (0.8)	3 (1.9)

System Organ Class Preferred Term	Age Group 6 to <12 Years (N=27) n (%)	Age Group ≥12 to ≤16 Years (N=128) n (%)	Total (N=155) n (%)
Metabolism And Nutrition Disorders	**6 (22.2)**	**34 (26.6)**	**40 (25.8)**
Decreased appetite	2 (7.4)	7 (5.5)	9 (5.8)
Dehydration	1 (3.7)	7 (5.5)	8 (5.2)
Vitamin D deficiency	2 (7.4)	6 (4.7)	8 (5.2)
Obesity	0	7 (5.5)	7 (4.5)
Musculoskeletal and connective tissue disorders	**7 (25.9)**	**79 (61.7)**	**86 (55.5)**
Scoliosis	2 (7.4)	35 (27.3)	37 (23.9)
Muscle spasms	2 (7.4)	29 (22.7)	31 (20.0)
Back pain	2 (7.4)	9 (7.0)	11 (7.1)
Arthralgia	0	10 (7.8)	10 (6.5)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**14 (51.9)**	**29 (22.7)**	**43 (27.7)**
Ewing's sarcoma	4 (14.8)	6 (4.7)	10 (6.5)
Osteosarcoma localized	2 (7.4)	2 (1.6)	4 (2.6)
Neuroblastoma	2 (7.4)	1 (0.8)	3 (1.9)
Brain neoplasm malignant	2 (7.4)	0	2 (1.3)
Nervous system disorders	**11 (40.7)**	**45 (35.2)**	**56 (36.1)**
Headache	3 (11.1)	14 (10.9)	17 (11.0)
Migraine	0	7 (5.5)	7 (4.5)
Neuralgia	2 (7.4)	5 (3.9)	7 (4.5)
Convulsion	2 (7.4)	0	2 (1.3)
Febrile convulsion	2 (7.4)	0	2 (1.3)
Psychiatric disorders	**10 (37)**	**38 (29.7)**	**48 (31)**
Anxiety	6 (22.2)	22 (17.2)	28 (18.1)
Depression	2 (7.4)	14 (10.9)	16 (10.3)
Insomnia	1 (3.7)	12 (9.4)	13 (8.4)
Attention deficit/hyperactivity disorder	1 (3.7)	8 (6.3)	9 (5.8)
Post-traumatic stress disorder	2 (7.4)	0	2 (1.3)
Respiratory, thoracic and mediastinal disorders	**10 (37.0)**	**42 (32.8)**	**52 (33.5)**
Asthma	3 (11.1)	24 (18.8)	27 (17.4)
Oropharyngeal pain	2 (7.4)	1 (0.8)	3 (1.9)
Sleep apnoea syndrome	2 (7.4)	1 (0.8)	3 (1.9)
Skin and subcutaneous tissue disorders	**9 (33.3)**	**46 (35.9)**	**55 (35.5)**
Pruritus	3 (11.1)	28 (21.9)	31 (20.0)
Alopecia	2 (7.4)	4 (3.1)	6 (3.9)
Surgical and medical procedures	**19 (70.4)**	**103 (80.5)**	**122 (78.7)**
Spinal fusion surgery	2 (7.4)	39 (30.5)	41 (26.5)
Central venous catheterization	5 (18.5)	13 (10.2)	18 (11.6)
Chemotherapy	4 (14.8)	8 (6.3)	12 (7.7)
Adenotonsillectomy	3 (11.1)	5 (3.9)	8 (5.2)
Chest wall operation	1 (3.7)	7 (5.5)	8 (5.2)
Tonsillectomy	3 (11.1)	3 (2.3)	6 (3.9)
Central venous catheter removal	2 (7.4)	0	2 (1.3)

System Organ Class Preferred Term	Age Group 6 to <12 Years (N=27) n (%)	Age Group ≥12 to ≤16 Years (N=128) n (%)	Total (N=155) n (%)
Vascular disorders	**3 (11.1)**	**18 (14.1)**	**21 (13.5)**
Hypotension	3 (11.1)	5 (3.9)	8 (5.2)
Hypertension	0	7 (5.5)	7 (4.5)

(Source: OTR3001's study report, Table 12, pages 79-80)

The most commonly reported medical history conditions (those reported in over 20% of patients) by MedDRA preferred term were constipation (43.2%), nausea (38.7%), spinal fusion surgery (26.5%), and scoliosis (23.9%). For in the 6 to less than 12 year group, the most commonly reported medical history conditions were constipation (55.6%), nausea (48.1%), seasonal allergy (25.9%), anaemia (22.2%), pyrexia (22.2%) and anxiety (22.2%). For the older age group, the most commonly reported medical history conditions were constipation (40.6%), nausea (36.7%), spinal fusion surgery (30.5%), scoliosis (27.3%), muscle spasms (22.7%), and pruritus (21.9%). Approximately 10% of patients had sickle cell anemia with persistent pain. Spinal fusion surgery and scoliosis were observed in more patients in the older age group, while non-orthopedic medical conditions were observed in more patients in the younger age group.

For patients dosed post-operatively, a summary of underlying surgery is presented below.

Table 17. Summary of Surgical History Prior to First Dose. Study OTR3001.

System Organ Class Preferred Term	Age Group 6 to <12 Years (N=27) n (%)	Age Group ≥12 to ≤16 Years (N=128) n (%)	Total (N=155) n (%)
Any underlying surgery procedure	**11 (40.7)**	**78 (60.9)**	**89 (57.4)**
Congenital, familial and genetic disorders	**0**	**1 (0.8)**	**1 (0.6)**
Pectus excavatum	0	1 (0.8)	1 (0.6)
Injury, poisoning and procedural complications	**0**	**1 (0.8)**	**1 (0.6)**
Femur fracture	0	1 (0.8)	1 (0.6)
Investigations	**2 (7.4)**	**8 (6.3)**	**10 (6.5)**
Biopsy	1 (3.7)	1 (0.8)	2 (1.3)
Biopsy bone	0	2 (1.6)	2 (1.3)
Mediastinoscopy	0	2 (1.6)	2 (1.3)
Biopsy bone marrow	1 (3.7)	0	1 (0.6)
Biopsy kidney	0	1 (0.8)	1 (0.6)
Laparoscopy	0	1 (0.8)	1 (0.6)
Lumbar puncture	0	1 (0.8)	1 (0.6)
Musculoskeletal and connective tissue disorders	**0**	**1 (0.8)**	**1 (0.6)**
Kyphosis	0	1 (0.8)	1 (0.6)
Surgical and Medical Procedures	**10 (37.0)**	**70 (54.7)**	**80 (51.6)**
Spinal fusion surgery	2 (7.4)	36 (28.1)	38 (24.5)

System Organ Class Preferred Term	Age Group 6 to <12 Years (N=27) n (%)	Age Group ≥12 to ≤16 Years (N=128) n (%)	Total (N=155) n (%)
Chest wall operation	1 (3.7)	7 (5.5)	8 (5.2)
Bone graft	1 (3.7)	3 (2.3)	4 (2.6)
Bone operation	1 (3.7)	2 (1.6)	3 (1.9)
Open reduction of fracture	1 (3.7)	2 (1.6)	3 (1.9)
Wound treatment	0	3 (2.3)	3 (1.9)
Debridement	0	2 (1.6)	2 (1.3)
Explorative laparotomy	0	2 (1.6)	2 (1.3)
Hemipelvectomy	0	2 (1.6)	2 (1.3)
Skin graft	1 (3.7)	1 (0.8)	2 (1.3)
Spinal operation	0	2 (1.6)	2 (1.3)
Acoustic neuroma removal	0	1 (0.8)	1 (0.6)
Central venous catheterisation	1 (3.7)	0	1 (0.6)
Chemotherapy	0	1 (0.8)	1 (0.6)
Cholecystectomy	0	1 (0.8)	1 (0.6)
Fracture debridement	0	1 (0.8)	1 (0.6)
Hip arthroplasty	0	1 (0.8)	1 (0.6)
Ileocolectomy	0	1 (0.8)	1 (0.6)
Implantable defribrillator insertion	1 (3.7)	0	1 (0.6)
Incisional drainage	0	1 (0.8)	1 (0.6)
Leg amputation	0	1 (0.8)	1 (0.6)
Liver transplant	0	1 (0.8)	1 (0.6)
Malignant tumour excision	1 (3.7)	0	1 (0.6)
Medical device implantation	0	1 (0.8)	1 (0.6)
Muscle flap operation	0	1 (0.8)	1 (0.6)
Nephrectomy	1 (3.7)	0	1 (0.6)
Osteotomy	0	1 (0.8)	1 (0.6)
Sarcoma excision	0	1 (0.8)	1 (0.6)
Small intestine operation	0	1 (0.8)	1 (0.6)
Spinal decompression	0	1 (0.8)	2 (1.3)
Tendon operation	0	1 (0.8)	2 (1.3)
Thoracoplasty	0	1 (0.8)	2 (1.3)
Toe amputation	0	1 (0.8)	2 (1.3)
Vascular operation	0	1 (0.8)	2 (1.3)

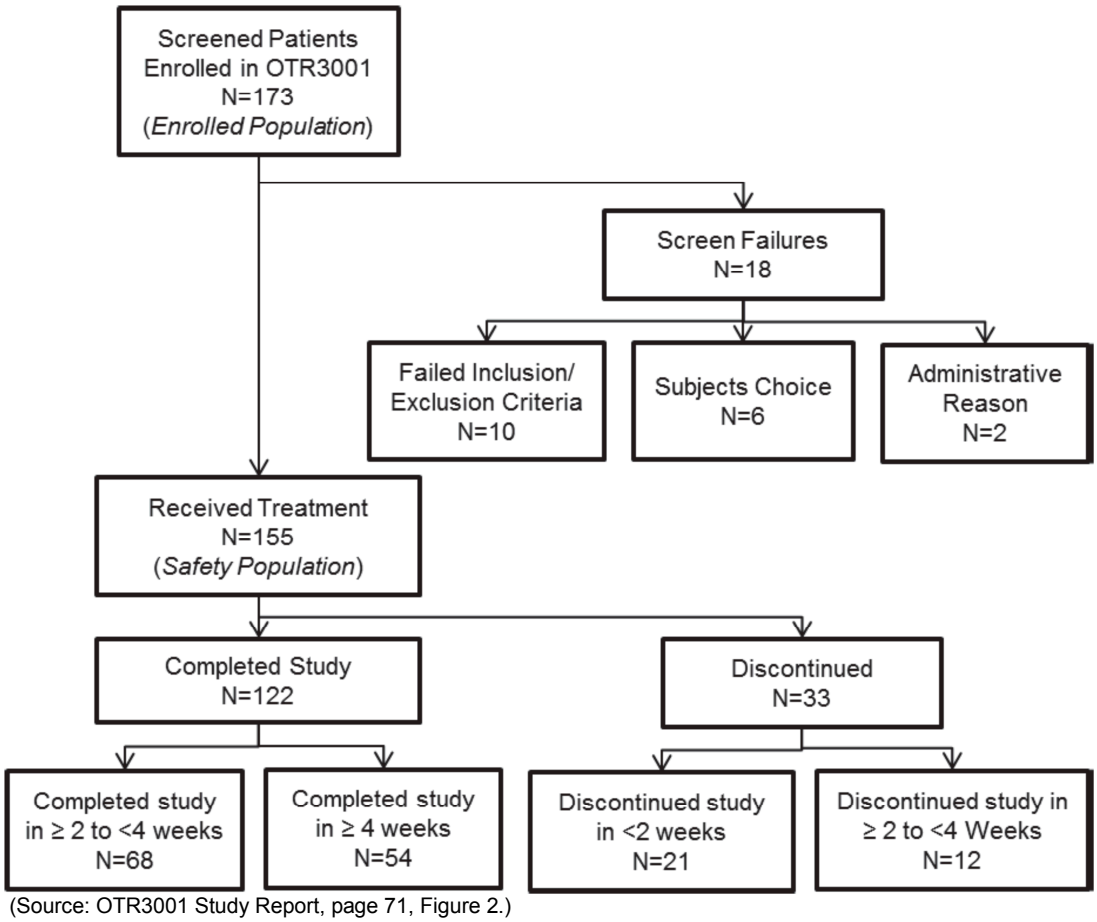
(Source: OTR3001's study report, Table 13, pages 81-82)

Eighty-nine (57.4%) out of the 155 patients in the safety population were dosed post-operatively. The most common procedures were spinal fusion and chest wall surgeries.

5.3.2.11.1.3 Patient Disposition

The following figure is a summary of the patient disposition.

Figure 5. Summary of Patient Disposition. Study OTR3001



(Source: OTR3001 Study Report, page 71, Figure 2.)

The following table, derived from Table 7 of the study's report, summarizes the patient disposition and reasons for discontinuation of the safety population by age group.

Table 18. Patient Disposition and Reasons for Discontinuation: Safety Population. Study OTR3001

Category	Age Group		Total (N=155) n (%)
	6 to < 12 Years (N=27) n (%)	≥ 12 to ≤ 16 Years (N=128) n (%)	
Completed study	17 (63.0)	105 (82.0)	122 (78.7)
Completed study in ≥2 to <4wks	6 (22.2)	62 (48.4)	68 (43.9)
Completed study in ≥4[a]	11 (40.7)	43 (33.6)	54 (34.8)
Discontinued study in <2 weeks	9 (33.3)	12 (9.4)	21 (13.5)
AE	3 (11.1)	4 (3.1)	7 (4.5)
Subject's choice	3 (11.1)	1 (0.8)	4 (2.6)
Lost to follow-up	0	0	0
Lack of therapeutic effect	0	1 (0.8)	1 (0.6)
Confirmed or suspected diversion	0	0	0
Administrative	3 (11.1)	6 (4.7)	9 (5.8)
Discontinued study in ≥2 to <4wks	1 (3.7)	11 (8.6)	12 (7.7)
AE	0	3 (2.3)	3 (1.9)
Subject's choice	0	3 (2.3)	3 (1.9)
Lost to follow-up	0	1 (0.8)	1 (0.6)
Lack of therapeutic effect	0	4 (3.1)	4 (2.6)
Confirmed or suspected diversion	0	0	0
Administrative	1 (3.7)	0	1 (0.6)

Abbreviations: AE = adverse event; N = number of patients in population groups and total; n = number of patients with data.
[a]There are 2 subjects with extended exposure in OTR3001 because the extension study was not available.
Note: Reasons for discontinuation are based on the End of Study (EOS) eCRF page.
Percentages are based on N.

As per the protocol, a patient was considered as completing the study if he/she completed at least 2 weeks of study drug dosing and did not need additional treatment with opioid medication for pain relief per the investigator's clinical judgment or if the patient completed the entire 4 weeks of study drug dosing. In the subjects who were treated less than 2 weeks, this could explain the 4 patients who were discontinued due to "subject's choice" or 8 of the patients who were discontinued for administrative reasons. One subject, was administratively terminated because he lived "out of state" after being dispensed the study drug. For the 4 patients who were treated for longer than 2 weeks and who discontinued due to subject's choice or administrative reasons, no further explanation was given.

One-hundred and twenty-two patients (78.7%), out of the 155 patients included in the safety population, completed the study. Sixty-eight patients (43.9%) completed ≤ 2 to

<4 weeks of study drug treatment and 54 patients (34.8%) completed ≥ 4 weeks of study drug treatment. The percentage of patients who completed ≥4 weeks of study drug treatment within each age group was similar. Twenty-one 21 (13.5%) discontinued from the study with less than 2 weeks of study drug treatment and 12 (7.7%) patients discontinued from the study with ≥ 2 to <4 weeks of treatment.

Percentage-wise, younger patients discontinued from the study in less than 2 weeks; the difference was due to AEs, administrative reasons, and "subject's choice". However, a higher percentage of older patients discontinued from the study in ≥ 2 to <4 weeks of treatment.

It is important to note that as per the Written Request agreement, "half of the patients must be exposed to study drug for at least four weeks". This requirement was clearly not met. In the 6 to less than 12 year cohort, only 40% of the subjects were exposed to that minimum and in the significantly larger older cohort only 33.6% met the requirement. Overall, 34.8% of the subjects were exposed for at least 4 wks.

5.3.2.11.2 Extent of Exposure

The following table summarizes the extent of exposure for the study drug.

Table 19. Summary of Extent of Exposure to OxyContin by Age and Overall: Safety Population. Study OTR3001.

Category	Age Group		Total
	6 to < 12 years (N=27)	≥ 12 to ≤ 16 Years (N=128)	(N=155)
Mean Weekly Dose During Study (mg/day)			
n	26	128	154
Mean (SD)	29.75 (13.458)	34.02 (18.260)	33.30 (17.577)
Median	26.80	30.00	29.25
Min, Max	10.0, 67.0	10.0, 140.0	10.0, 140.0
Minimum Weekly Dose During Study (mg/day)			
n	26	128	154
Mean (SD)	17.88 (8.738)	17.50 (11.346)	17.56 (10.925)
Median	15.00	15.00	15.00
Min, Max	10.0, 40.0	10.0, 80.0	10.0, 80.0
Maximum Weekly Dose During Study (mg/day)			
n	26	128	154
Mean (SD)	33.08 (14.972)	41.80 (24.772)	40.32 (23.596)
Median	30.00	40.00	40.0

Min, Max	20.0, 80.0	10.0, 160.0	10.0, 160.0
Number of Days on Therapy			
n	26	128	154
Mean (SD)	20.2 (9.50)	20.8 (8.12)	20.7 (8.34)
Median	24.0	18.0	18.0
Min, Max	2, 30	1, 43	1, 43
Extent of Exposure, n (%)			
Any Exposure	26 (96.3)	128 (100.0)	154 (99.4)
>= 1 Week	23 (85.2)	124 (96.9)	147 (94.8)
>= 2 Weeks	18 (66.7)	113 (88.3)	131 (84.5)
>= 3 Weeks	14 (51.9)	55 (43.0)	69 (44.5)
>= 4 Weeks	11 (40.7)	43 (33.6)	54 (34.8)
Dose Changes, n (%)			
Any Up-Titration	4 (14.8)	21 (16.4)	25 (16.1)
Any Down-Titration	5 (18.5)	45 (35.2)	50 (32.3)

(Source: Derived from Study OTR3001's report, Table 12.1.4.1, page 209).

5.3.2.11.3 Protocol Deviations

As per OTR3001's report, "the percentages of patients with major protocol violations were similar between the overall safety population (82 patients, 52.9%) and the 2 age groups (15 younger patients, 55.6%; 67 older patients, 52.3%)". The table below, taken from Table 9 of the study's report, summarizes the major protocol deviations.

Table 20. Number and Percent of Patient with Major Protocol Deviations and Violations: Safety Population. Study OTR3001

Category	Age Group		
	6 to < 12 Years (N=27) n (%)	≥ 12 to ≤ 16 Years (N=128) n (%)	Total (N=155) n (%)
Any major protocol violation	15 (55.6)	67 (52.3)	82 (52.9)
Assessment safety	7 (25.9)	48 (37.5)	55 (35.5)
Assessment non-safety	3 (11.1)	17 (13.3)	20 (12.9)
Study drug	4 (14.8)	10 (7.8)	14 (9.0)
Inclusion criteria	1 (3.7)	6 (4.7)	7 (4.5)
Informed consent	2 (7.4)	3 (2.3)	5 (3.2)
Other	0	4 (3.1)	4 (2.6)

The Sponsor did not provide any further breakdown or explanation regarding this seemingly large number of major protocol deviations. Purdue did provide in the Appendix 16.2.2 a very long list of all protocol deviations and violations for the safety

population. I performed a search for "Major Violation" to have a better understanding of these protocol deviations and their potential impact on the reliability of the data. Here are various examples of what I found: "on visit 3, vital signs assessment not performed", SAE report not sent within 24 hours of first knowledge, "pre-dose PK not done because the subject took the study medication prior to going in for her visit", PK samples (pre and post dose) not drawn", PI explained study to the mom and patient but IC was not signed until 2 days later (start of study), "patient was 71.4% compliant with study medication between V1 and V2", and "day 1 30 minute post dose vitals, oximetry not done". Many of these major protocol violations found in the appendix were non-clinical assessments or administrative. In conclusion, these findings do not significantly impact the interpretation of the data from this study.

5.3.2.11.4 Summary of Safety and Efficacy Findings

In Study OTR3001, adverse events were as expected for this patient population and for this medication class. Vomiting, nausea, and headache were the most frequently reported treatment-related adverse events (TEAEs). Headache was the most frequently reported individual TEAE that led to study discontinuation. The 4 deaths and the majority of nonfatal SAEs that occurred during the study were not considered related to the study drug by the investigator.

In general, clinical laboratory tests and vital sign assessments did not reveal any apparent safety concerns. There were no significant changes from baseline in mean respiratory rate, degree of hemoglobin-oxygen saturation, or somnolence scores in the two age groups.

As per the Sponsor's summary, pain control with OxyContin was "good": Mean pain-right- now scores (VAS) in the older group decreased from 44.58 at baseline to 35.58 (morning) and 35.30 (evening) at Week 4. Among younger patients, scores
(FPS-R) decreased from 4.44 at baseline to 3.13 (morning) and 3.42 (evening) at Week 4. Overall, few (16.1%) patients needed to increase dose. Supplemental pain medication (opioid) was administered to 73.5% and (non-opioid) to 59.4% of patients. Use of supplemental short-term opioid medications and non-opioid supplemental pain medications was approximately the same in the 2 age groups.

5.3.3 Study OXP1005

The following summary of the design of Study OXP1005 was derived from the revised protocol incorporating Amendment 6, dated February 12, 2014. This study was terminated prematurely by Purdue on 31 Mar 2004 due to "administrative reasons".

Title: 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.

5.3.3.1 Dates Conducted:

Study Start Date: 22 Jan 2003
Study End Date: 2 Apr 2004

5.3.3.2 Objectives:

The primary objectives were:

- 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.

The secondary objective was:

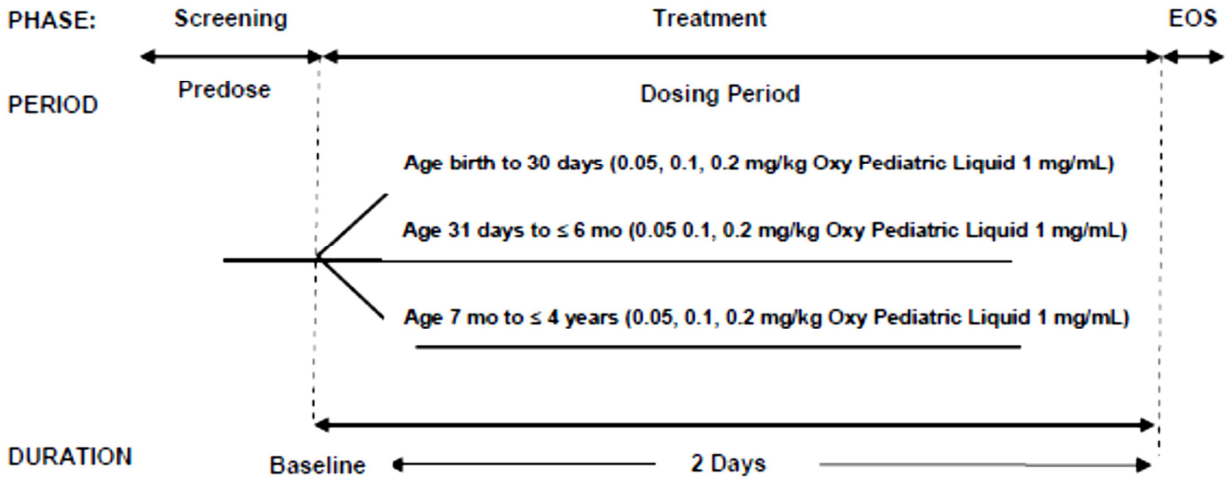
- To assess the efficacy of Oxy Pediatric Liquid 1 mg/mL in pediatric patients from birth to ≤4 years of age using supplemental analgesic requirement as the endpoint.

5.3.3.3 Study Design

Study OXP1005 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). The second amendment to the protocol specified that patients were to be approximately evenly distributed over the entire age range in each stratum and across both genders. The duration of the study was up to 2 days. All enrolled patients were permitted to receive opioids, PCA or oral morphine was the preferred supplemental medication for pain relief. In addition, NSAIDs and acetaminophen were also permitted for supplemental pain relief.

Figure 6. OXP1005 Study Schematic



Note: EOS = End of Study
(Source: OXP1005 Study Report, Figure 1, page 23)

5.3.3.4 Population

The study population was to include male and female pediatric patients from birth to ≤ 4 years of age who had, or were anticipated to have, moderate to severe pain requiring treatment with opioid analgesics for at least 2 days. A sufficient number of patients were to be enrolled to achieve at least 60 PK-evaluable patients, with approximately equal numbers of patients in each of the three age groups (i.e., birth to 30 days, 31 days to ≤ 6 months, and7 months to ≤ 4 years). Patients were to be approximately evenly distributed over the entire age range in each age group and across both genders.

5.3.3.5 Inclusion Criteria

Patients were to have met all of the following criteria:

- Male or female patients from birth through age 4.
- Gestational age ≥ 36 weeks at birth (for children < 1 year of age).
- Body weight ≥ 2.5 kg.
- Moderate to severe pain, current or anticipated, requiring opioid analgesic therapy for at least 2 days.
- An inpatient at the time of enrollment.
- Sufficient alertness to be assessed for treatment-related side effects and level of pain.
- Signed informed consent provided by a parent or guardian prior to beginning protocol-specific procedures.
- Must be opioid-naïve prior to study entry or preoperatively (for surgical patients).

5.3.3.6 Exclusion Criteria:

Patients were to have been excluded if any of the following applied:

- American Society of Anesthesiologist Physical Status ≥ 4 (severe disease that is life threatening).
- Unable to take clear liquids orally.
- History of sleep apnea.
- Cystic fibrosis.
- Malabsorption syndromes.
- Allergy to oxycodone.
- Current oxycodone therapy (within 72 hours prior to the first dose of study drug)
- Receiving clonidine or dexmedetomidine for sedation/analgesia.
- Clinically significant renal dysfunction as evidenced by creatinine ≥ 1.2 mg/dL.
- Clinically significant hepatic dysfunction as evidenced by bilirubin ≥ 18 mg/dL and/or AST ≥ 100 IU/L and ALT ≥ 80 IU/L.
- Impaired respiratory reserve including bronchopulmonary dysplasia, or being currently on a ventilator (unless the ventilator setting was on Volume Support or Continuous Positive Airway Pressure, or Positive End-Expiratory Pressure with ≤ 5 TORR, such that spontaneous respiratory rate could be monitored).
- Receiving > 25% FiO2
- Impaired cardiovascular stability (e.g., on the day of surgery for cardiac surgery patients).
- Use of paralytic agents.
- Unable to contribute at least 5 mL of blood for the study, based on the calculation for allowable blood loss.
- Patients who received an investigational drug within 30 days of screening and who met all other criteria were evaluated on a case-by-case basis by the investigator and the sponsor to determine study eligibility.
- Patients with an intracardiac or intracranial experimental device inserted within 30 days of screening.
- Family members of employees of Purdue, CCRI, or the clinical investigative site staff.
- Patients who, in the opinion of the investigative staff, were not well suited for the study.
- Children who were consistently exposed to opiates in utero due to maternal opiate addiction.
- Patients for whom the use of opioids is contraindicated.

5.3.2.7 Withdrawal/Discontinuation Criteria

Patients were to be discontinued or be withdrawn from the study under any of the following circumstances:

- Patient was unable to tolerate the study drug.
- Patient or his or her parent(s)/legal guardian requested withdrawal from the trial.
- In the case of surgical patients, the patient's pain was evaluated by the investigator 24 hours post-surgery, using the Pain Measurement Algorithm and if it appeared that the patient no longer required an opioid analgesic to treat his/her pain, the patient would not be included in the study.

The protocol anticipated that in some cases the child might put up resistance during the study because he/she was afraid of the investigation and/or procedure. Therefore, resistance from the child was judged continuously throughout the study. If the investigator deemed there was more resistance than was considered normal for the child's daily routine, for example excessive or abnormal behavior, the child could be withdrawn from the study. This was added in Amendment 1 for the sites located in the Netherlands and dated 5 Jun 2003.

If any patient was discontinued from the study, the investigator should have recorded the reason in the Case Report Form (CRF), along with all End of Study Assessments (physical exam, vitals, pulse oximetry, somnolence evaluation, pain scores and laboratory exams). The staff was to make every effort to collect all PK samples in accordance with the time windows provided for the last dose for patients discontinuing the study. If an adverse event was the reason for discontinuation, an additional blood sample for PK analysis should have been collected, it could even be collected at home.

A patient was considered to have completed the study if all scheduled doses of the study drug had been administered and if the patient was followed until the last scheduled PK blood draw, which was 4 to 8 hours after the last dose.

5.3.3.8 Study Methods

5.3.3.8.1 Schedule of Visits and Procedures

The following table (Source: OXP1005 Study's report, page 34) summarizes the schedule of visits and procedures during the study.

Table 21. Schedule of Visits and Procedures Flow Chart. Study OXP1005

		Study Period		
		Baseline	Dosing	End of Study
Informed consent	X			
Demographics	X			
Inclusion/ Exclusion	X	X		
Medical history	X	X		
Prior medications[1]		X		
Physical examination	X	X		X
Laboratory tests		X[2]		X
Surgical Stress		X		
Vital signs and (SpO_2)		X	X	X
Somnolence evaluation[3]		X	X	X
Study drug administration[4]			X	
PK blood samples[5]			X	
Pain scores[3]		X	X	X
Supplemental pain medication[6]			X	X
Drug accountability			X	X
Adverse events		X	X	X
Concomitant medications		X	X	X[7]
Urine collection				X[8]

[1] All medication taken within the 7 days prior to study drug dosing was recorded. All opioid medications taken within 30 days prior to study drug administration were also recorded (added by Amendment 1, 13-Nov-2002).
[2] Baseline safety lab tests may have been performed at screening or at baseline except for postoperative patients whose laboratory tests must have been done postoperatively.
[3] Performed at baseline (before administration of study drug) and at 0.5, 1, 2, and 3 hours after the first dose, immediately prior to and 1 hour after each subsequent dose, and at the end of study.
[4] Study drug was administered q6h for a total of 6 or 7 doses as determined by the investigator.
[5] A total of 9 PK samples were collected at designated time windows.Patients with body weight ≤ 5 kg provided 4 PK samples only. All samples were collected at least 1 hour apart from the previous collection.
[6] All patients were allowed to receive morphine as supplemental pain medication. If a patient was unable to take morphine then the investigator may have prescr bed an appropriate supplemental pain medication other than oxycodone.
[7] The investigator determined whether analgesic medication was given after the study based on the patient's clinical condition.
[8] Urine was collected (as large an amount as possible) for 6 hours after the last dose.

Netherlands-specific Amendment 1 stipulated that "children receiving opioids had continuous electronic monitoring of their physiological parameters e.g., pulse oximetry, throughout the entire treatment".

5.3.3.8.1.1 Screening and Baseline

Screening procedures were scheduled to be performed any time up to 14 days prior to study drug administration. These procedures consisted of obtaining demographic information, medical history, physical examination, checking eligibility, and obtaining signature of informed consent. Laboratory tests were performed at the screening visit or at baseline, except for postoperative patients whose laboratory tests had to be performed after the operation.

Baseline procedures were performed before study drug administration. These procedures consisted of updating medical history and physical examination, collecting medication history during the 7 days prior to study drug dosing, obtaining vital signs, pulse oximetry measurement, somnolence evaluation, and pain score. Opioid medication history during the 30 days prior to study drug dosing would also be collected. Laboratory tests were performed for post-operative patients. The clinical conditions for postoperative patients were assessed by the investigator to confirm eligibility for enrollment into the study.

5.3.3.8.1.2 Study Drug Dosing Period

Study drug dosing could begin when the patient was ready to take clear oral liquid. Patients were administered Oxy Pediatric Liquid orally every 6 hours for a total of 6 to 7 doses.

5.3.3.8.1.3 Blood Sample Collections for Pharmacokinetic Analysis

As per the protocol, a total of nine 1-mL blood samples (for serum oxycodone and its metabolites) were to be collected from each patient with body weight > 5 kg or only 4 blood samples for patients with body weight ≤ 5 kg with at least 1-hour interval between them. The schedule for blood draws is summarized in the table below.

Table 22. Schedule of PK Blood Sample Collection. Study OXP1005

Time	Dose	PK Samples[1,2]		
		No of Samples	Time Windows Post Dose	Actual Time Elapsed Since 1st Dose
0 hr	1			
		3	0.5 hr to <2 hr*	0.5 hr to <2 hr*
			2 hr to <4 hr*	2 hr to <4 hr*
			4 hr to <6 hr	4 hr to <6 hr
6 hr	2	No PK sampling		
12 hr	3			
		1	2 hr to < 6 hr*	14 hr to <18 hr*
18 hr	4			
		1	2 hr to < 6 hr*	20 hr to <24 hr*
24 hr	5			
		1	2 hr to < 6 hr*	26 hr to <30 hr*
30 hr	6			
		3 (PK samples drawn **ONLY if this is the last dose**)	0.5 hr to <2 hr	30.5 hr to <32 hr
			2 hr to < 4 hr	32 hr to <34hr
			4 hr to 8 hr	34 hr to 38 hr
36 hr	7			
		3	0.5 hr to <2hr	36.5 hr to <38 hr
			2 hr to <4 hr	38 hr to <40 hr
			4 hr to 8 hr	40 hr to 44 hr

[1]If the study staff had knowledge (either before or just after the administration of a dose) of early discharge from the hospital or discontinuation from the study then that dose was to be considered the last dose and every effort was to be made to collect all PK samples in accordance with the time windows provided for the last dose.
[2]There must be at least a one-hour interval between each sample.
* These samples will NOT be taken for children with body weight ≤ 5 kg.
(Source: OXP1005 protocol, Table 9.4.1B, page 22.)

5.3.3.8.1.4 End-of-Study Procedures (EOS)

EOS procedures were to be performed 6 to 8 hours following the last dose, after the last PK blood sample and urine collection, or at the time of discontinuation. EOS procedures consisted of physical examination, vital sign measurement, pulse oximetry, somnolence assessment, pain score, supplemental pain medication usage, and clinical laboratory tests. Treatment after the EOS was determined by the patient's physician, based on the patient's clinical condition.

5.3.3.8.2 Efficacy Variables

5.3.3.8.2.1 Supplemental Pain Medication

Pain intensity was monitored throughout the treatment. If the oxycodone treatment was not sufficient to diminish the pain to a satisfactory level as determined by the investigator or designated nurse, supplemental pain medication was given to the patient. The nurse recorded the pain score on a numerical scale before administering any supplemental pain medication. Patients could receive oral morphine (0.1 to 0.3 mg/kg q2h) or nurse-controlled analgesia via PCA pumps with morphine sulfate 15 mcg/kg per dose with an 8-minute lockout for a maximum of 6 doses per hour.

All doses of PCA supplemental pain medication were to be recorded by total amount of morphine (mg) administered in 1-hour period, number of doses in 1-hour period**,** and route of administration on the case report form. All other supplemental pain medications were recorded by exact clock time for each dose, dose in milligrams, and route of administration on the case report form.

If a patient was unable to take morphine, the investigator could prescribe an appropriate opioid supplemental pain medication other than oxycodone, at doses equivalent to these morphine doses. “NSAIDS” and acetaminophen were also permitted

5.3.3.8.2.2 Pain Intensity

Pain intensity ("pain right now") was to be assessed using the numerical scale 0 = no pain to 10 = unbearable pain, at baseline, and intermittently throughout the study to confirm adequate overall analgesic care. Time points for the assessments are listed below:

- At baseline.
- After the first dose: at 0.5, 1, 2, 3, and 5.5 hours post-dose.
- After each subsequent dose at the 1 and 5.5-hours time points.
- At the end of study.
- Immediately prior to administration of supplemental pain medication (PCA or non-PCA).

5.3.3.9 Treatments

5.3.3.9.1 Treatments Administered

Patients with moderate or severe pain were treated with Oxy Pediatric Liquid (1mg/mL) as the primary analgesic. Oxy Pediatric Liquid was given orally every 6 hours for a total of 6 or 7 doses.

An ascending dose regimen was used with the intention to study 3 dose levels: 0.05 mg/kg, 0.1 mg/kg, and 0.2 mg/kg per dose. A group-sequential ascending dose regimen was used to ensure the safety of the patients. Due to the large number of centers that were anticipated to be recruited into the study, an Investigator Steering Committee was constituted to review the safety data and make a decision for the dose level of the next

cohort. The Investigator Steering Committee consisted of physicians appointed at the initiation of the study.

Although in the United States, the department of Health and Human Services recommends a starting dose of 0.2 mg/kg of oxycodone every 3 to 4 hours to treat children, and due to the very young age of the children to be recruited for the study, the 0.05 mg/kg starting dose was selected as a predictably ineffective dose. This was done to define the bottom of the dose response, with the 0.1 mg/kg dose selected as the expected middle point on the dose response curve. To validate the 0.05 mg/kg, 0.1 mg/kg, and 0.2 mg/kg dosing regimen, clinical trial simulations using data from children enrolled into *An Open-Label, Randomized, Cross-Over Comparison of Plasma Oxycodone Concentrations in Children After the Administration of Single Dose of Controlled-Release Oxycodone (OxyContin) and Immediate-Release Oxycodone* (study OC96-0602) were completed.

For each age group, after the first cohort had completed the treatment, the Investigator Steering Committee was to review the data and determine whether the dose should be escalated. Enrollment was to be delayed while the Investigator Steering Committee came to a decision. The anticipated potential outcome of the deliberation was:

- No safety concern, proceed with dose escalation
- Safety concern, increase current dose cohort size and re-assess, or
- Safety concern, evaluate next cohort at lower dose instead of higher dose.

At least 3 members of the Investigator Steering Committee were required to be present for a decision. If any member of the Investigator Steering Committee voted not to escalate the dose, the dose was not escalated. The next cohort (approximately 7 patients) received the dose determined by the Investigator Steering Committee. The same safety evaluation was performed after the treatment for each dose cohort, and the Investigator Steering Committee reviewed the safety data and made the decision on the next dose level for each subsequent cohort for each age group.

The 30- to 36-hour treatment duration was necessary in order to obtain 3 steady-state PK samples which were essential for achieving the primary objective.

Study drug dosing was to begin when the patient was ready to take clear oral liquids. The investigator determined the timing of the first dose based on each patient's clinical condition (preferably at 8 AM).

5.3.3.9.2 Prior and Concomitant Therapy

All medications, including over-the-counter medications, vitamins, and minerals taken by the patient in the 7 days prior to study entry were to be recorded on the CRF, including name, dose, route of administration of the drug, and duration of the treatment. Additionally, all opioid medication history during the 30 days prior to the study drug were to be collected.

Continuous infusion of morphine or other opioid was required to be discontinued at least 1 hour prior to study drug administration. Epidural medications were required to be discontinued at least 4 hours prior to study drug administration.

All doses of PCA supplemental pain medication were to be recorded by total amount (mg) administered in a 1-hour period, number of doses in a 1-hour period, and route of administration on the case report form. Each site was to administer PCA so that patients had adequate pain relief. Pain scores were to be collected prior to each administration of PCA, as well as at the scheduled times. All other supplemental pain medications were to be recorded by exact clock times, as previously discussed.

Patients could receive oral morphine (0.1 to 0.3 mg/kg every 2 hours) or nurse-controlled analgesia via PCA pumps with morphine sulfate 15 mcg/kg per dose as previously discussed.

5.3.3.9.2.1 Prohibited Concomitant Medications

Grapefruit juice and the medications listed on the following table were not permitted from 24 hours before the study drug administration to EOS or until all AEs had been resolved.

Table 23. Prohibited Concomitant Medications for Study OXP1005

Medications
Clonidine hydrochloride for sedation/analgesia
Oral Trovafloxacin
CYP2D6 inhibitors including, but not limited to:
nefazodone
Antipsychotics, such as fluphenazine, haloperidol, perphenazine or thioridazine
cimetidine
CYP3A inhibitors including, but not limited to:
Azole antifungals such as ketoconazole, itraconazole or fluconazole
clarithromycin
erythromycin

Derived from Table 3, page 31 of OXP1005's study report.

5.3.3.10 OXP1005 Results

5.3.3.10.1 Study Population

5.3.3.10.1.1 Patient Demographics

The table below, derived from Table 7 of the study's report, is a summary of the demographic and baseline characteristics of the safety population:

Table 24. Safety Population Demographics and Baseline Characteristics. Study OXP1005

All Patients Characteristics	Oxy Pediatric Liquid 1mg/mL 0.05 mg/kg (n = 26)	0.1 mg/kg (n = 17)	0.2 mg/kg (n = 17)	Total (N = 60)
Age (days)				
Mean (SD)	258.8 (374.00)	531.0 (557.23)	547.0 (592.04)	417.6 (508.10)
Median	87.0	204.0	227.0	165.5
Min, Max	1, 1246	71, 1763	71, 1728	1, 1763
Age Group, n (%)				
0 to 30 Days	12 (46.2)	0	0	12 (20.0)
31 Days to ≤ 6 Mo	7 (26.9)	9 (52.9)	8 (47.1)	24 (40.0)
7 Mo to ≤ 4 Years	7 (26.9)	8 (47.1)	9 (52.9)	24 (40.0)
Sex, n (%)				
Male	15 (57.7)	4 (23.5)	10 (58.8)	29 (48.3)
Female	11 (42.3)	13 (76.5)	7 (41.2)	31 (51.7)
Race, n (%)				
White	22 (84.6)	10 (58.8)	10 (58.8)	42 (70.0)
Black or African American	0	1 (5.9)	1 (5.9)	2 (3.3)
Asian	0	1 (5.9)	1 (5.9)	2 (3.3)
Other	4 (15.4)	5 (29.4)	5 (29.4)	14 (23.3)
Ethnicity, n (%)				
Hispanic or Latino	3 (11.5)	5 (29.4)	2 (11.8)	10 (16.7)
Not Hispanic or Latino	23 (88.5)	12 (70.6)	15 (88.2)	50 (83.3)
Weight (kg)				
Mean (SD)	6.63 (4.868)	8.90 (4.695)	9.40 (4.847)	8.06 (4.900)
Median	4.55	7.40	7.90	6.20
Min, Max	2.4, 22.0	4.0, 20.6	4.3, 20.0	2.4, 22.0
Surgical Stress Score				
Mean (SD)	11.6 (3.57)	13.8 (4.29)	15.8 (3.63)	13.4 (4.14)
Median	11.0	16.0	16.0	15.0
Min, Max	6, 17	5, 18	8, 22	5, 22

Note: surgical stress scores classified the degree of surgical stress (1 to 10 = minor, 11 to 20 = moderate, 21 to 30 = severe).

5.3.3.10.1.2 Baseline Medical Conditions

The table below summarizes the medical history conditions for 10% or more of patients in the overall safety population.

Table 25. Baseline Medical Conditions Occurring in ≥ 10% of Patients. Study OXP1005.

	Oxy Pediatric Liquid 1mg/mL			
System Organ Class Preferred Term	0.05 mg/kg (N=26) n (%)	0.1mg/kg (N=17) n (%)	0.2mg/kg (N=17) n (%)	Total (N=60) n (%)
Congenital, familial and genetic disorders	**22 (84.6)**	**14 (82.4)**	**17 (100.0)**	**53 (88.3)**
Atrial septal defect	4 (15.4)	6 (35.3)	4 (23.5)	14 (23.3)
Coarctation of the aorta	4 (15.4)	0	3 (17.6)	7 (11.7)
Ventricular septal defect	5 (19.2)	7 (41.2)	6 (35.3)	18 (30.0)
Injury, Poisoning And Procedural Complications	**1 (3.8)**	**11 (64.7)**	**10 (58.8)**	**39 (60.0)**
Postoperative fever	1 (3.8)	7 (41.2)	4 (18.2)	11 (18.3)
Procedural pain	0	10 (58.8)	10 (58.8)	20 (33.3)
Investigations	**2 (7.7)**	**5 (29.4)**	**7 (41.2)**	**14 (23.3)**
Catheterisation cardiac	0	3 (17.6)	5 (29.4)	8 (13.3)
Oxygen saturation decreased	0	2 (11.8)	6 (35.3)	8 (13.3)
Respiratory, thoracic and mediastinal disorders	**3 (15.8)**	**9 (52.9)**	**9 (52.9)**	**20 (33.3)**
Pulmonary oedema	0	5 (29.4)	8 (47.1)	13 (21.7)
Surgical and medical procedures	**25 (96.2)**	**16 (94.1)**	**17 (100.0)**	**58 (96.7)**
Atrial septal defect repair	1 (3.8)	7 (41.2)	7 (41.2)	15 (25.0)
Cardiac operation	2 (7.7)	3 (17.6)	4 (23.5)	9 (15.0)
Systemic-pulmonary artery shunt	1 (3.8)	2 (11.8)	6 (35.3)	9 (15.0)
Ventricular septal defect repair	4 (15.4)	7 (41.2)	5 (29.4)	16 (26.7)

(Source; OXP1005's report, page 56, Table 9)
*Numbers shown on table represent the actual number of individual patients. Patients may have had more than one baseline medical condition.

5.3.3.10.2 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. The following table summarizes the extent of exposure of the study drug for Study OXP1005.

Table 26. Extent of Exposure to Oxy Pediatric Liquid: Safety Population. Study OXP1005.

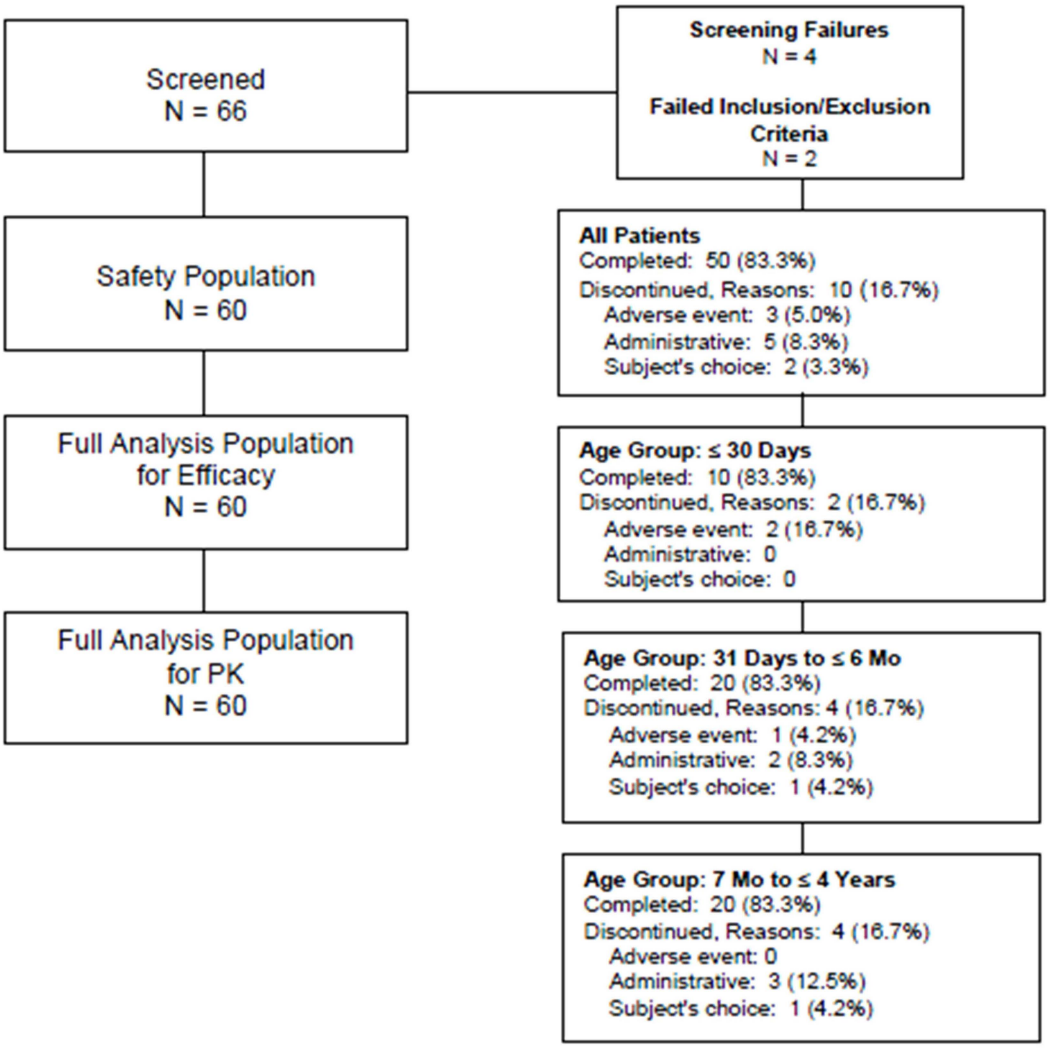
Extent of Exposure (Doses) All Patients	Oxy Pediatric Liquid 1 mg/mL 0.05 mg/kg (n = 26) n (%)	0.1 mg/kg (n = 17) n (%)	0.2 mg/kg (n = 17) n (%)	Total (N = 60) n (%)
1 dose	26 (100)	17 (100)	17 (100)	60 (100)
2 doses	25 (96.2)	17 (100)	15 (88.2)	57 (95.0)
3 doses	25 (96.2)	16 (94.1)	15 (88.2)	56 (93.3)
4 doses	24 (92.3)	15 (88.2)	15 (88.2)	54 (90.0)
5 doses	23 (88.5)	15 (88.2)	15 (88.2)	53 (88.3)
6 doses	22 (84.6)	15 (88.2)	15 (88.2)	52 (86.7)
7 doses	1 (3.8)	0	1 (5.9)	2 (3.3)
No. of Doses				
Mean (SD)	5.6 (1.20)	5.6 (1.18)	5.5 (1.70)	5.6 (1.33)
Median	6.0	6.0	6.0	6.0
Min, Max	1, 7	2, 6	1, 7	1, 7
Time from First to Last Dose (Hours)				
Mean (SD)	28.0	27.6	27.1	27.6
Median	30.0	30.0	30.0	30.0
Min, Max	0, 36	6, 31	0, 37	0, 37

(Source: Study OXP1005's report, Table 14, page 65)

5.3.3.10.3 Patient Disposition

The following figure, (taken from the study's report, page 51) is a summary of the patient disposition for Study OXP1005:

Figure 7. Patient Disposition and Reasons for Discontinuation by Age Group: Safety Population. Study OXP1005.



The following table, derived from Table 6 of the study's report, further illustrates the reasons for discontinuation in the safety population

Table 27. Patient Disposition and Reasons for Discontinuation by Age Group: Safety Population. Study OXP1005.

	Oxy Pediatric Liquid 1mg/ml			
Age Group	**0.05 mg/kg (n = 26)**	**0.1 mg/kg (n = 17)**	**0.2 mg/kg (n = 17)**	**Total (N = 60)**
All Patients				
Completed, n (%)	21 (80.8)	15 (88.2)	14 (82.4)	50 (83.3)
Discontinued, n (%)	5 (19.2)	2 (11.8)	3 (17.6)	10 (16.7)
Adverse event	2 (7.7)	0	1 (5.9)	3 (5.0)
Subject's choice	1 (3.8)	1 (5.9)	0	2 (3.3)
Administrative	2 (7.7)	1 (5.9)	2 (11.8)	5 (8.3)
Birth to 30 Days	**n = 12**	**n = 0**	**n = 0**	**N = 12**
Completed, n (%)	10 (83.3)			10 (83.3)
Discontinued, n (%)	2 (16.7)	0	0	2 (16.7)
Adverse event	2 (16.7)	0	0	2 (16.7)
Subject's choice	0	0	0	0
Administrative	0	0	0	0
31 Days to ≤ 6 Mo	**n = 7**	**n = 9**	**n = 8**	**N = 24**
Completed, n (%)	6 (85.7)	7 (77.8)	7 (87.5)	20 (83.3)
Discontinued, n (%)	1 (14.3)	2 (22.2)	1 (12.5)	4 (16.7)
Adverse event	0	0	1 (12.5)	1 (4.2)
Subject's choice	0	1 (11.1)	0	1 (4.2)
Administrative	1 (14.3)	1 (11.1)	0	2 (8.3)
7 Mo to ≤ 4 Years	**n = 7**	**n = 8**	**n = 9**	**N = 24**
Completed, n (%)	5 (71.4)	8 (100.0)	7 (77.8)	20 (83.3)
Discontinued, n (%)	2 (28.6)	0	2 (22.2)	4 (16.7)
Adverse event	0	0	0	0
Subject's choice	1 (14.3)	0	0	1 (4.2)
Administrative	1 (14.3)	0	2 (22.2)	3 (12.5)

5.3.3.10.4 Protocol Deviations

There were 41 reported deviations during the conduct of the study. With the exception of one case which, in which stock medication was given to the patient instead of the study drug and there were issues with medication compliance, all were considered minor. The deviations are as follow:

- Exclusion criteria met – 24 (minor)
- Inclusion criteria not met – 2 (minor)
- Prohibited medication used – 11 (minor)
- Treatment deviations – 3 (minor)
    - Subject was started on a dose higher than what would have been given if calculated by weight
    - Subject received only Dose 1 but PK blood sample was drawn as if for Dose 3

- Use of stock medication in lieu of study drug
- Non-compliance – 1 (major)

5.3.3.10.5 Summary of Safety Findings

An in-depth look at the safety data for this study will be discussed in Section 7. It appears that administration of Oxy Pediatric Liquid in children aged from birth to 4 years of age did not reveal any unusual safety results of concern in regards to clinical laboratory tests and vital sign assessments.

Adverse events were as expected for this patient population and for this medication class. The most common TEAEs in ≥ 5% of all patients were, vomiting (8%), pyrexia (8%), hemoglobin decreased (7%), tachycardia (5%), and hypertension (5%). Half of the patients in the safety population experienced TEAEs: 7 patients (58%) in the ≤ 30 days age group, 11 (46%) in the 31 days to ≤ 6 months age group, and 12 (50%) in the 7 months to ≤ 4 years age group. There were no deaths during this study.

There was no statistically or clinically significant dose-response relationship observed with respect to supplemental pain medication use or pain scores in children from childbirth through age 4.

5.3.4 Summaries of Additional Studies

5.3.4.1 Study OTR1020

This was an open-label study to characterize the PK and safety of single-dose and multiple-dose reformulated OxyContin (ORF) tablets in pediatric inpatients aged 6 to 16 years. Supplemental pain medications were permitted with the exception of oxycodone-containing products.

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 years and 25 aged ≥ 12 to ≤ 16 years), 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.

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. Seven patients (23.3%) were administered 5 doses (maximum number allowed on study): 2 patients (40%) in the younger age group and 5 patients (20%) in the older age group. 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).

All of the patients in the younger age group (6 to < 12 years) and 80% in the older age group (12-16 years) used supplemental pain medications. In general, safety assessments, including clinical laboratory evaluations, did not reveal any unusual safety results of concern for this medication class.

No patient died during the study. One patient had 1 SAE that was not considered related to the study drug. No patient had severe AEs and no patient experienced an AE leading to treatment discontinuation.

5.3.4.2 Study OTR3002

This study, conducted between January 2012 and December 2013, was a phase 3B, open-label, extension study for OTR3001 to characterize the long-term safety of reformulated OxyContin tablets in pediatric patients 6 to 17 years of age (inclusive). Supplemental pain medications were permitted (including oxycodone-containing products). Only patients who completed the 4-week treatment period of OTR3001 could be enrolled and the intent was to recruit all the patients who met this criteria. However, Purdue closed the study due to "administrative reasons" and only 23 patients were enrolled. Once enrolled, patients could continue on the same OxyContin dose or, if necessary, the dose be adjusted for a total dose between 20-240mg per day. Dose up-titration for efficacy reasons could occur only after the patient had been treated for ≥ 48 hours with the same dose and the maximum dose for a single uptitration was not to exceed 25% of the patient's current dose. The treatment phase was supposed to last up to 6 months, followed by a 7-10 day follow-up period. Similarly to OTR3001, patients were divided in a "younger age group" (6 to < 12 years) and an "older age group" (12-16 years). There were 9 patients in the younger age group and 14 in the older age group. The following table, derived from Table 3 of the study's report, summarized the extent of exposure to OxyContin.

Table 28. Cumulative Extent of Exposure to Study Drug For Patients Enrolled in Study OTR3001 and OTR3002

	Age Group		
Category	**6 to < 12 years (N=9)**	**≥ 12 to ≤ 16 Years (N=14)**	**Total (N=23)**
Mean Weekly Dose During Core and Extension Studies (mg/day)			
n	9	14	23
Mean (SD)	31.49 (12.735)	27.74 (10.601)	29.21 (11.352)
Median	29.1	21.1	25.2
Min, Max	19.7, 56.2	19.4, 48.8	19.4, 56.2
Number of Days on Therapy During Core and Extension			
n	9	14	23
Mean (SD)	160.4 (59.39)	158.8 (62.53)	159.4 (59.94)
Median	198	199	198
Min, Max	45, 209	58, 216	45, 216
Number of Days on Therapy During Extension			
n	9	14	23
Mean (SD)	131.8 (60.24)	126.9 (60.87)	128.8 (59.29)
Median	169	169	169

Category	Age Group		
	6 to < 12 years (N=9)	≥ 12 to ≤ 16 Years (N=14)	Total (N=23)
Min, Max	15, 182	26, 184	15, 184
Extent of Exposure, n (%)			
Any Exposure	9 (100.0)	14 (100.0)	23 (100.0)
≥ 4 Week	9 (100.0)	14 (100.0)	23 (100.0)
≥ 8 Weeks	8 (88.9)	14 (100.0)	22 (95.7)
≥ 12 Weeks	8 (88.9)	12 (85.7)	20 (87.0)
≥ 16 Weeks	7 (77.8)	10 (71.4)	17 (73.9)
≥ 20 Weeks	6 (66.7)	9 (64.3)	15 (65.2)
≥ 24 Weeks	6 (66.7))	8 (57.1)	14 (60.9)
≥ 28 Weeks	5 (55.6)	8 (57.1)	13 (56.5)
Dose Changes During OTR3002, n (%)			
Any Up-Titration	5 (55.6)	6 (42.9)	11 (47.8)
Any Down-Titration	5 (55.6)	5 (35.7)	10 (43.5)

The median duration of exposure (OTR3001 and OTR3002 combined) was 198 days overall, and the median daily dose was 25.2 mg. The majority of patients (13 or 56.5%) received supplemental opioid analgesic during the extension study. In general, the treatment-emergent adverse events (TEAEs) observed in OTR3002 studies were similar to those expected with systemic use mu-opioid agonist analgesics. The most common TEAEs during OTR3002 occurred in the SOCs of gastrointestinal disorders (including vomiting, 4 patients, 17.4%), and general disorders and administration site conditions (including pyrexia, 5 patients, 21.7%). Most of these events were considered by the investigator to be mild or moderate in intensity; 3 patients (13.0%) experienced severe TEAEs during the extension study, and 1 of these 3 patients (4.3%) experienced a TEAE of fatigue that was considered by the investigator to be severe and related to treatment. There were no deaths or study drug discontinuations due to TEAEs during OTR3002.

Four of the 23 (17.4%) patients experienced nonfatal treatment-emergent SAEs in the extension study. Two (8.7%) of these patients experienced a sickle cell anemia crisis (1 in the younger age group and 1 in the older age group). One (4.3%) patient in the younger age group experienced pyrexia, 1 (4.3%) patient in the in the older age group experience vomiting, back pain, and headache. All SAEs were considered by the investigator to be not related or unlikely related to treatment.

No new or unexpected information regarding the safety of OxyContin was collected during the OTR3002, although the small number of patients enrolled in this study limits the generalization of this conclusion.

5.3.4.3 Study OC96-0602

This study, conducted between April 1997 and November 1998, compared the pharmacokinetics (PK) of single doses of the original (non-abuse deterrent) 10-mg OxyContin and 5-mg immediate-release (IR) oxycodone tablets administered to children aged 6 to 12 years.

It was initially designed as a single-dose, open-label, randomized, 2-period crossover PK study in children of both sexes aged 5 to 12 years. The children participating in this study were exclusively inpatient, previously receiving opiates other than oxycodone, and were expected to continue to need opiates for at least 4 days. Treatment consisted of one dose of each formulation of oxycodone (IR and original OxyContin), separated by a washout period of at least 48 hours. Blood samples were taken for 12 hours after the IR oxycodone and for up to 36 hours after the original OxyContin administration.

The Sponsor planned to recruit 24 subjects (to complete 20). However, only 13 subjects (7 males and 6 females ages 6-12) were enrolled because the results from the first 11 completed subjects purportedly provided sufficient study data. All of the enrolled 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.

"Consistent with controlled-release characteristics, OxyContin when administered to subjects aged 6 to 12 years, produced relatively rapid increases to peak plasma concentrations for oxycodone and its metabolites, followed by measurable concentrations sustained beyond 24 hours. IR oxycodone produced similar early peak plasma concentrations for oxycodone and metabolites, but consistent with shorter-acting immediate-release characteristics, plasma concentrations declined more rapidly. Plasma oxymorphone concentrations were negligible."

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. All other adverse events occurred in 1 or 2 subjects each. Adverse events judged to be drug-related were pruritus, nausea, and vomiting. There was no apparent difference between IR oxycodone and OxyContin® in the incidence or type of adverse events. There were no deaths or serious adverse events. In summary, there were no unexpected safety concerns in either the IR oxycodone or OxyContin formulation.

5.3.4.4 Study OXP3004

The purpose of this study, conducted between March 2003 and February 2004, was to evaluate the safety of the conversion from immediate-release oxycodone (OxyIR) to controlled-release oxycodone (the original OxyContin formulation) in children aged 6 to ≤ 16 years. PK modeling performed on the results obtained from Study OC96-0602 (discussed above) indicated that the 1:1 conversion ratio from OxyIR to OxyContin recommended for adults in the approved OxyContin tablets package insert was also appropriate for children. This study evaluated the safety of the 1:1 conversion ratio by measuring respiratory rate, hemoglobinoxygen saturation, and somnolence in the pediatric population.

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. 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 every 6 hours using the 1:1 conversion stated above. All patients were allowed to receive PCA morphine, "NSAIDs" and acetaminophen 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, with adjustments to the doses permitted according to the investigator's assessment.

The Sponsor planned to enroll 100 patients for the conversion and long-term phases, with roughly 40 patients in the 6 to less than 12 years of age range and 60 on the 12 to 16 years group. In reality, on 10 patients were enrolled and only 7 completed the study.

The study was terminated early for "administrative reasons", which the Sponsor reports were unrelated to safety and efficacy. Conclusions are, therefore, limited based on the small number of patients in the study and conclusions regarding efficacy cannot be made.

There were no unanticipated safety findings. No patient died during the study. Two serious adverse events occurred during the study and were not considered to be related to the study drug.

6 Review of Efficacy

Efficacy Summary

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. To support the efficacy of the test product in a pediatric population, Purdue submitted two studies, OTR3001 and OXP3003. However, study OTR3001 was an open-label study and cannot, by design, be considered for efficacy support. It should be noted these studies were designed and conducted in the context of the PWR over the course of a decade. Oxycodone is a drug with a well-understood mechanism of action. Thus, there is little biological reason to think that the drug would be less effective in children older than 2 years of age vs. and adults at similar target site concentrations. If done in accordance to today's standard, we would require studies to evaluate the safety, dose response profile, and the pharmacokinetic profile of the drug on this population and then extrapolate efficacy for patients as young as 2 years of age. Significant portions of the text below come from Dr. Feng Li's statistical review.

As previously discussed in Section 5.3.1, 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 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.

Overall, the efficacy study responded fairly to the corresponding requirements specified in the PWR. However, 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.

6.1 Indication

OxyContin is 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.

6.1.1 Methods

The PWR specified that Study 2 should have been 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 have also included an assessment of efficacy (i.e., pain intensity evaluations and rescue medication usage) and safety (i.e., adverse events). The study should have enrolled a 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.

For Study OXP3003, 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.

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

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 prematurely. There was no imputation method proposed for missing efficacy assessments.

6.1.2 Demographics

The demographic and baseline characteristics were comparable across treatment groups. About 40% of the patients were less than 12 years old and the majority of the patients were female (63%). Please see Section 5.3.1.10.1 for details for patient demographics and baseline characteristics.

6.1.3 Subject Disposition

Study OXP3003 was terminated early due to “administrative 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. For details, see Section 5.3.1.10.1.3.

6.1.4 Analysis of Primary Endpoint(s)

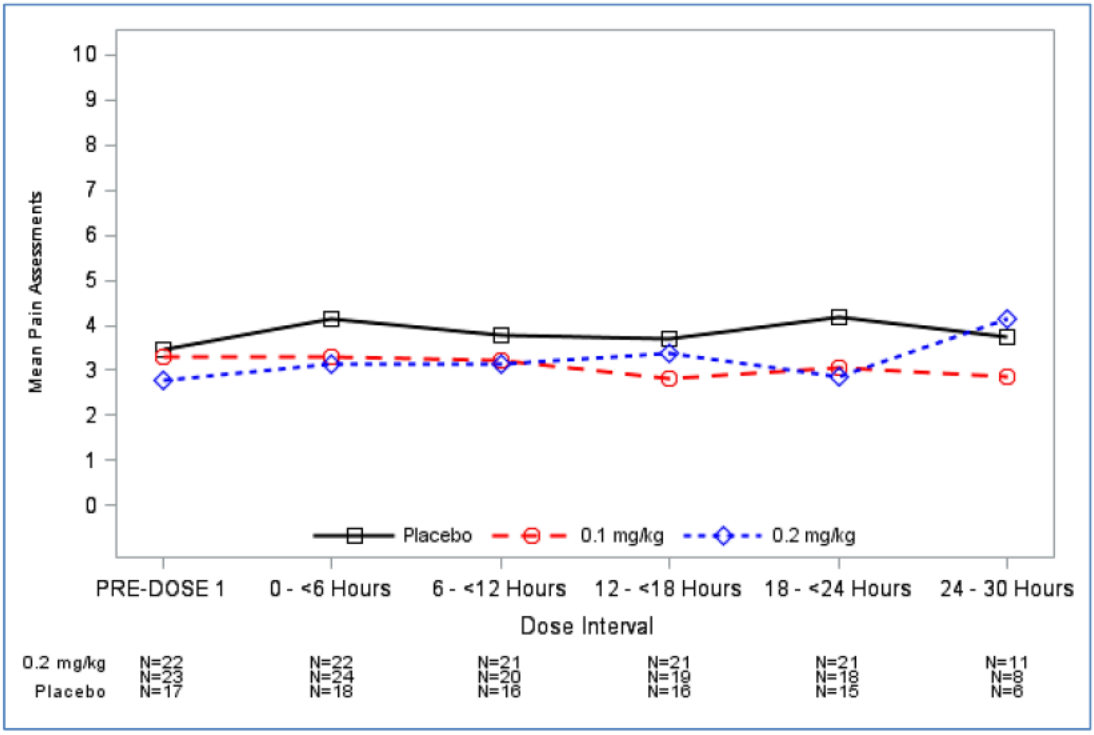
The primary endpoint for Study OXP3003 should have been the difference in immediate-rescue pain medication utilization between the active and placebo groups. Differences in pain scores are not appropriate primary endpoints for this population as we expect patients to have adequate pain control at all times during the study.

Nevertheless, the Sponsor provided a table of summary of efficacy results with p-values from the Jonckheere-Terpstra test for non-increasing dose response (see Table 11 in Section 5.3.1.10.4). Confidence intervals for the treatment differences were not submitted. Dr. Feng Li, the statistical reviewer, was able to reproduce these results and noted that the p-values provided in the table are all one-sided. Dr. Li explains:

> 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≥T2≥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.

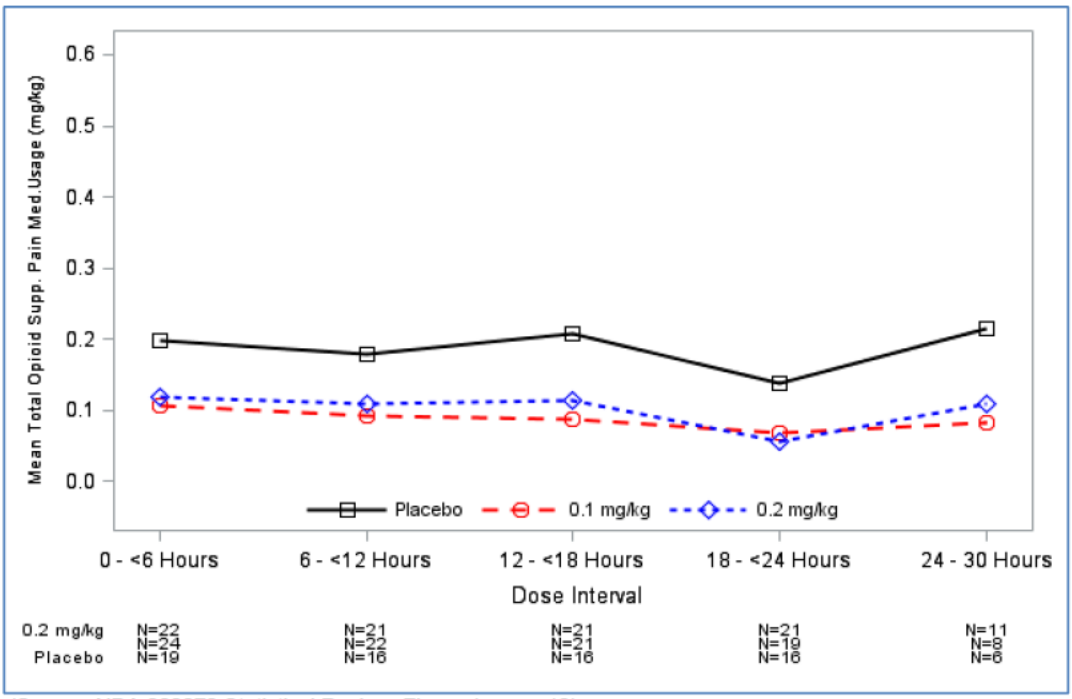
The average pain score and total supplemental opioid usage are depicted by dose intervals for each treatment group in the figures below. For all treatment groups, the average pain was not high at baseline and well-controlled during the study (Figure 8). Figure 8 shows that the separation among the pain curves for the treatments are small; as they should be if pain is being adequately treated for these patients. In contrast, the separation of the curve for the total supplemental opioid usage of the placebo patients from those of the oxycodone treated patients (Figure 9) is notable. 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.

Figure 8. Pain Assessments by Dose Interval



(Source: NDA 022272 Statistical Review, Figure 1, page 12)

Figure 9. Total Supplemental Opioids by Dose Interval



(Source: NDA 022272 Statistical Review, Figure 1, page 12)

6.1.5 Analysis of Secondary Endpoints(s)

Not applicable.

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

The Sponsor presented subgroup summaries for Study OXP3003 in the Summary of Clinical Efficacy (Module 2.7.3) within this submission. Dr. Li also conducted subgroup descriptive statistics and produced plots (see Statistical Review) for visual comparisons by dose intervals. Dr. Li notes that "findings from the subgroup analyses were generally consistent with those observed in the overall population".

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Dr. Feng Li notes that 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."

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

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.

Dr. Li notes in his Statistical Review that 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. Dr. Li further elaborates:

> 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.

Dr. Li concludes that "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".

It is of utmost importance to note in our discussion of efficacy that although OXP3003 was poorly designed and executed in this regard, the Division would have asked for a completely different study if requested today. Because the mechanism of action of oxycodone is well-characterized, by today's standards we would require a study to evaluate the safety, dose response profile, and the pharmacokinetic profile of the drug on this population and then extrapolate efficacy for patients as young as 2 years of age. Thus, based on the pharmacokinetic data submitted, which can be extrapolated to patients as young as 2 years old, Purdue has demonstrated the efficacy of Oxy Pediatric Liquid for acute pain for the said population. (b) (4)

7 Review of Safety

Safety Summary

In general, the safety data in this population submitted with this supplemental NDA is consistent with the known safety profile of oxycodone.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The overall clinical program for this OxyContin Pediatric Written Request (PWR) supplement for the treatment of moderate-to-severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time included the three studies require for the PWR (OXP1005, OXP3003, OTR3001), three pharmacokinetic studies (OXP3004, OTR1020, and OC96-0602) and one extension study to OTR3001 for the purpose of collecting long-term safety data (OTR3002).

The analysis of the safety data is limited by various factors. There was only one, albeit relatively small, placebo-controlled, double-blind study (OXP3003) and it was terminated prematurely due to administrative reasons. Although this study was placebo-controlled, for obvious ethical reasons these patients were also treated with supplemental opioid medications, which is the medication class of the test drug and thus, confounding the true relationship of adverse events (AEs) with the study drug. The other two studies required by the PWR were not open-label. One of them, OXP1005 was small and was also terminated prematurely. Study OTR3001, although the largest of the 3, was also limited by its open-label design.

The differences in the design of these 3 studies (e.g., opioid-naïve vs. opioid tolerant, Oxy Pediatric Liquid vs. OxyContin, 2 day duration vs. 4 week duration, major physiological differences due to the vast age differences in the pediatric patients studied) are also confounding factors, making direct comparisons with each other difficult, if not impossible.

For these reasons, I will discuss most sections of the safety analysis by individual studies.

7.1.2 Categorization of Adverse Events

The Applicant used the MedDRA (Medical Dictionary for Regulatory Activities) V13.0 thesaurus to map the AE verbatim to lowest level term, preferred term, and System Organ Class (SOC) for summary purposes.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

In supporting the safety and tolerability of OxyContin and Oxycodone Pediatric Liquid, Purdue presented the pooled study data organized as follows in the Summary of Safety:

- Group A: 261 patients treated with oxycodone the 3 pediatric pain trials (OXP1005, OXP3003 and OTR3001) identified in the PWR. These 3 trials used either the Oxycodone Pediatric Liquid (Studies OXP3003 and OXP1005) or reformulated extended-release tablets of OxyContin (Study OTR3001).
- Group B: 314 patients treated with OXY from 6 pediatric pain trials (OC96-0602, OXP1005, OXP3003, OTR3001, OXP3004, and OTR1020). This group provides meaningful data for the pediatric population used in the population PK analyses.
- Group C: Subset of Group A and comprises pooled data only from oxycodone-treated patients in PWR Studies 2 and 3. These 2 trials consisted of pediatric patients of similar age (5 or 6 to 16 years of age) who were treated with similar oxycodone dosages.
- Group D: Subset of Group B and comprises data only from the treated patients in Studies OTR1020 and OTR3001, both of which used the reformulated extended-release OxyContin tablet (ORF). This pooling was used primarily for PK analysis.

The following table summarizes the pooling strategy and the number of oxycodone-treated patients in each group.

Table 29. Pooling Strategy and Number of Patients Analyzed

Trial No.	Analysis Population			
	Group A[a]	Group B	Group C	Group D
OXP1005	60	60	-	-
OXP3003	46[a]	46[a]	46[a]	-
OTR3001	155[b]	155	155	155
OXP3004	-	10	-	-
OTR1020	-	30	-	30
OC96-0602[c]	-	13	-	-
Total n	**261**	**314**	**201**	**185**

(Source: Section 6.4 of the ISS Statistical Analysis Plan)
[a] Number of patients who received oxycodone HCl; excludes patients who received placebo.
[b] Selected safety data from 23 patients enrolled in Study OTR3002, an optional long-term extension to Study OTR3001, are included in several additional pooled safety analyses for Group A.
[c] Single-dose study.

Study OTR3002 was an extension study with patients recruited from completers of OTR3001 and is not included in Group B for this reason. Study OTR3002 was summarized in Section 5.3.4.2.

For the reasons stated in Section 7.1.1 (open-label vs. placebo-controlled, opioid naïve vs. opioid tolerant, 2 days duration vs. 4 weeks duration), I will discuss most sections of

the safety analysis by individual studies since pooling of the data is of limited value. Deaths and nonfatal Serious Adverse Events (SEAs) will be discussed for Group B. The rest of the safety analysis will be discussed by the individual studies in Group A.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure information has been discussed for the primary Written Request studies.

7.2.2 Explorations for Dose Response

Not applicable.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

The routine clinical testing conducted during the studies conducted for the Pediatric Written Request appears adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please see Section 4.4 (Clinical Pharmacology) of this review. No new data was submitted.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The opioid class of drugs has been associated with abuse, addiction, and fatal respiratory depression and contains a boxed warning describing these potential adverse events in the label.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred in Studies OXP3003, OXP1005, OTR3002, OC96-0602, OTR1020 or OTR3004.

Four deaths occurred in Study OTR3001, although 1 of them was not treatment-emergent. Of the 3 treatment-emergent deaths, 2 occurred in the younger age group (6 to <12 years) and 1 in the older age group 12-16 years). None of these deaths were considered to be related to the study drug and each of these patients who died had a malignant neoplasm.

7.3.1.1 Individual Patient Death Summaries Study OTR3001

The following, reviewer-constructed table summarizes the SAE's that lead to death. As discussed earlier, these occurred only on Study OTR3001 and using re-formulated OxyContin tablets and not the Oxy Pediatric liquid.

Table 30. Listing of SAEs That Lead to Death

Subject	-Study Day of Death -Total Daily Dose** -Relation to Study Drug Dosing	Narrative	Reviewer Comment
0513001 7 y/o F	-Study day #5* -25 mg daily dose ->4 hours post dose	SAE: breathing irregularity, coma, convulsion (MedDRA preferred terms: Respiratory disorder, Coma, Convulsion) 7-year-old white female with a history neuroblastoma Stage 4 with metastasis to bone/bone marrow and CNS. Patient was started on OxyContin 15mg bid but was decreased to 15mg AM /10mg PM on day 2 due to AE of somnolence. On day 3 the patient reported worsening edema (oedema) and was treated with dexamethasone. On study day 5, the patient presented to the hospital with AEs of headache and oliguria. A few hours later, the patient developed breathing irregularity, coma, and convulsion, prior to death. The SAEs were considered by the investigator to be severe in severity and not related to the study drug. The investigator attributed the patient's death to the progression her malignancy. The last dose of study drug prior to the onset of the SAEs was OxyContin 15 mg (AM)/ 10 mg (PM).	Likely unrelated
0513002 15 y/o F	-Study day #18* -35 mg daily dose ->4 hours post dose	SAE: hypoxia and coma (MedDRA preferred term: Hypoxia, Coma) 15-year-old white female with medical h/o recurrent rhabdomyosarcoma with multiple metastases. Patient was started on OxyContin 15mg bid which was increased to 15mg AM/20mg PM on day 3. On day 7, she took OxyContin 20mg bid but then backed down to 15mg AM/20mg PM on day 8 for unclear reasons. On day 18, she developed SAEs of coma and hypoxia prior to her death. These SAEs considered by the investigator severe and attributed to the progression of her malignancy and not related to the study drug. She took her last dose of study drug before dying. Other AEs reported during the study were anxiety, ascites, edema, decrease oxygen saturation, tachycardia, and decreased urine output. The last dose of study drug prior to the onset of the SAEs was OxyContin 15 mg AM/20 mg PM.	Likely unrelated

Subject	-Study Day of Death -Total Daily Dose** -Relation to Study Drug Dosing	Narrative	Reviewer Comment
0512001 10 y/o M	-Study day #4* -40 mg daily dose ->4 hours post dose	SAE: Respiratory and cardiac arrest (MedDRA preferred term: Cardio-respiratory Arrest) 10-year-old male with a history of neuroblastoma who was hospitalized for significant swelling in legs, scrotum, and abdomen a day prior to the start of the study drug. On day 1 he was started on OxyContin 10mg bid and diuretics. The edema did not reduce and caused significant breathing difficulties. On day 2, OxyContin was increased to 20mg bid, more diuretics and morphium. The parents requested for the subject to discontinue the patient from the study because his pain could not be controlled by oral medications on day 4 and IV morphine was started. Later that day, the patient developed a cardiopulmonary arrest and expired. The investigator considered the event to be severe and not related to the study drug.	Dose uptitration not done as per protocol. However, outcome is likely unrelated to the study drug
0051001 16y/o F	N/A	SAE: ALL worsening (MedDRA preferred term: Malignant Neoplasm Progression) 16-year-old black female with a history of ovarian granulosa cell tumor, bone marrow transplantation, parasagittal mass, hemiparesis, and partial seizures. On day 1 the patient received one dose of OxyContin 60mg. Her parents withdrew her from the study on day 2 because of lack of therapeutic effect. 15 days after the first and only dose, the patient was admitted to the hospital for pain and fever with a SAE of ALL worsening, considered by the investigator severe in severity and not related to the study drug but to malignancy progression. She was discharged on day 19 but readmitted on day 22 with labored breathing and increased pain. 25 days after the only OxyContin dose, she was started on inhaled fentanyl and the next day she began having Cheyne-Stokes respirations, became obtunded and died.	Unrelated

*Treatment-Emergent
**Total daily dose of OxyContin

7.3.2 Nonfatal Serious Adverse Events

The following table was derived from Table 2.8.1.1 of the Summary of Clinical Safety, which contained some errors that I have corrected summarizes all nonfatal treatment-emergent SAEs in the 3 main studies (OXP3003, OTR3001, and OXP1005 [Group A]). Nonfatal TEAEs will be discussed by individual study for the remaining studies submitted with the application in Section 7.3.2.1.

Table 31. All Nonfatal Treatment-Emergent SAEs by Age Group (Group A)

MedDRA SOC Preferred Term	Age Group			5 – 16 y Combined[b] (N=201) n (rate)	Overall[b] (N=261) n (rate)
	Birth – 4 y[a] (N=60) n (rate)	5 - < 12 y[b] (N=46) n (rate)	12 – 16 y[b] (N=155) n (rate)		
Total n (%) with any nonfatal SAE	**3 (5.0)**	**9 (20.0)**	**32 (20.6)**	**41 (20.4)**	**44 (17.0)**
Blood and Lymphatic System disorders	**0**	**3 (6.5)**	**5 (3.2)**	**8 (4.0)**	**8 (3.1)**
Febrile neutropenia	0	1 (2.2)	4 (2.6)	5 (2.5)	5 (1.9)
Neutropenia	0	2 (4.3)	1 (0.6)	3 (1.5)	3 (1.1)
Ear and labyrinth disorders	**0**	**0**	**1 (0.6)**	**1 (0.5)**	**1 (0.4)**
Vertigo	0	0	1 (0.6)	1 (0.5)	1 (0.4)
Eye disorders	**0**	**0**	**1 (0.6)**	**1 (0.5)**	**1 (0.4)**
Diplopia	0	0	1 (0.6)	1 (0.5)	1 (0.4)
Gastrointestinal disorders	**1 (1.7)**	**1 (2.2)**	**5 (3.2)**	**6 (3.0)**	**7 (2.7))**
Abdominal pain	1 (1.7)	0	1 (0.6)	1 (0.4)	2 (0.8)
Vomiting	0	0	2 (1.3)	2 (1.0)	2 (0.8)
Diarrhoea	0	0	1 (0.6)	1 (0.5)	1 (0.4)
Pancreatitis acute	0	0	1 (0.6)	1 (0.5)	1 (0.4)
Stomatitis	0	1 (2.2)	0	1 (0.5)	1 (0.4)
General disorders and Administration Site Conditions	**0**	**2 (4.3)**	**6 (3.9)**	**8 (4.0)**	**8 (3.1)**
Vomiting	0	2 (4.3)	4 (2.6)	6 (3.0)	6 (2.3)
Pain	0	0	2 (1.3)	2 (1.0)	2 (0.8)
Hepatobiliary disorders	**0**	**2 (4.3)**	**0**	**2 (1.0)**	**2 (0.8)**
Bile duct stone	0	1 (2.2)	0	1 (0.5)	1 (0.4)
Cholangitis	0	1 (2.2)	0	1 (0.5)	1 (0.4)
Injury, Poisoning and Procedural Complications	**0**	**0**	**5 (3.2)**	**5 (2.5)**	**5 (1.9)**
Seroma	0	0	2 (1.3)	2 (1.0)	2 (0.8)
Fall	0	0	1 (0.6)	1 (0.5)	1 (0.4)
Post procedural complication	0	0	1 (0.6)	1 (0.5)	1 (0.4)
Procedural pain	0	0	1 (0.6)	1 (0.5)	1 (0.4)

MedDRA SOC Preferred Term	Age Group			5 – 16 y Combined[b] (N=201) n (rate)	Overall[b] (N=261) n (rate)
	Birth – 4 y[a] (N=60) n (rate)	5 - < 12 y[b] (N=46) n (rate)	12 – 16 y[b] (N=155) n (rate)		
Metabolism and nutrition disorders	**1 (1.7)**	**0**	**0**	**0**	**1 (0.4)**
Decreased appetite	1 (1.7)	0	0	0	1 (0.4)
Musculoskeletal and connective tissue disorders	**0**	**1 (2.2)**	**0**	**1 (0.5)**	**1 (0.4)**
Back pain	0	1 (2.2)	0	1 (0.5)	1 (0.4)
Nervous System disorders	**0**	**0**	**6 (3.9)**	**6 (3.0)**	**6 (2.3)**
Headache	0	0	2 (1.3)	2 (1.0)	2 (0.8)
Balance disorder	0	0	1 (0.6)	1 (0.5)	1 (0.4)
Dizziness	0	0	1 (0.6)	1 (0.5)	1 (0.4)
Lethargy	0	0	1 (0.6)	1 (0.5)	1 (0.4)
Status migranosus	0	0	1 (0.6)	1 (0.5)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	**1 (1.7)**	**0**	**1 (0.6)**	**1 (0.5)**	**2 (0.8)**
Epistaxis	0	0	1 (0.6)	1 (0.5)	1 (0.4)
Infantile apnoeic attack	1 (1.7)	0	0	0	1 (0.4)
Skin and subcutaneous tissue disorders	**0**	**0**	**1 (0.6)**	**1 (0.5)**	**1 (0.4)**
Rash	0	0	**1 (0.6)**	1 (0.5)	1 (0.4)
Vascular disorders	**0**	**0**	**1 (0.6)**	**1 (0.5)**	**1 (0.4)**
Axillary vein thrombosis	0	0	1 (0.6)	1 (0.5)	1 (0.4)

Percentages are based on the number of patients in the respective age groups as the denominator.
Multiple SAEs can be reported by each patient.
[a] Study OXP1005 = Only Oxy Pediatric Liquid 1mg/mL.
[b] Includes subjects in oxy Pediatric Liquid 1mg/mL and OxyContin tablets.

Three (11.4%) of the 44 treatment-emergent SAEs occurred in the birth-4 year cohort while 9 (20.5%) and 32 (72.7%) occurred in the 5-12 and 12-16 year cohorts. respectively. This is likely because there were significantly more subjects in the 12-16 year group vs. the 5-12 year group. The incidence SAEs within each age cohort was 5% in the birth-4 group vs. 20% and 20.6% in the 5-12 and 12-16 groups, respectively. Again, the data suggest that nonfatal SAEs were more common in the older cohorts. This could possibly be explained by the severity of the underlying conditions in the older cohort and the duration of treatment (in OXP3001 and OXP1005 subjects were only treated for 2 days). SAEs led to discontinuation in 6 patients which will be further discussed in Section 7.3.3.

When considered as a whole, the following System Organ Classes (SOCs) appear to have the most common treatment-emergent nonfatal SAEs: 8 (3.1%) in Blood and lymphatic disorders, 8 (3.1%) in General disorders and Administration Site Conditions, 7 (2.7%) in Gastrointestinal disorders, 6 (2.3%) in the Nervous system disorders, and 5

(1.9%) in the Injury, Poisoning and Procedural Complications SOC. Although the Injury, Poisoning and Procedural Complications SOC contains Preferred Terms (PTs) that are unlikely related to the study drug (e.g., Procedural Pain, Post Procedural complication) the other SOCs contain PTs that are mostly expected for this medication class. The most common PT's were (in descending order): vomiting (2.3%), febrile neutropenia (1.9%), neutropenia (1.1%), abdominal pain (0.8%), and headaches (0.8%).

7.3.2.1 Individual Summaries of Nonfatal SAEs

No nonfatal SAEs were reported for studies OC96-0602 and OXP3004. Individual summaries for patients with TEAEs will be provided per study bellow.

7.3.2.1.1 Nonfatal SAE Case Summaries for Study OXP3003

Subject 26005
SAE: Pericardial effusion. (MedDRA preferred term: Pericardial effusion)
This is a 14 y/o Asian male with a history of rheumatic aortic and mitral valve disease, severe aortic and mitral regurgitation, and he was post-operative for a mitral valve repair and aortic valve replacement. This patient was randomized to placebo oral solution and he developed atelectasis and a pericardial effusion. He received morphine PCA for pain. On day 3, an echocardiogram revealed increasing pericardial effusion in addition to continual reduction in the left ventricular function.
Reviewer's impression: Unrelated to study drug.

Subject 36002
SAE: Choledocholithiasis. (MedDRA preferred term: Bile duct stone)
This is a 10 y/o white female with a history of epilepsy, choledocholithiasis 3 months prior to the study, and a recent laparoscopic cholecystectomy. After the procedure, the patient was randomized to Oxy Pediatric Liquid 0.1mg/kg every six hours. She also received PCA morphine, a total of 8.66 mg on day 1 and on day 2, a total of 13.72 mg. On day 2, laboratory exams showed elevated liver enzymes (ALT 719 U/L, AST 577 U/L), which were attributed to cholangitis and suspected to be due to a bile duct stone. The study drug was stopped and she was discontinued from the study due to this SAE, which was considered moderate in severity and unrelated to study drug. She also experienced severe colic pain and became pyrexic with a 40°C temperature, which resolved following removal of a bile stone the next day. The Cholangitis and choledocholithiasis were considered resolved by day 5 and the patient was discharged home on day 7.
Reviewer's impression: Unlikely relationship to study drug.

Subject 17004:
SAE: Pneumonia. (MedDRA preferred term: Pneumonia)
This is a 14 y/o white male with a history of ADHD, obesity, scoliosis, constipation, tachycardia, right atypical pneumothorax, and status post-spinal fusion. The patient was randomized to Oxy Pediatric Liquid 0.2mg/kg every 6 hours and also received PCA

morphine on day 1 (a total of 20 mg) and day 2 (a total of 7 mg). The last dose of study drug was on day 2. The patient completed the study per protocol. On day 10, the patient developed fever of 100.2 F, pulse 141, respiration 28, and O_2 saturation on room air of 95% with symptoms of diaphoresis, pallor, lethargy, and anxiety. Rales were heard in the right middle lung lobe and right base. Outside laboratory and chest X-ray results showed right atelectasis, which was present during previous hospitalization, and right lower lobe pneumonia. The next day he was hospitalized and treated with antibiotics. On day 14 the pneumonia resolved and he was discharged home. Pneumonia was considered severe in severity and not related to the study.
Reviewer's impression: Unrelated to study drug.

Subject 36005
SAE: Febris. (MedDRA preferred term: Pyrexia)
This is a 9 y/o white female in Finland with a history of congenital reticulocytosis and status post-splenectomy. She was randomized to Oxy Pediatric Liquid 0.2mg/kg every 6 hours and completed the study per protocol. She was discharged home on day 6. On day 13 she was hospitalized with fever and was treated with antibiotics. Fever was considered mild in severity and not related to the study drug.
Reviewer's impression: Unrelated to study drug.

7.3.2.1.2 Nonfatal SAE Case Summaries for Study OTR3001

Subject 0006003
SAE: Diplopia, intermittent vomiting, vertigo, disequilibrium, dizziness, headache, and lethargy. (MedDRA preferred terms: Diplopia, Vomiting, Vertigo, Balance Disorder, Dizziness, Headache, and Lethargy)
This is a 16 y/o white female with a history of acoustic neuroma removal. On day 1, she was started on OxyContin 10mg bid. On day 3, she presented to the emergency room with complaints of dizziness, nausea, emesis, and blurry vision for approximately 1 day. She also complained of 9 days without bowel movements. Physical exam revealed ataxic gait. The patient was hospitalized due to SAEs. The events were considered moderate in severity by the investigator and possibly related to the study drug, which was discontinued upon hospitalization. Symptoms resolved and the patient was discharged from the hospital the day after hospitalization.
Reviewer's impression: Likely related to the study drug.

Subject 0042004
SAE: Fever 100.8°F, and post-operative chest pain. (MedDRA preferred terms: Pyrexia, Procedural pain)
This is a 13 y/o white male with a history asthma/wheezing and pectus excavatum, status post-surgery for a Nuss procedure (to correct pectus excavatum deformity) with thoracoscopy. Post-operatively, he was noted to have "mild bilateral, mid axillary incisional pain, a second focus pain on the right side of his chest deep to his nipple and some mild back pain". On day one the patient was started on OxyContin 20mg bid, which was decreased to 20mg AM/10mg PM by day 4. On day 8, the dose was further

reduced to OxyContin 10mg bid because, according to the investigator, the patient's pain was well-controlled. However, on that same day, the patient complained of increased chest and back pain, trouble breathing/talking due to pain worsened by deep breaths and fever of 100.8°F and he presented to the emergency room. The investigator assessed both SAEs (pyrexia and procedural pain) severe in severity and not related to study medication. A chest X-ray revealed the Nuss bar had not changed in position, an unchanged right apical pneumothorax, interval decrease in small bilateral pleural effusions and decreased subsegmental atelectasis at the left base. The surgical team recommended a consult for the pain team, which recommended continuing use of morphine and ibuprofen as needed along with an increase of OxyContin to 20mg AM and 10mg PM. The fever resolved the same day he had presented to the emergency room (day 8) and he was discharged back home. He received the last dose of OxyContin on day 15. The investigator opined that the pain suffered by the patient was within expected levels a typical person would experience after a Nuss Bar placement. Post-operative pain resolved on day 20.
Reviewer's impression: SAEs more likely to be related to surgical procedure. Unlikely related to study drug.

Subject 0006014
SAE: Chemotherapy-induced Neutropenic Fever. (MedDRA preferred term: Febrile neutropenia)
This is a 16 y/o white Hispanic male with a history of non-metastatic left tibial osteosarcoma, anemia, low blood pressure, metabolic imbalance, and various orthopedic reconstructive surgeries after the resection of his left proximal tibia. Concomitant medications included paracetamol, fluoxetine (which inhibits various CYP450 pathways involved in the clearance of the test drug), gabapentin, and lorazepam. On day1, the patient had normal platelets and white blood cell counts and was started on OxyContin 50mg bid which was decreased to 50mg Am and 30mg PM by day 9. The dose was decreased further on day 10 to OxyContin 30mg bid although no explanation is given for this change. On days 15 and 16 the patient received cisplatin and doxorubicin chemotherapy. On day 22, OxyContin was decreased to 20mg bid. On day 28, the study drug was discontinued and the patient completed the study. However, laboratory tests showed thrombocytopenia and neutropenia which were considered by the investigator as severe in severity and unlikely to be related to the study drug. On day 32, the patient presented to the emergency room with an SAE of chemotherapy-induced neutropenic fever of 103°F (considered by the investigator as severe in severity and unlikely to be related to the study drug) and was hospitalized to the Hematology/Oncology department. Workup was negative for blood cultures and a a Doppler was negative for deep venous thrombosis. Fevers continued to spike despite treatment with antibiotics and vancomycin was started but the patient had facial swelling, pruritus and rash with his first vancomycin dose. Due to the patient's pancytopenic status, he received a blood transfusion on day 34. Patient remained in the hospital until day 40.

Reviewer's impression: SAE is more likely to result from a combination of chemotherapeutic agents and thus, unlikely to be related to study drug.

Subject 00009006
SAE: Status migrainosis. (MedDRA preferred term: Status migranosus)
This is a 16 y/o black female with a history of sickle cell disease, multiple vaso-occlusive episodes, splenectomy, and migraine headaches. This patient started with a headache the day prior to starting OxyContin 40mg bid for pain related to a vaso-occlusive crisis. That same day (day 1), she began experiencing intermitted and vomiting purportedly related to her headache. The next day she began having more severe headaches with nausea, vomiting, photophobia, and decreased food intake. On day 8, the investigator was contacted due to increase leg pain (from the previous vaso-occlusive crisis) and OxyContin was increased to 50mg bid. On day 12 she visited the Neurology clinic and was diagnosed with status migrainosis and was admitted to the hospital for treatment. The investigator assessed this SAE as severe in severity and unlikely to be related to the study drug. She was treated with Norco for her leg pain, IV valproic acid and Depakote PO bid for her migraine headache with positive results. She was discharged from the hospital on day 13 and OxyContin was discontinued. The investigators decided to terminate the patient's participation from the study as the patient did not believe the study drug was helping with pain.
Reviewer's impression: SAE is unlikely to be related to study drug.

Subject 0009010
SAE: Low-grade fevers, worsening back pain, neutropenia. (MedDRA preferred terms: Pyrexia, Back pain, Neutropenia,)
This is an 11 y/o white male with a history of Erwing's sarcoma, previous chemotherapy-induced neutropenia and immunosuppression, alopecia, episodes of anemia, mouth/jaw pain, gait disturbance and episodes of hands/fingers paraesthesias. The patient was started on OxyContin 10mg bid. On day 9 the study drug was discontinued because the mother felt his pain was improved and that he no longer needed the medication. On day 14 the patient became neutropenic and 2 days later, he began to complain about back and mouth pain, which was treated with Norco and morphine. That same day (day 16) he experienced a low-grade fever of 100.5°F. He was hospitalized for febrile neutropenia on day 17. Physical exam revealed oral lesions and tachycardia. The investigator assessed these SAEs as severe in severity and unlikely to be related to the study drug. The back pain improved on his first hospitalization day and the neutropenia and pyrexia resolved on his second and last day of hospitalization (day 18). He was treated with ceftriaxone, piperacillin-tazobactam, and morphine. Neutropenia was deemed likely related to chemotherapy and the back pain due to granulocyte colony-stimulating factor (GCSF) treatment.
Reviewer's impression: Unlikely to be related to study drug.

Subject 0009011
SAE: Fever, neutropenia, mucositis (oral). (MedDRA preferred terms: Pyrexia, Neutropenia, and Stomatitis)
This is a 10 y/o black female with a history of osteosarcoma, liver and renal toxicity secondary to methotrexate toxicity, a history of radical tibial resection and allograft reconstruction, and a history of euphoria while on OxyContin. She was started on OxyContin 40mg bid. The investigator decided to wean her off OxyContin on day 14 because her pain had improved and the next day, the dose was reduced to 40mg AM and 30mg PM. On day 16, the OxyContin was reduced to 30mg bid with further reductions until she took the last dose of the study drug on day 20 and she was considered to have completed the study the next day. On day 26, the mother reported the patient had a fever of 105°F, throat pain, decreased oral intake, nausea, vomiting, and bleeding at the site of surgical incision with no purulent discharge and the patient was hospitalized. In addition to neutropenia, laboratory exams revealed thrombocytopenia and anemia. The investigator considered the SAE of fever to be mild in severity, mucositis to be moderate in severity, and neutropenia to be severe in severity. All 3 SAEs were not considered related to the study drug. Fever and neutropenia were attributed to infection and mucositis to chemotherapy. The fever resolved upon admission to the hospital and the mucositis the next day (day 27). On that day the patient developed pruritus and hives secondary to morphine PCA treatment. The patient was treated with ceftriaxone, piperacillin-tazobactam, and gentamicin. Neutropenia resolved on day 28.
Reviewer's impression: Unlikely to be related to study drug.

Subject 0009015
SAE: Osteomyelitis (MedDRA preferred term: Osteomyelitis)
This is a 14 y/o white female with a history multiple injuries resulting from a 40-foot fall from a bridge and numerous vascular, orthopedic, and reconstructive surgeries related to this trauma. The patient was started on OxyContin 20mg bid and she took the last dose on day 8. She was considered to have completed the study on day 14. At a follow-up orthopedic visit on day 23, she was hospitalized after a physical exam raised concerns regarding a deep musculoskeletal infection on her right ankle. CBC was normal but an MRI revealed fractures and suspected osteomyelitis in the tibia, distal fibula, and talus area. That same day an SAE of osteomyelitis was reported. The investigator assessed this SAE as moderate in severity and unlikely to be related to the study drug but to trauma and multiple surgeries. Her antibiotic was changed from cephalexin to IV cefazolin. On day 25, right ankle arthrotomy, bone biopsy, and external fixation were performed. Wound growth culture that day revealed a s*taphylococcus aureus* infection. Physical therapy, psychological services, and other surgical interventions were performed over the next weeks. The patient was discharged from the hospital on day 52 with the following final diagnoses: complex right lower extremity wound, grade 3B open fracture of the ankle, right multi-ligamentous knee with buckle handle lateral meniscus, and depression.
Reviewer's impression: Unrelated to study drug.

Subject 0801001
SAE: Febrile – unknown causes (MedDRA preferred term: pyrexia)
Other AEs: decreased hemoglobin
This is a 12 y/o white female with a history of Erwing's sarcoma at L5, chemotherapy, radiotherapy, right lower limb weakness, and spinal cord compression. On day 1, laboratory tests showed hemoglobin of 111g/L (reference range: 116-148 g/L) and OxyContin 20mg bid was started. From day 9 through day 13, she received IV eptoposide and ifosfamide for the treatment of her Erwing's sarcoma. On day 27 she arrived at the clinic shivering, tachycardic, hypotensive (BP: 100/59), febrile, and with a mild headache. Pyrexia was considered by the investigator to be severe in severity an related to immunosuppressants and not to study drug. She was hospitalized with a temperature of 37.7°C, which increased to 38.1°C. Laboratory exams showed a WBC count of 28.34 x 10^9/L (reference range: 4.3-12 x 10^9/L), hemoglogin of 85/L, RBC of 3.04 x 10^{12}/L (reference range: 4.2-5.6 x 10^{12}/L), and a platelet count of 60 x 10^9/L (reference range: 150-425 x 10^9/L). Catheter blood culture and urine culture were negative. She was treated with IV ceftazidime, RBC transfusion, oxycodone, morphine, tramadol, and paracetamol. On day 29 a laboratory test showed a hemoglobin value of 88g/L but no AE associated with this funding was reported. On Day 30 the fever resolved and the patient was discharged home.
Reviewer's impression: Unlikely to be related to study drug.

Subject 0801002
SAE: Febrile neutropenia and C-Difficile Gastroenteritis (MedDRA preferred term: Febrile neutropenia and Gastroenteritis Clostridial)
This is a 12 y/o white female with a history of Hepatitis A and B, hepatic steatosis, hepatosplenomegaly, anemia, acute lymphoblastic leukemia NOS, chemotherapy, continuous veno-venous hemofiltration, intermittent thrombocytopenia, mediastinal mass, platelet dysfunction, renal failure, superior vena cava obstruction, main bronchus compression, vocal cord weakness, febrile neutropenia, abdominal and chest pain, diarrhea, hypotension, neutropenia pseudomonas sepsis, disseminated shingles on T5 dermatome, hyperlipidemia secondary to TPN, thoracic cavity drainage, depression, vincristine-related neuropathy, and epistaxis. The patient was started OxyContin 20mg bid. On day 13, she began to experience nausea and abdominal pain. The investigator assessed these AEs as moderate in severity and not related to study drug but no rationale for this conclusion was given in the study report or the CRF. These AEs of nausea and abdominal pain could easily be related to the study drug, as they are common for this medication class. The patient was given paracetamol and ondansetron. The patient was hospitalized on day 14 with an SAE of febrile neutropenia, which was considered by the investigator as severe in severity and not related to study drug but to the underlying disease process. The hospital physician did note that the patient had a previous Pediatric Intensive Care Unit admission for pseudomonas sepsis and that her abdomen continued to be tender since her last admission. It was also mentioned that the patient had been experiencing more

headaches and nausea since the last hospitalization. Upon admission she had 2 fever spikes higher than 38°C. The patient was treated with IV ceftazidime, fluconazole (which is a moderate inhibitor of the CYP3A4 enzyme involved in oxycodone's metabolism), and paracetamol. Febrile neutropenia, abdominal pain, and nausea resolved on day 16 and the patient was discharged home. She began to experience dysuria (considered mild in severity and not related to study drug), pyrexia, and vomiting (both considered moderate in severity and not related to study drug) on day 19. On day 22 she reported to the clinic with diarrhea and vomiting and on day 24 she was re-hospitalized for these AEs. A stool specimen was positive for Clostridium difficile and an SAE of "gastroenteritis clostridial" was reported. The patient was treated with metronidazole, IV fluids, and morphine. The SAE resolved on day 29 and she was discharged from the hospital. She received her last dose of study drug and completed the study on day 27.
Reviewer's impression: Unlikely to be related to study drug.

Subject 0521002
SAE: Complication of scoliosis surgery, surgery to remove loose screw and rash on the skin (MedDRA preferred terms: Post procedural complication and Rash)
This is a 16 y/o white male with a history of scoliosis and corrective surgery 7 days prior to starting OxyContin 20mg bid. OxyContin was reduced to 20mg AM and 15mg pm on day 15 and then it was further reduced to 15mg bid the next day. On day 26, the patient reported to the hospital with a change in posture of the spine/neck. The next day he had a contrast CT scan and developed an SAE of rash. The investigator considered the rash moderate in severity and related to the contrast. He was treated with chlorphenamine and the rash resolved on day 28 and he was discharged home. That same day, the patient took the last dose of the study drug and was considered to have completed the study the next day (day 29). The CT scan showed various screws laid external to the vertebral bodies (from the surgery prior to starting the study). An SAE of post procedural complication was reported and the patient was schedule for surgery the following week.
Reviewer's impression: Unlikely to be related to study drug.

Subject 0507005
SAE: Neutropenic fever x 2 (MedDRA preferred term: Febrile neutropenia)
Other AEs: decreased lymphocyte count
This is a 16 y/o white female with a history of Erwing's sarcoma, post-operative anemia, and constipation. The patient had normal lymphocyte count the day he was started on OxyContin 10mg AM and 15mg PM. On day 9, she was hospitalized with a fever, sore throat, rhinorrhea, vomiting, abdominal pain, HR of 117 BPM, BP of 100/70 and physical exam showed an aphthous ulcer in the mouth. Laboratory exams showed WBC count of 0.4 x 10^3/µL (reference range: 4-10 x 10^3/µL), hemoglobin of 8.7g/dL (reference range:12-15 g/dL), RBC of 3.23 x 10^6/µL (reference range: 4-5 x 10^6/µL), and a platelet count of 173 x 10^3/µL (reference range: 175-350 x 10^3/µL). That same day, and SAE of neutropenia fever (considered moderate in severity and not related to study drug) and

an AE of influenza and vomiting (from which she recovered the same day) were reported. The patient was treated with packed blood cells, piperacillin-tazobactam, paracetamol, and ibuprofen and the SAE resolved on day 14 and she was discharged from the hospital. On days 16-20 she received the chemotherapeutic agents ifosfamide and etoposide and on 25 she was readmitted fever and bacteremia. Another SAE of neutropenic fever was reported the same day and it was considered moderate in severity and not to be related to study drug but to chemotherapy. She was treated in a similar way than during her previous admission and she recovered from the SAE on day 28 and was discharged home. That same day she received her last study drug dose and completed the study. That day, a laboratory test showed a decreased absolute lymphocyte count of 290 x 10^6/L (toxicity grade 4).
Reviewer's impression: Unlikely to be related to study drug.

Subject 0507006
SAE: Neutropenic fever (MedDRA preferred term: Febrile neutropenia)
Other AEs: elevated ALT, elevated AST
This is a 10 y/o white female with a history of left distal femur osteosarcoma and chemotherapy treatment with cisplatin and doxorubicin on days 1-2 prior to starting the study. On day 1, the patient had normal ALT and AST values and was started on OxyContin 10mg bid. On day 9, the patient was hospitalized with and SAE of neutropenic fever (38.4°C) considered to be moderate in severity and not related to study drug but the chemotherapy. Laboratory exams showed WBC count of 3.3 x 10^3/µL (reference range: 5-13 x 10^3/µL), hemoglobin of 10.4 g/dL (reference range: 12-14 g/dL), 18.1% neutrophil (reference range: 29.8-71.4%) and a platelet count of 36 x 10^3/µL (reference range: 175-350 x 10^3/µL). Physical exam was unremarkable and no other complaints were reported upon admission. Patient was treated with vancomycin although blood cultures and tests for respiratory viruses were negative. On day 11, she started to complain of hip pain and a skin and subcutaneous abscess was found (considered mild in severity and not related to the study drug). The next day, a biopsy was positive for *Pseudomonas* and was treated with Tazocin and ciprofloxacin leading to resolution of the abscess. On day 23, she received methotrexate as part of her chemotherapy protocol. On day 26, she received the last dose of study drug. That day, laboratory tests showed ALT value of 315 U/L and an elevated AST value of 234 U/L and an AE was reported (considered mild in severity and not related to the study drug) and attributed to the treatment with methotrexate. AEs were ongoing at the time of study termination and no further information was given.
Reviewer's impression: Unlikely to be related to study drug.

Subject 9007001
SAE: Elevated glucose, Pain due to sickle cell (MedDRA preferred term: Pain)
Other AE: Elevated glucose
This is a 14 y/o black female with a history of sickle cell disease with multiple vaso-occlusive episodes, obesity, oppositional defiant disorder, ADHD, and insulin resistance. She was started on OxyContin 30mg bid and had an elevated blood glucose

value of 5.7mmol/L (reference range: 3.6-5.5 mmol/L) at baseline. On day 8, the dose was increased to 30mg AM and 40mg PM followed by an increase to 40mg bid on the next day. She presented to the emergency room on day 16 with pain which was considered severe in severity and related to her sickle cell condition and not to the study drug. Her primary care physician recommended her removing her from the study that same day due to lack of therapeutic effect. However, her last dose of the study drug was on day 14, 2 days earlier. A blood glucose level on the day of her emergency room visit was 16.5 mmol/L (toxicity grade 3). She was treated in the hospital for pain with hydromorphone and fentanyl with no success. The patient reported 10/10 pain but did not appear to be in pain. Social work consultation revealed "complex psychosocial stressors that could have been contributing to the pain presentation. She was discharged from the hospital on day 19.
Reviewer's impression: Unlikely relation to study drug.

Subject 9007006
SAE: Multiple falls/Congenital club foot (MedDRA preferred term: Fall)
Other AE: Elevated glucose
This is a 14 y/o white male with a history of bilateral club feet, obesity, cardiac murmur, hypercholesterolemia and various orthopedic surgeries. He began treatment with OxyContin 30mg bid which was reduced to 30mg AM and 15mg PM on day 8, and then further reduced to 15mg bid the next day. The study drug was further tapered to 10mg bid by day 16. On day 17, he was hospitalized with an SAE of multiple falls/congenital club foot, considered severe in severity and not related to the study drug by the investigator. During one of his falls, he landed on the left external fixator and a surgical revision was conducted during his first day in the hospital. He was discharged home on day 28.
Reviewer's impression: Unlikely relation to study drug.

Subject 0087001
SAE: Headache, fever, thrombus in left axillary vein, and gangrenous right 5th toe (MedDRA preferred terms: Headache, , pyrexia, axillary vein thrombosis, gangrene)
Additional AEs: epistaxis
This is a 16 y/o black male with a history of Systemic Lupus Erythematosus (SLE), antiphospholipid syndrome and multiple complications related to it, to include various vascular surgical interventions. He was started on OxyContin 30mg bid. On day 5 he developed and SAE of headaches associated with photophobia and phonophobia, considered severe in severity and unrelated to the study drug but to anticoagulant therapy by the investigator. That same day, he developed epistaxis, deemed mild in severity and unrelated. On admission, a head CT showed complete opacification of the left frontal sinus and focal thickening of the left maxillary sinus. A chest X-ray showed some atelectasis. He continued to have mild-moderate headaches. An MRI/MRA/MRV showed significant sinus disease on day 7 and he was discharged home. The study drug was tapered off during the next few days and he took the last dose on day 29. On day 31, the headaches resolved. He was readmitted to the hospital on day 34 with

fever (mild in severity) and an axillary vein thrombosis (moderate in severity) which were considered unrelated to the study drug. On day 37, he had an episode of gangrene on one of his toes, considered severe in severity and unrelated to study drug. The toe was amputated the following month.
Reviewer's impression: Unlikely relation to study drug.

Subject 0038002
SAE: Acute exacerbation of lower back, Leg pain (MedDRA preferred terms: Pain)
This is a 16 y/o Hispanic male with a history of lumbar disk avulsion fracture, gait problems, bilateral leg pain, lumbar spinal stenosis, and lumbar radiculopathy. He was started on OxyContin 40mg bid but it was reduced to 40mg AM and 30mg PM on day 3. On day 11 he complained of pain and an AE of "agitation" (considered moderate and unrelated by the investigator but no reasoning was provided). He was treated with diphenhydramine and haloperidol IM although there was no history of psychiatric disorders. On day 22 he presented to the emergency room with acute exacerbation of back pain (severe in severity and unrelated as per the investigator), the study drug was discontinued and he was removed from the study. The next day he was hospitalized and treated with hydromorphone. An MRI showed asymmetric edema within paraspinal soft tissues and he was treated with corticosteroid injections. He was discharged home 6 days later but readmitted a week later with similar complaints. Definitive treatment was lumbar discectomy.
Reviewer's impression: Unrelated to study drug.

Subject 0027004
SAE: Neutropenic fever (MedDRA preferred term: Febrile neutropenia)
This is a 15 y/o white female with a history of osteosarcoma, radical resection of right tibia 6 days prior to the start of the study, and periodic pancytopenia secondary to chemotherapy. She was started on OxyContin 30mg bid which was slowly increased to 50mg bid by day 10. On day 21, she started on cisplatin and doxorubicin chemotherapy. The dose was decreased to 40mg bid on day 27. On day 30, she was hospitalized with an SAE of neutropenic fever of 100.9°F (considered severe in severity and unrelated to the study drug). Workup for infection source was negative. Laboratory exams showed pancytopenia with ANC of 0.06 k/µL (reference range: 1.4-8.0 k/µL), WBC of 0.7 k k/µL (reference range: 3.8-9.8 k/µL), RBC of 3.18 M/µL (reference range: 3.9-5.3 M/µL), hemoglobin 10.0 g/dL (reference range: 10.8-14.5 g/dL), hematocrit of 28.6, and platelet count of 46 k/µL (reference range: 175-345 k/µL). That day, she was started on vancomycin and cefepime. On day 31, she received packed red blood cells and platelets. That same day, the SAE of neutropenic fever resolved, she received the last dose of the study drug, completed the study, and was discharged from the hospital.
Reviewer's impression: Likely not related to study drug.

Subject 0080001
SAE: Worsening vaso-occlusive pain crisis, fever (MedDRA preferred terms: Sickle cell anaemia with crisis, pyrexia)
This is a 14 y/o black female with a history of sickle cell disease with multiple vaso-occlusive episodes, stroke, obesity, iron overload secondary to repeated red blood cell transfusions, hypertension, and acquired immunodeficiency. The patient was started on OxyContin 20mg AM and 10mg PM but was decreased to 10mg bid the next day. On day 16, she began to experience back pain, which worsened progressively. Reportedly, the pain became so intense that the study drug was no longer being effective. On day 18, the patient was hospitalized with a fever of 38.5°C. An SAE of worsening vaso-occlusive pain crisis (severe in severity) and pyrexia (moderate in severity), both considered not related to the study drug. She was treated with aggressive hydration, red blood cell transfusion, fentanyl, and ceftriaxone. All workup exams were negative for sources of infection. On day 21, she was discharged home.
Reviewer's impression: Unlikely relationship to study drug.

Subject 0533001
SAE: Abdominal pain, intermittent vomiting, and diarrhea (MedDRA preferred terms: Abdominal pain, vomiting, diarrhoea)
This is a 14 y/o white female with a history of Erwing's sarcoma, thrombocytopenia, spinal cord compression, and adrenal hyperplasia. She was started on OxyContin 10mg bid. On day 15, chemotherapy was started with irinotecan and temozolimide. On day 17, she took the last dose of the study drug, withdrew consent, and was discontinued from the study. It does not seem to be related to AEs although I could not find a specific reason. Chemotherapy was completed on day 19. On day 21, she began experiencing SAEs of abdominal pain, diarrhea, and vomiting, considered severe in severity and related to chemotherapy by the investigator. She was hospitalized on day 22 with fever and treated with ceftriaxone, piperacillin, granisetron, loperamide, ranitidine, and morphine. She was discharged home on day 23.
Reviewer's impression: Unlikely relationship to study drug.

Subject 0065001
SAE: Neutropenia, cellulitis at right hip biopsy site, fever (MedDRA preferred terms: Neutropenia, post procedural cellulitis, pyrexia)
Other significant AEs: increased ALT, decreased hemoglobin
This is a 14 y/o white female with a history of stage IV neuroblastoma and related surgeries and complications to include acquired growth hormone deficiency, central hypothyroidism, poor dentition due to chemo and radiotherapy, scoliosis, and cataracts (due to radiation treatment). The patient received chemotherapy prior to starting the study. She was started on OxyContin 15mg bid. On day 1, laboratory tests showed that WBC counts were below normal at 1.4 (normal > 4.5), thrombocytopenia of 31 (normal >150), neutropenia of 0.1 (normal >1.8), hemoglobin of 7.4 (normal >12), ALT of 39 (normal <35). These were considered mild and not related to the study drug. The next

day the patient presented to the emergency room with worsened labs and a fever. SAEs of neutropenia, pyrexia, and cellulitis at right hip biopsy site were reported. The fever resolved on day 4, the neutropenia resolved by day 6, while the cellulitis resolved by day 16. On day 29 the patient took the last dose of the study drug and completed the study. That same day, ALT was 108 IU/L (toxicity grade 2) and hemoglobin was 98g/L (toxicity grade 2).
Reviewer's impression: Unlikely relationship to study drug.

Subject 0075014
SAE: Back wound seroma (MedDRA preferred term: Seroma)
Other significant AEs: decreased hemoglobin
This is a 13 y/o white male with a history of osteochondrosis and spinal fusion surgery. He was started on OxyContin 20mg bid. On day 10, an SAE of back wound seroma was reported, considered moderate and related to the spinal fusion surgery prior to the beginning of the study rather than to the study drug. He was hospitalized for irrigation and excisional debridement with wound vac application. ON admission, laboratory values showed a hematocrit of 26% and hemoglobin of 8.8 gm/dL (normal >11.4 gm/dL). After the treatment described and antibiotics, the seroma was deemed recovered on day 15 and he was discharged home. He took the last dose of the study drug and completed the study on day 19.
Reviewer's impression: Unlikely relationship to study drug.

Subject 0075015
SAE: Back wound seroma (MedDRA preferred term: Seroma)
This is a 15 y/o white female with a history of hypothyroidism and spinal fusion surgery for scoliosis immediately preceding the study. The patient was started on OxyContin 20mg bid and on day 7, she presented to the emergency room with a complaint of increased drainage from her back wound and was hospitalized. The seroma was considered moderate in severity and related to her back surgery. On admission, C-reactive protein was 3.24 mg/dL (reference range: 0-0.49 mg/dL), hematocrit was 30.4% hemoglobin 10.3 g/dL, and erythrocyte sedimentation rate of 80 mm/hr (reference range: 0-20 mm/hr). Irrigation and debridement wound with wound VAC placement were performed and she was treated with clindamycin, diazepam, and morphine. The SAE resolved on day 12. She completed the study on day 16.
Reviewer's impression: Unrelated to study drug.

Subject 0075020
SAE: Acute pancreatitis (MedDRA preferred term: Pancreatitis Acute)
This is a 15 y/o Puerto Rican female with a history of pancreatitis 11 years prior to the study and recent spinal fusion surgery for scoliosis. She was started on OxyContin 10mg bid and on a follow up visit to her surgeon on day 5, she complained of abdominal pain, constipation, and back wound discharge. These were considered mild in severity and not related to the study. She was treated with cephalexin and work-up for abdominal pain was performed. Laboratory tests revealed an elevated amylase value

of 193 U/L (reference range: 13-60 U/L). A repeat laboratory exam 3 days later revealed further increases in this value and the patient was admitted on day 9 for further evaluation of abdominal pain and elevated pancreatic enzymes. On admission, amylase was 261 U/L and lipase was 279 U/L (reference range: 13-60 U/L) and an SAE of acute pancreatitis was reported, considered moderated in severity and not related to the study drug but to her history of pancreatitis. The next day (day 10), the SAE was considered resolved and she was discharged from the hospital. She completed the study on day 18.
Reviewer's impression: Unlikely relationship to study drug.

7.3.2.1.3 Nonfatal SAE Case Summaries for Study OXP1005

Subject 0037006
SAE: Abdominal pain, loss of appetite (MedDRA preferred terms: Abdominal pain, anorexia)
Other AEs: fever (pyrexia)
This is a 3-year-old female of mixed race with a history of cloacal anomaly, renal scars, colostomy, and status post-posterior sagittal anorectoplasty who was assigned to Oxy Pediatric Liquid 0.2mg/kg every 6 hours. That same day (day 1) she experienced nausea, vomiting, and itching, which was considered mild and possibly related to the study drug. The patient was treated with chlorpheniramine and these symptoms resolved. The patient was discontinued from the study on day 2 for "administrative reasons" (which I was not able to figure out) and due to a painful and failing IV cannula. On day 10, the patient was hospitalized with abdominal pain, anorexia (considered serious but unrelated to the study drug), fever, and suprapubic tenderness. The patient was treated with antibiotics and antipyretics and was discharged from the hospital the next day.
Reviewer's impression: Unlikely relationship to study drug.

Subject 0038008
SAE: Obstructive apnea (MedDRA preferred term: Infantile apnoeic attack)
Patient 0038008 is a 13-day-old neonate with a history of aortic arch, patent ductus arteriosus, obstructive apnea, and status post-operative repair of an esophageal atresia and trachea-esophageal fistula when he began treatment with Oxy Pediatric Liquid 0.05mg/kg. That same day he developed the MedDRA preferred term, infantile apnoeic attack. The event was attributed to the failure of successfully suctioning excessive and thick nasal secretions. The event resolved with deep suctioning, manual bag ventilations and re-intubation. The SAE of obstructive apnea was considered unrelated to the study and moderate but life-threatening by the investigator. The study drug was stopped and he was discontinued from the study.
Reviewer's impression: Possible relationship to study drug.

7.3.2.1.4 Nonfatal SAE Case Summary for Study OTR1020

Subject 0010009
SAE: Spinal hardware problem
This is a 12-year-old white female with a history of idiopathic scoliosis and status post-spinal fusion with instrumentation and bone graft. The patient was started on 15mg of oxycodone controlled-released bid and received supplemental hydromorphone. She completed the study the next day. On day 5 the patient experienced the SAE of spinal hardware problem, which was considered moderate in severity and unrelated to the study drug. However, the patient had a prolonged hospitalization.
Reviewer's impression: Unrelated

7.3.2.1.5 Nonfatal SAE Case Summaries for Study OTR3002

Subjects in this study were recruited from patients who had completed Study OTR3001.

Subject 0509001
SAE: Vomiting worsening, back pain worsening, headache worsening (MedDRA preferred terms: Vomiting, back pain, headache)
This is a 12-year-old white female with a history of recurrent urinary tract infections, acute lymphoblastic leukemia, spinal compression fracture, *helicobacter pylori* infection, and intervertebral disc disorder who completed 4 weeks of OxyContin 30mg bid in Study OTR3001. She was admitted to OTR3002 on OxyContin 20mg bid and on day 5 she hospitalized with SAEs of worsening vomiting, headache, and back pain (all considered mild by the investigator and attributed to her leukemia). The test drug was temporarily stopped for less than 24 hours. MRI of the lumbosacral spine revealed 20-30% collapse of the anterior aspect of the vertebra. During hospitalization, a pediatric neurologist found signs of fluctuations in pulse and blood pressure had the impression of "dysautonomia as well as sacral region sensitivity". The SAEs resolved the next day and the patient was discharged from the hospital. The patient completed the study on OxyContin 20mg bid.
Reviewer's impression: Likely unrelated

Subject 0024001
SAE: Sickle cell pain crisis x 4 ocurrences (MedDRA preferred terms Sickle cell anaemia with crisis)
This is a 14-year-old black female with a history of sickle cell anemia with multiple vaso-occlusive crises, Raynaud's phenomenon, anxiety, osteopenia, constipation, and acute chest syndrome. She completed OTR3001 on OxyContin 10mg bid and was enrolled on OTR3002. During the course of the next 5 months, this patient had a total of 4 vaso-occlusive episodes with multiple admissions, obviously attributed to her sickle cell disease and not to the study drug. The study drug was interrupted at least one while she received IV morphine. During this time, the OxyContin dose fluctuated between 10mg bid, 15mg bid, 15mg AM and 20mg PM. She completed the study at a 10mg bid dose.
Reviewer's impression: Unrelated to study drug

Subject 0025001
SAE: Fever (MedDRA preferred term: Pyrexia)
This is a 11-year-old white female with a history of optic nerve glioma, headaches, anemia, low phosphorus, and back pain from chemotherapy. She completed the OTR3001 on OxyContin 10mg bid, which she continued when she was enrolled on OTR3002. A month later she received chemotherapy (carboplatin and vincristine). A day after the chemotherapy treatment, the patient was hospitalized with a temperature of 100.6°F, blood pressure95/50 mm Hg, pulse 100 beats/min, respirations 16 breaths/min, and SpO2 96%. Treatment included IV hydration, IV potassium chloride, IV ondansetron, ibuprofen, paracetamol, and multiple doses of IV morphine for abdominal pain. The next day the SAE resolved and she was discharged home. The SAE of pyrexia was considered moderate and not related to the study drug but to chemotherapy. The patient was able to complete the study on OxyContin 10mg bid.
Reviewer's impression: Unrelated to study drug

Subject 0027001
SAE: Obstipation (MedDRA preferred term: Constipation)
This is a 10-year-old white male with a history of ADHD, constipation, osteomyelitis, MRSA infection, GERD, PTSD, right pleural effusion, nephroblastoma, nephrectomy, elevated transaminases, low neutrophil and lymphocyte count, and anemia. He completed OTR3001 on OxyContin 30mg AM and 20mg PM, which he continued when he started OTR3002. A month later the dose was increased to 30mg bid and exactly 3 months later he experienced an AE of constipation (moderated and possibly related to the study drug) and he was treated with a laxative. Seven weeks later he completed the study on 30mg bid. Thirteen days after the completion of the study, the patient was hospitalized with abdominal pain and constipation. Allegedly, the last bowel movement was 2 weeks prior with no resolution despite the use of daily laxatives. The SAE of constipation was considered moderate and probably related to the study drug. During the hospitalization, the patient was treated with polyethylene glycol (macrogol), metoclopramide, lorazepam, and magnesium hydroxide. He was discharged home the next day.
Reviewer's impression: Probably related to study drug

Subject 0026002
SAE: Vasoocclusive Crisis (MedDRA preferred term: Sickle cell anaemia with crisis))
This is an 11-year-old black female with a history of sickle cell anemia with multiple vaso-occlusive episodes, adenotonsillectomy, seizures, constipation, and sleep apnea. She completed OTR3001 on OxyContin 10mg bid and was enrolled on OTR3002 on the same dose. On day 18, she complained that she could not fully move her legs due to severe pain and she was admitted to the hospital with an SAE of vaso-occlusive crisis (considered severe in severity and not related to the study drug but to her sickle cell disease). While she was hospitalized she continued on the study drug and received

supplemental IV morphine. Six days later, she recovered and was discharged home. She completed the study on OxyContin 10mg bid.
Reviewer's impression: Unrelated to the study drug

7.3.3 Dropouts and/or Discontinuations

7.3.3.1 Study OXP3003

The following table, derived from Table 7 of the study's report, summarizes Study OXP3003 discontinuation and reasons for discontinuation.

Table 32. Summary of Reasons for Study Discontinuation. Study OXP3003.

		Oxy Pediatric Liquid 1mg/ml		
Age Group	**Placebo (n = 19)**	**0.1 mg/kg (n = 24)**	**0.2 mg/kg (n = 22)**	**Total (N = 65)**
All Patients				
Discontinued, n (%)	4 (21.1)	6 (25.0)	1 (4.5)	11 (16.9)
Adverse event	1 (5.3)	1 (4.2)	0	2 (3.1)
Subject's choice	3 (15.8)	3 (12.5)	1 (4.5)	7 (10.8)
Administrative	0	2 (8.3)	0	2 (3.1)
Age Group: 5 to <12 years	**n = 7**	**n = 10**	**n = 9**	**N = 26**
Discontinued, n (%)	1 (14.3)	3 (30.0)	0	4 (15.4)
Adverse event	0	1 (10.0)	0	1 (3.8)
Subject's choice	1 (14.3)	1 (10.0)	0	2 (7.7)
Administrative	0	1 (10.0)	0	1 (3.8)
Age Group: 12 years to ≤ 16	**n = 12**	**n = 14**	**n = 13**	**N = 39**
Discontinued, n (%)	3 (25.0)	3 (21.4)	1 (7.7)	7 (17.9)
Adverse event	1 (8.3)	0	0	1 (2.6)
Subject's choice	2 (16.7)	2 (14.3)	1 (7.7)	5 (12.8)
Administrative	0	1 (7.1)	0	1 (2.6)

Only 2 patients had an adverse event leading to discontinuation in Study OXP3001. One 10 years-old female patient, subject 36002, was randomized to Oxy Pediatric Liquid 0.1mg/kg, which she received for 2 days. She had a laparoscopic cholecystectomy the day prior to starting the test drug. She developed the nonfatal SAEs of cholelithiasis and bile duct stone and was discontinued from the study. She is discussed in more detail in Section 7.3.2.1.1.

Another patient, subject 0053002, was a 14 years-old male with history of Arnold-Chiari malformation, hydrocephaly, paraplegia, spina bifida/lumbar meningomyelocele. He had anemia (treated with a packed red blood cell transfusion), pruritus, fever, constipation, and bilateral pedal edema on the days between the screening visit and the start of the treatment period 4 days later. At the start of the treatment period he was started on the placebo solution every 6 hours. Additionally, he was receiving PCA

morphine (a total of 5mg on day 1 and 8 mg on day 2) but no other supplemental pain medication. On day 1, he experienced vomiting, considered severe and probably related to the study drug (although he received placebo, this was a double-blind, placebo controlled trial) and he was discontinued from the study that day.

The study drug dose was reduced for 1 patient, an 11 years-old female (Subject 0049007) in the Oxy Pediatric Liquid 0.1 mg/kg group who experienced nausea (considered possibly related), fever (considered unrelated), and pruritus (considered possibly related) on the first day of treatment. On the second day of treatment she complained of pruritus (considered possibly related) and the test drug was reduced again. For a 14 years-old female (Subject 0049001), assigned to the Oxy Pediatric Liquid 0.2 mg/kg group, the study treatment was interrupted because she experienced vomiting (considered unrelated by the CI although it can be associated with opioid treatment).

7.3.3.2 Study OTR3001

The following is a summary of Study OTR3001's patient discontinuations/withdrawals.

Table 33. Summary of Reasons for Study Discontinuation. Study OTR3001

Category	Age Group		Total (N=155) n (%)
	6 to < 12 Years (N=27) n (%)	≥ 12 to ≤ 16 Years (N=128) n (%)	
Discontinued study in <2 weeks	9 (33.3)	12 (9.4)	21 (13.5)
AE	3 (11.1)	4 (3.1)	7 (4.5)
Subject's choice	3 (11.1)	1 (0.8)	4 (2.6)
Lost to follow-up	0	0	0
Lack of therapeutic effect	0	1 (0.8)	1 (0.6)
Confirmed or suspected diversion	0	0	0
Administrative	3 (11.1)	6 (4.7)	9 (5.8)
Discontinued study in ≥2 to <4wks	1 (3.7)	11 (8.6)	12 (7.7)
AE	0	3 (2.3)	3 (1.9)
Subject's choice	0	3 (2.3)	3 (1.9)
Lost to follow-up	0	1 (0.8)	1 (0.6)
Lack of therapeutic effect	0	4 (3.1)	4 (2.6)
Confirmed or suspected diversion	0	0	0
Administrative	1 (3.7)	0	1 (0.6)

Source: derived from table 7 of OTR3001's study report
Abbreviations: AE = adverse event; N = number of patients in population groups and total; n = number of patients with data.
[a]There are 2 subjects with extended exposure in OTR3001 because the extension study was not available.
Note: Reasons for discontinuation are based on the End of Study (EOS) eCRF page.
Percentages are based on N

The following table summarizes the incidence of TEAEs leading to study drug discontinuation by System Organ Class (SOC) and preferred term for the safety population.

Table 34. Incidence of TEAEs Leading to Study Drug Discontinuation by SOC and Preferred Term. Study OTR3001

System Organ Class (SOC) Preferred Term	Age Group		Total (N=155) n (%)
	6 to <12 Years (N=27) n (%)	≥12 to ≥16 Years (N=128) n (%)	
Any TEAEs Leading to Study Discontinuation	**3 (11.1)**	**7 (5.5)**	**10 (6.5)**
Ear and labyrinth disorders	**0**	**1 (0.8)**	**1 (0.6)**
Vertigo	0	1 (0.8)	1 (0.6)
Eye disorders	**0**	**1 (0.8)**	**1 (0.6)**
Diplopia	0	1 (0.8)	1 (0.6)
Gastrointestinal disorders	**0**	**1 (0.8)**	**1 (0.6)**
Vomiting	0	1 (0.8)	1 (0.6)
General disorders and administration site conditions	**1 (3.7)**	**1 (0.8)**	**2 (1.3)**
Irritability	1 (3.7)	0	1 (0.6)
Pain	0	1 (0.8)	1 (0.6)
Nervous system disorders	**1 (3.7)**	**3 (2.3)**	**4 (2.6)**
Headache	1 (3.7)	2 (1.6)	3 (1.9)
Coma	1 (3.7)	1 (0.8)	2 (1.3)
Dizziness	0	2 (1.6)	2 (1.3)
Balance disorder	0	1 (0.8)	1 (0.6)
Convulsion	1 (3.7)	0	1 (0.6)
Lethargy	0	1 (0.8)	1 (0.6)
Psychiatric disorders	1 (3.7)	**1 (0.8)**	**2 (1.3)**
Abnormal dreams	1 (3.7)	0	1 (0.6)
Euphoric mood	0	1 (0.8)	1 (0.6)
Renal and urinary disorders	**1 (3.7)**	**1 (0.8)**	**2 (1.3)**
Oliguria	1 (3.7)	0	1 (0.6)
Urinary retention	0	1 (0.8)	1 (0.6)
Respiratory, thoracic and mediastinal disorders	**1 (3.7)**	**1 (0.8)**	**2 (1.3)**
Hypoxia	0	1 (0.8)	1 (0.6)
Respiratory disorder	1 (3.7)	0	1 (0.6)
Skin and subcutaneous tissue disorders	**1 (3.7)**	**3 (2.3)**	**4 (2.6)**
Hyperhidrosis	0	1 (0.8)	1 (0.6)
Pruritus	0	1 (0.8)	1 (0.6)
Rash pruritic	1 (3.7)	0	1 (0.6)
Urticaria	0	1 (0.8)	1 (0.6)

(Source: Study OTR3001's report, Table 34, page 122)
Note: Patients who experienced 2 or more adverse events within the same SOC or preferred term were counted only once.
N = number of patients in population groups and total.
n = number of patients with data.
Percentages are based on N.

Headache was the single most frequent TEAE leading to discontinuation. The most frequent SOCs were "Nervous system disorders" and "Skin and subcutaneous disorders", the last one encompassing overlapping preferred terms such as pruritus, rash pruritic, and urticaria.

In total, 10 (6.5%) patients discontinued the study drug due to TEAEs. Three (11.1%) of these 10 patients were in the 6 to less than 12 years old group and 7 (5.5%) in the 12 to 16 years group. Two of these patients died and their individual case summaries are discussed in Section 7.3.1.1. Another 2 of these patients (0038002 and 0006003) were discussed in the nonfatal SAEs section for study OTR3001, Section 7.3.2.1.2. I will briefly summarize the remaining 6 patients below.

Patient 0009009 is a 16 y/o white Hispanic female with a medical history of sickle cell disease, cholecystectomy, GERD, constipation, pruritus, muscle spasms, and hypothyroidism. She was started on OxyContin 80mg bid and the same day, she reported AEs of dizziness, headache, and worsening pruritus, possibly related to the study drug. She was treated with methadone, oxycodone SR, and diphenhydramine. The next day, she reported AEs of nausea and vomiting and was treated with ondansetron. She took the last dose on day 3 and was discontinued due to the AEs dizziness, headache, and worsening pruritus. Reviewer's comment: possibly related.

Patient 0005004 is a 13 y/o white female with history of depression, anemia, chronic abdominal pain, acute lymphocytic leukemia, constipation, nausea, gastritis, and fungal infection due to neutropenia secondary to chemotherapy. She was started on OxyContin 20mg AM and 10mg PM which was reduced to 10mg bid by day 16 after reporting AEs of euphoria (moderate and definitely related to the study drug) and urinary retention (mild and definitely related to the study drug). On day 17 she took the last dose of the study drug and was discontinued from the study due to these AEs.

Patient 0017001 is an 11y/o white Hispanic female with a history of allergic dermatitis and a left hand injury due to a venomous snake bite and related left hand sympathetic dystrophy and skin graft. She was started on OxyContin 10mg AM and 15mg PM and on day 4 she reported the AEs of abnormal dreams (moderate in severity and probably related) and irritability (severe and probably related to the study drug). She was discontinued from the study on day on day 8 due to these AEs, which resolved within 2 days of study drug discontinuation.

Patient 0520001 is an 8 y/o white male with a history of medulloblastoma, ventriculoperitoneal shunt insertion, seizures, hormonal replacement, and a number of complications to the CNS neoplasm the chemotherapy used to treat it. He was started on OxyContin 10mg bid and on day 2, he reported AEs of pruritus and pruritic rash (both considered moderate in severity and probably related to the study drug). He took the last dose of the study that day and was discontinued from the study with resolution of AEs the next day.

Patient 0075018 is a 13 y/o white female with a history of adolescent idiopathic scoliosis and status post-spinal fusion. She was started on OxyContin 20mg bid and on day 12 she reported an AE of hyperhidrosis (considered moderate in severity and probably related to the study drug). She took the last dose of the study drug on day 13 and was withdrawn from the study the next day, with resolution of the AE 2 days later.

Patient 0031001 is a 16 y/o white male with a history of constipation and pectus excavatum. He took a single dose of OxyContin 10mg and developed an AE of urticaria. He was withdrawn from the study the next day. The AE was "ongoing".

Patient 0038002 is a 16 y/o white male with a medical history of L4 avulsion fracture and disc herniation at L3/L4 after a Jui Jitsu injury a few months prior to the study.

7.3.3.3 Study OXP1005

The following table, derived from Table 6 of the study's report, summarizes the reasons for discontinuation from Study OXP1005.

Table 35. Summary of Reasons for Discontinuation. Study OXP1005.

	Oxy Pediatric Liquid 1mg/ml			
Age Group	0.05 mg/kg (n = 26)	0.1 mg/kg (n = 17)	0.2 mg/kg (n = 17)	Total (N = 60)
All Patients				
Discontinued, n (%)	5 (19.2)	2 (11.8)	3 (17.6)	10 (16.7)
Adverse event	2 (7.7)	0	1 (5.9)	3 (5.0)
Subject's choice	1 (3.8)	1 (5.9)	0	2 (3.3)
Administrative	2 (7.7)	1 (5.9)	2 (11.8)	5 (8.3)
Birth to 30 Days	**n = 12**	**n = 0**	**n = 0**	**N = 12**
Discontinued, n (%)	2 (16.7)	0	0	2 (16.7)
Adverse event	2 (16.7)	0	0	2 (16.7)
Subject's choice	0	0	0	0
Administrative	0	0	0	0
31 Days to ≤ 6 Mo	**n = 7**	**n = 9**	**n = 8**	**N = 24**
Discontinued, n (%)	1 (14.3)	2 (22.2)	1 (12.5)	4 (16.7)
Adverse event	0	0	1 (12.5)	1 (4.2)
Subject's choice	0	1 (11.1)	0	1 (4.2)
Administrative	1 (14.3)	1 (11.1)	0	2 (8.3)
7 Mo to ≤ 4 Years	**n = 7**	**n = 8**	**n = 9**	**N = 24**
Discontinued, n (%)	2 (28.6)	0	2 (22.2)	4 (16.7)
Adverse event	0	0	0	0
Subject's choice	1 (14.3)	0	0	1 (4.2)
Administrative	1 (14.3)	0	2 (22.2)	3 (12.5)

The following patients discontinued the study drug permanently or discontinued from the study due to adverse events.

Patient 0038008 was a 13-day-old neonate with a history of aortic arch, patent ductus arteriosus, obstructive apnea, and status post-operative repair of an esophageal atresia and trachea-esophageal fistula when he began treatment with Oxy Pediatric Liquid 0.05mg/kg. That same day he developed the MedDRA preferred term, infantile apnoeic attack. The event was attributed to the failure of successfully suctioning excessive and thick nasal secretions. The event resolved with deep suctioning, manual bag ventilations and re-intubation. This patient is discussed in Section 7.3.2.1.3.

Patient 0064004 was also a 10-day-old neonate with a history of congenial intestinal malformation, bile vomiting, hyperbilirubinemia, and laparotomy when he began treatment with Oxy Pediatric Liquid 0.05mg/kg every 6 hours. He was on his second day of treatment when he developed “bile vomiting/neonate” or the preferred term, vomiting neonatal (considered moderate and unrelated to the study drug). The study drug was continued for one more day but was discontinued permanently due to the vomiting.

Patient 0034023 was a 2-month-old with a history of neonatal jaundice, atrial septal defect, failure to thrive ventricular septal defect, pulmonary edema, status post-op for ventricular and septal defect closure when he began treatment with Oxy Pediatric Liquid 0.2mg/kg every 6 hours. He had a somnolence score of 1 pre-dose and 30 minutes post dose. He developed excessive sedation on day 1, considered mild and probably related to the study drug. The study drug was discontinued and he was discontinued from the study.

7.3.4 Significant Adverse Events

Because oxycodone is a full mu agonist, signs of central nervous system depression (altered level of consciousness, decreased respiratory drive, hypoxia, and cardiovascular collapse) are of particular concern. However, these safety concerns will be explored in later sections of this review (e.g., vital signs, hemoglobin-oxygen saturation data, ect.).

7.3.5 Submission Specific Primary Safety Concerns

As discussed above.

7.4 Supportive Safety Results

Not applicable.

7.4.1 Common Adverse Events

7.4.1.1 OXP3003

The following reviewer-constructed table summarizes treatment-emergent events (TEAEs) occurring in at least two individuals in descending frequency.

Table 36. TEAEs* Occurring in ≥2 Patients. OXP3003

MedDRA Preferred Term	Oxy Pediatric Liquid 0.10 mg/kg N = 24 n (%)	Oxy Pediatric Liquid 0.20 mg/kg N = 22 n (%)	Placebo N = 19 n (%)	Total N = 65 n (%)
Pyrexia	3 (12.5%)	8 (36.4%)	3 (15.8%)	14 (21.5%)
Pruritus	4 (16.7%)	4 (18.2%)	2 (10.5%)	10 (15.4%)
Vomiting	1 (4.2%)	3 (13.6%)	4 (21.1%)	8 (12.3%)
Nausea	1 (4.2%)	1 (4.5%)	2 (10.5%)	4 (6.2%)
Procedural nausea	2 (8.3%)	0	2 (10.5%)	4 (6.2%)
Headache	1 (4.2%)	2 (9.1%)	1 (5.3%)	4 (6.2%)
Constipation	0	2 (9.1%)	0	2 (3.1%)
Pleural effusion	1 (4.2%)	1 (4.5%)	0	2 (3.1%)
Blood pressure increased	0	1 (4.5%)	1 (5.3%)	2 (3.1%)
Hypertension	1 (4.2%)	1 (4.5%)	0	2 (3.1%)

(Source: Reviewer-constructed with JReview)
*More than one TEAE can be reported by one patient.

In the safety population, 36 patients (55%) had TEAEs. In the placebo group, 13 patients (68%) had TEAEs. Of the patients receiving treatment with Oxy Pediatric Liquid, 23 patients (50%) had treatment-emergent AEs. The most frequent treatment-emergent adverse events (TEAEs) were nausea (6.2%), vomiting (12.3%), pyrexia (21.5%), headache (6.2%), and pruritus (15.4%).

7.4.1.2 OTR3001

The most frequently reported TEAEs (≥10% of patients) in the safety population by preferred term were vomiting (reported by 34 patients or 21.9% of the population), nausea (reported by 23 patients or 14.8%) headache (reported by 22 patients or 4.2%), pyrexia (in 18 patients or 11.6%), and constipation (in 16 patients or 10.3%).

When divided by age group, the most frequently reported TEAEs (≥10% of patients) by preferred term were vomiting (6 patients or 22.2% of the safety population in the same age group), pyrexia (6 patients or 22.2%), and constipation (4 patients or 14.8%) in the younger patients. For the older cohort, the most frequently reported TEAEs were vomiting (28 patients or 21.9%), headache (19 patients or 14.8%), and nausea (20 patients or 15.6%) in the older patients.

The incidences of gastrointestinal disorders in the overall safety population and both age groups were similar. However, the incidences of constipation and diarrhea were higher in the younger age group. Pyrexia was more frequent in the younger age group, while dizziness occurred only in the older age group.

The following table (reference: OTR 3001's report, Table 25, page 107) summarizes the incidence of TEAEs reported in ≥5% of patients in any age group.

Table 37. Incidence of TEAEs Reported in ≥5% of Patients in Any Age Group: Safety Population. Study OTR3001.

System Organ Class Preferred Term	Age Group		Total (N=155) n (%)
	6 to <12 Years (N=27) n (%)	≥12 to ≥16 Years (N=128) n (%)	
Any TEAEs	**19 (70.4)**	**89 (69.5)**	**108 (69.7)**
Gastrointestinal disorders	**12 (44.4)**	**51 (39.8)**	**63 (40.6)**
Vomiting	6 (22.2)	28 (21.9)	34 (21.9)
Nausea	3 (11.1)	20 (15.6)	23 (14.8)
Constipation	4 (14.8)	12 (9.4)	16 (10.3)
Diarrhoea	3 (11.1)	5 (3.9)	8 (5.2)
General disorders and administration site conditions	**9 (33.3)**	**28 (21.9)**	**37 (23.9)**
Pyrexia	6 (22.2)	12 (9.4)	18 (11.6)
Nervous system disorders	**3 (11.1)**	**36 (28.1)**	**39 (25.2)**
Headache	3 (11.1)	19 (14.8)	22 (14.2)
Dizziness	0	12 (9.4)	12 (7.7)
Skin and subcutaneous tissue disorders	**4 (14.8)**	**22 (17.2)**	**26 (16.8)**
Pruritus	3 (11.1)	7 (5.5)	10 (6.5)

(Source: OTR3001's study report, Table 25, page 107)
Note: Patients who experienced 2 or more adverse events within the same SOC or preferred term were counted only once.
TEAEs that occurred in >5% of patients for each preferred term in any age group are presented.
Percentages are based on N.

AE's such as vomiting and nausea can have a wide-spectrum of severity. To help visualize the degree of severity of these common side effects, I have constructed a table categorizing by severity the TEAE's occurring in ≥5% within each age cohort.

Table 38. TEAEs Occurring in ≥5% of Patients by Severity; Safety Population, Ages ≥6 to ≤12 (N=27). Study OTR3001

MedDRA Preferred Term	CI's Assessment of Severity			Total n (%)
	Mild n (%)	Moderate n (%)	Severe n (%)	
Vomiting	4 (14.8%)	4 (14.8%)	0	8 (29.6%)
Pyrexia	5 (18.5%)	2 (7.4%)	0	7 (25.9%)
Haemoglobin decreased	4 (14.8%)	1 (3.7%)	0	5 (18.5%)
Headache	4 (14.8%)	1 (3.7%)	0	5 (18.5%)
Neutrophil count decreased	5 (18.5%)	0	0	5 (18.5%)
Constipation	4 (14.8%)	0	0	4 (14.8%)
Pruritus	2 (7.4%)	2 (7.4%)	0	4 (14.8%)
White blood cell count decreased	4 (14.8%)	0	0	4 (14.8%)
Alanine aminotransferase increased	3 (11.1%)	0	0	3 (11.1%)
Diarrhoea	2 (7.4%)	1 (3.7%)	0	3 (11.1%)
Nausea	2 (7.4%)	1 (3.7%)	0	3 (11.1%)
Platelet count decreased	3 (11.1%)	0	0	3 (11.1%)
Anaemia	1 (3.7%)	0	1 (3.7%	2 (7.4%)
Anxiety	0	2 (7.4%)	0	2 (7.4%)
Back pain	1 (3.7%)	1 (3.7%)	0	2 (7.4%)
Dyspnoea	1 (3.7%	1 (3.7%)	0	2 (7.4%)
Neutropenia	0	0	2 (7.4%)	2 (7.4%)
Oxygen saturation decreased	0	2 (7.4%)	0	2 (7.4%)
Somnolence	0	2 (7.4%)	0	2 (7.4%)
Total (% of TEAEs for age group)	45 (66.1%)	20 (29.4%)	3 (4.4%)	68 (100%)

(Reference: Reviewer-constructed with JMP v11.)
Individual patients can have more than one TEAE.
CI = Clinical investigator

Table 39. TEAEs Occurring in ≥5% of Patients by Severity; Safety Population, Ages ≥12 to ≤16 (N=128). Study OTR3001

MedDRA Preferred Term	CI's Assessment of Severity			Total n (%)
	Mild n (%)	Moderate n (%)	Severe n (%)	
Nausea	20 (15.6%)	14 (10.9%)	0	34 (26.6%)
Vomiting	21 (16.4%)	11 (8.6%)	1 (0.8%)	33 (25.8%)
Headache	13 (10.2%)	8 (6.3%)	2 (1.6%)	23 (18.0%)
Pyrexia	14 (10.9%)	2 (1.6%)	2 (1.6%)	18 (14.1%)
Dizziness	10 (7.8%)	5 (3.9%)	0	15 (11.7%)
Constipation	8 (6.3%)	4 (3.1%)	1 (0.8%)	13 (10.2%)
Haemoglobin decreased	9 (7.0%)	2 (1.6%)	0	11 (8.6%)
Decreased appetite	7 (5.5%)	0	0	7 (5.5%)
Fatigue	4 (3.1%)	3 (2.3%)	0	7 (5.5%)
Platelet count decreased	6 (4.7%)	0	1 (0.8%)	7 (5.5%)
Pruritus	4 (3.1%)	2 (1.6%)	1 (0.8%)	7 (5.5%)
Total (% of TEAEs for age group)	116 (66.3%)	51 (29.1%)	8 (4.6)	175 (100%)

(Reference: Reviewer-constructed with JMP v11.)
Individual patients can have more than one TEAE.
CI = Clinical investigator

In summary, TEAEs were of similar in frequency in the younger and older cohorts in every category (mild, moderate or severe). Mild TEAEs were, by far, the most common adverse events in both age groups, occurring more than twice as the moderate adverse events. Severe TEAEs occurred in similar frequency in the younger and older age groups (4.4% and 4.6% respectively). The conclusions on the frequency of TEAEs in this study are limited by the lack of a placebo-controlled comparison against the test drug.

7.4.1.3 OXP1005

A total of 30/60 patients (50%) in the safety population had a TEAE: 7 patients (58%) in the ≤ 30 days age group, 11 (46%) in the 31 days to ≤ 6 months age group, and 12 (50%) in the 7 months to ≤ 4 years age group. There were no SAEs in Study OXP1005. The following table summarizes TEAEs occurring in more than 5% of patients of the safety population by dose.

Table 40. Incidence of TEAEs in ≥5% of Patients in the Safety Population by Dose. Study OXP1005.

System Organ Class Preferred Term	Oxy Pediatric Liquid 1mg/mL 0.05 mg/kg (N=26) n (%)	 0.1mg/kg (N=17) n (%)	 0.2mg/kg (N=17) n (%)	Total (N=60) n (%)
Any Adverse Event	**13 (50)**	**9 (53)**	**8 (47)**	**30 (50)**
Cardiac disorders	**1 (4)**	**1 (6)**	**1 (6)**	**3 (5)**
Tachycardia	1 (4)	1 (6)	1 (6)	3 (5)
Eye disorders	**0**	**0**	**1 (6)**	**1 (2)**
Eye swelling	0	0	1 (6)	1 (2)
Gastrointestinal disorders	**3 (12)**	**0**	**4 (24)**	**7 (12)**
Abdominal pain	0	0	1 (6)	1 (2)
Constipation	0	0	1 (6)	1 (2)
Nausea	0	0	1 (6)	1 (2)
Vomiting	2 (8)	0	3 (18)	5 (8)
General disorders and administration site	**1 (4)**	**2 (12)**	**2 (12)**	**5 (8)**
Pyrexia	1 (4)	2 (12)	2 (12)	5 (8)
Injury, poisoning and procedural complications	**0**	**1 (6)**	**0**	**1 (2)**
Postoperative fever	0	1 (6)	0	1 (2)
Investigations	**4 (15)**	**2 (12)**	**0**	**6 (10)**
Haemoglobin decreased	2 (8)	2 (12)	0	4 (7)
Platelet count decreased	0	1 (6)	0	1 (2)
Metabolism and nutrition disorders	**0**	**1 (6)**	**1 (6)**	**2 (3)**
Decreased appetite	0	0	1 (6)	1 (2)
Hypokalaemia	0	1 (6)	0	1 (2)
Nervous system disorders	**0**	**0**	**1 (6)**	**1 (2)**
Sedation	0	0	1 (6)	1 (2)
Renal and urinary disorders	**0**	**0**	**1 (6)**	**1 (2)**
Urinary retention	0	0	1 (6)	1 (2)
Respiratory, thoracic and mediastinal disorders	**2 (8)**	**1 (6)**	**1 (6)**	**4 (7)**
Atelectasis	0	1 (6)	0	1 (2)
Pulmonary oedema	0	0	1 (6)	1 (2)
Skin and subcutaneous tissue disorders	**1 (4)**	**1 (6)**	**0**	**2 (3)**
Pruritus	0	1 (6)	0	1 (2)
Vascular disorders	**2 (8)**	**1 (6)**	**2 (12)**	**5 (8)**
Hypertension	2 (8)	0	1 (6)	3 (5)
Hypotension	0	1 (6)	1 (6)	2 (3)

(Source: OPX1005's report, Table 15, page 67)
Percentages are based on N.
Multiple occurrences of the same adverse event in 1 individual are counted only once.

The most common TEAEs in ≥ 5% of all patients were, vomiting (8%), pyrexia (8%), hemoglobin decreased (7%), tachycardia (5%), and hypertension (5%).

In an effort to better understand the TEAEs profile in the context of different age groups, I have created the following tables categorizing by severity the TEAE's occurring in ≥5% within each age cohort.

Table 41. TEAEs Occurring in ≥5% of Patients by Severity; Safety Population, Ages Birth to ≤ 1month (N=12). Study OXP1005

MedDRA Preferred Term	CI's Assessment of Severity			Total n (%)
	Mild n (%)	Moderate n (%)	Severe n (%)	
Haemoglobin decreased	2 (22.2%)	0	0	2 (22.2%)
Atelectasis neonatal	1 (11.1%)	0	0	1 (11.1%)
Blood pressure diastolic decreased	1 (11.1%)	0	0	1 (11.1%)
Blood pressure systolic increased	1 (11.1%)	0	0	1 (11.1%)
Hyperbilirubinaemia neonatal	0	1 (11.1%)	0	1 (11.1%)
Infantile apnoeic attack	0	1 (11.1%)	0	1 (11.1%)
Respiratory rate decreased	1 (11.1%)	0	0	1 (11.1%)
Vomiting neonatal	0	1 (11.1%)	0	1 (11.1%)
Total (% of TEAEs for age group)	6 (66.7%)	3 (33.3%)	0	9 (100%)

Reference: Reviewer-constructed with JMP v11.)
Individual patients can have more than one TEAE.
Percentages are based on number of TEAEs.
CI = Clinical investigator

No severe TEAEs occurred in the birth to less than a month-old cohort. In total, 9 TEAEs were reported by 7 (58.3%) of the 12 patients. Twice as many mild TEAEs occurred compared against moderate in severity TEAEs. However, the small number of patients enrolled and the fact that only one AE occurred in more than 1 patient in this age group limit the generalization of this conclusion, as it could have occurred by chance alone. It should be noted that patients in this age cohort were only treated with Oxy Pediatric Liquid 1mg/mL on a 0.05mg/kg dose. Six of the 12 patients in this age group were less than a week old.

In the 31 days to ≤6 month-old cohort there were no severe TEAEs in 24 patients. In total, there were 13 TEAEs reported by 8 (33.3%) of the 24 patients. Only two Preferred Terms surpassed the threshold of occurring more than once: "vomiting" with 4 events (all considered "mild" in severity) but all reported by 1 (4.2%) patient and "hypertension" with 2 events (all considered "mild" in severity) in 2 (8.3%) patients. Just like in the youngest cohort of this study, the small number of patients in this age cohort limits the generalization of this conclusion. In this age cohort, patients were distributed evenly on each of the three dose regimens (0.05mg/kg, 0.1mg/kg, and 0.2mg/kg). The age distribution within this group was distributed fairly evenly throughout the age spectrum.

In the 7 months to ≤4 years-old age group there were no serious TEAEs. In total, there were 43 TEAEs reported by 18 (75%) of the 24 patients. The subjects in this age range were distributed evenly on each of the three dose regimens. The age distribution within

this group was distributed fairly evenly throughout the age spectrum. The following table summarizes TEAEs occurring in 2 of more subjects.

Table 42. TEAEs Occurring in ≥2 Patients by Severity; Safety Population, Ages Birth to 7 months to ≤4 years (N=24). Study OXP1005

MedDRA Preferred Term	CI's Assessment of Severity			Total n (%)
	Mild n (%)	Moderate n (%)	Severe n (%)	
Pyrexia	3 (12.5%)	2 (8.3%)	0	5 (20.8%)
Vomiting	3 (12.5%)	1 (4.2%)	0	4 (16.7%)
Haemoglobin decreased	3 (12.5%)	0	0	3 (12.5%)
Hypertension	3 (12.5%)	0	0	3 (12.5%)
Pruritus	3 (12.5%)	0	0	3 (12.5%)
Aspartate aminotransferase increased	1 (4.2%)	1 (4.2%)	0	2 (8.3%)
Tachycardia	2 (8.3%)	0	0	2 (8.3%)
Total (% of TEAEs for age group)	19 (79.2%)	4 (16.7%)	0	22 (91.7%)*

Reference: Reviewer-constructed with JMP v11.)
Individual patients can have more than one TEAE.
*Multiple occurrences of the same adverse event in 1 individual are counted only once.
Percentages are based on number of TEAEs.
CI = Clinical investigator

Pyrexia and vomiting were the only two TEAEs which occurred in more than 10% of patients in this age group, occurring in 20.8% and 16.7% of patients respectively. Just like in all the other age groups, the overwhelming majority of TEAEs were mild (79.2%).

In summary, although the age range in Study OXP1005 provides us with a unique opportunity to assess the safety profile of oxycodone from birth through four years of age, the limited number of subjects enrolled limit any conclusions we can draw from the study. Particularly interesting would have been a better characterization of each specific age group, neonates in specific, but when divided in smaller groups, the smaller numbers curtail any meaningful analysis of safety. The conclusions on the frequency of TEAEs in this study are further limited by the lack of a placebo-controlled comparison against the test drug. In general, mild TEAEs were at least twice as common as moderate TEAEs. There were no serious TEAEs in any age group. The most common TEAEs were vomiting and pyrexia, which is consistent with the other studies submitted with this application.

7.4.2 Laboratory Findings

7.4.2.1 Study OXP3003

Mean values, mean changes, and maximum increases and decreases in individual selected laboratory values for the safety population (all ages) are contained in the table below.

Table 43. Summary of Selected Laboratory Data – Mean and Mean Changes from Baseline. Study OXP3003.

Laboratory Tests (Units)	Placebo (N=19	Oxy Pediatric Liquid 1mg/mL	
		0.1 mg/kg (N=24)	0.2 mg/kg (N= 22)
Hematology			
Red Blood Cells (10^12/L)			
n	17	22	21
Baseline Mean (SD)	4.11 (0.68)	3.77 (0.66)	4.0 (0.76)
End of Study Mean (SD)	3.89 (0.72)	3.58 (0.58)	3.64 (0.70)
Change from Baseline			
Mean (SD)	-0.23 (0.32)	-0.19 (0.51)	-0.38 (0.65)
Min, Max	-1.11, 0.24	-1.54, 0.73	-2.27, 0.34
Hemoglobin (g/L)			
n	17	22	21
Baseline Mean (SD)	119.9 (21.3)	109.9 (18.2)	118.7 (21.7)
End of Study Mean (SD)	3.89 (0.72)	3.58 (0.58)	3.64 (0.70)
Change from Baseline			
Mean (SD)	-6.2 (8.2)	-5.6 (3.7)	-11.4 (21.3)
Min, Max	-29, 8	-46, 20	-83, 11
Hematocrit (fraction)			
n	17	22	21
Baseline Mean (SD)	0.35 (0.06)	0.31 (0.09)	0.35 (0.07)
End of Study Mean (SD)	0.34 (0.07)	0.29 (0.08)	0.32 (0.06)
Change from Baseline			
Mean (SD)	-0.02 (0.03)	-0.02 (0.04)	-0.03 (0.06)
Min, Max	-0.09, 0.02	-0.13, 0.06	-0.19, 0.03
Platelet (10^9/L)			
n	17	22	21
Baseline Mean (SD)	218.3 (78.6)	177.9 (60.7)	208.0 (71.6)
End of Study Mean (SD)	227.6 (98.1)	178.5 (53.7)	219.0 (71.7)
Change from Baseline			

Laboratory Tests (Units)	Placebo (N=19	Oxy Pediatric Liquid 1mg/mL	
		0.1 mg/kg (N=24)	0.2 mg/kg (N= 22)
Mean (SD)	9.4 (35.7)	0.6 (60.8)	11.0 (51.6)
Min, Max	-54, 75	-150, 114	-104, 129
White Blood Cells (10^9/L)			
n	17	21	21
Baseline Mean (SD)	13.2 (4.8)	12.0 (6.0)	9.9 (3.8)
End of Study Mean (SD)	12.7 (6.0)	3.58 (0.58)	3.64 (0.70)
Change from Baseline			
Mean (SD)	-0.49 (3.40)	-1.09 (3.72)	-1.84 (3.72)
Min, Max	-4.7, 7.1	-11.2, 4.8	-9.0, 7.6
Neutrophils (fraction)			
n	16	21	12
Baseline Mean (SD)	0.77 (0.16)	0.77 (0.14)	0.75 (0.19)
End of Study Mean (SD)	0.78 (0.11)	0.73 (0.15)	0.72 (0.12)
Change from Baseline			
Mean (SD)	0.01 (0.15)	-0.04 (0.13)	-0.03 (0.16)
Min, Max	-0.17, 0.39	-0.22, 0.31	-0.41, 0.20
Blood Chemistry (SGOT) Aspartate Transferase (U/L)			
n	14	18	17
Baseline Mean (SD)	70.1 (47.2)	82.7 (67.8)	62.1 (42.9)
End of Study Mean (SD)	41.0 (19.7)	85.7 (125.4)	60.1 (35.2)
Change from Baseline			
Mean (SD)	-29.1 (33.0)	3.0 (83.0)	-2.0 (35.7)
Min, Max	-98, 5	-126, 308	-73, 89
(SGPT) Alanine Transferase (U/L)			
n	14	18	16
Baseline Mean (SD)	47.5 (76.4)	33.4 (35.5)	31.3 (14.5)
End of Study Mean (SD)	32.9 (33.6)	64.9 (163.4)	41.6 (43.9)
Change from Baseline			
Mean (SD)	-14.6 (44.9)	31.6 (128.8)	10.3 (41.9)
Min, Max	-167, 7	-7, 547	-15, 164
Total Bilirubin (umol/L)			
n	14	18	15
Baseline Mean (SD)	15.5 (12.8)	17.1 (18.0)	12.8 (7.9)
End of Study Mean (SD)	9.5 (5.9)	10.2 (6.5)	9.7 (5.2)
Change from Baseline			
Mean (SD)	-6.01 (10.40)	-6.93 (13.83)	-3.06 (5.35)

Laboratory Tests (Units)	Placebo (N=19	Oxy Pediatric Liquid 1mg/mL	
		0.1 mg/kg (N=24)	0.2 mg/kg (N= 22)
Min, Max	-30.8, 1.7	-51.3, 5.1	-12.0, 3.4
Blood Urea Nitrogen (mmol/L)			
n	16	19	20
Baseline Mean (SD)	3.4 (1.5)	4.0 (1.6)	5.9 (10.7)
End of Study Mean (SD)	3.7 (1.6)	3.8 (2.0)	3.4 (1.8)
Change from Baseline			
Mean (SD)	0.32 (0.91)	-0.15 (1.38)	-2.49 (9.99)
Min, Max	-1.1, 2.1	-3.4, 1.8	-44.3, 3.2
Creatinine (umol/L)			
n	16	19	19
Baseline Mean (SD)	53.0 (10.7)	50.4 (16.4)	53.0 (16.1)
End of Study Mean (SD)	51.5 (10.8)	45.19 (13.4)	50.3 (15.7)
Change from Baseline			
Mean (SD)	-1.50 (8.79)	-5.21 (8.81)	-2.63 (8.67)
Min, Max	-15.0, 17.7	-25.6, 6.2	-17.7, 10.6

(Source: OXP3003's report, Table 14.3.4.1)
Patients are only presented in the table if they have both a baseline and post-baseline value.
Baseline is defined as the last reported result before first study medication intake.
For patient 0036002 the hematocrit values of 0.36% and 0.34% should have been 36% and 34% respectively. This causes the values to be incorrectly assigned as out of normal range.

In general, mean changes in laboratory data parameters were small and not clinically notable overall. The generalization of this observation is limited by the small number of subjects and the short exposure to the study drug.

The following table presents data for all clinical laboratory hematologic values shifting from normal at baseline to abnormal at end of study in the safety population.

Table 44. Shift Table for Hematologic Parameters From Baseline to End of Study. OXP3003

Shift Category/ Laboratory Parameter	End of Study Oxy Pediatric Liquid 1 mg/mL		
	n/NN (%)		
Dose Groups - All Patients	**Placebo (n = 19)**	**0.1 mg/kg (n = 24)**	**0.2 mg/kg (n = 22)**
Normal to Low			
Red Blood Cells (x10^12/L)	4/19 (21)	6/24 (25)	4/22 (18)
Hemoglobin (g/L)	2/19 (11)	3/24 (13)	2/22 (9)
Hematocrit (fraction)	1/19 (5)	4/24 (17)	1/22 (5)
Platelet (x10^9/L)	1/19 (5)	3/24 (13)	1/22 (5)
White Blood Cells (x10^9/L)	0	0	1/22 (5)
Lymphocytes (fraction)	1/19 (5)	0	0
Eosinophils (fraction)	0	1/24 (4)	0
Normal to High			
Platelet (x10^9/L)	1/19 (5)	0	0
White Blood Cells (x10^9/L)	1/19 (5)	1/24 (4)	1/22 (5)
Neutrophils (fraction)	1/19 (5)	0	0
Eosinophils (fraction)	1/19 (5)	1/24 (4)	1/22 (5)
Monocytes (fraction)	4/19 (21)	3/24 (13)	2/22 (9)

(Source: OXP3003's report, Table 22, page 74)
1. Low, normal and high is defined using the standardized local laboratory ranges.
2. If a laboratory measurement is present but there is no local laboratory range, that measurement will be presented as not done.
3. For patient 0036002 the hematocrit values of 0.36% and 0.34% should have been 36% and 34% respectively. This causes the values to be incorrectly assigned as out of normal range.

The most common shifts from normal at baseline to low values at end of study in ≥ 10% of patients were for red blood cells, hemoglobin, hematocrit, and platelets, and the most common shift from normal to high values in ≥ 10% of patients was for monocytes (fraction).

The following table presents data for all blood chemistry values shifting from normal at baseline to abnormal at the end of the study in the safety population.

Table 45. Shift Table for Blood Chemistry Parameters From Baseline to End of Study. OXP3003

Shift Category/ Laboratory Parameter		End of Study Oxy Pediatric Liquid 1 mg/mL	
	n/NN (%)		
Dose Groups - All Patients	**Placebo (n = 19)**	**0.1 mg/kg (n = 24)**	**0.2 mg/kg (n = 22)**
Normal to Low			
Alanine Transferase (SGPT) (U/L)	3/19 (16)	0	0
Blood Urea Nitrogen (mmol/L)	0	1/24 (4)	3/22 (14)
Creatinine (umol/L)	3/19 (16)	2/24 (8)	0
Normal to High			
Aspartate Transferase (SGOT) (U/L)	0	2/24 (8)	2/22 (9)
Alanine Transferase (SGPT) (U/L)	1/19 (5)	0	1/22 (5)
Total Bilirubin (umol/L)	1/19 (5)	0	0
Blood Urea Nitrogen (mmol/L)	0	1/24 (4)	0

(Source: OXP3003's report, Table 22, page 74)
1. Low, normal and high is defined using the standardized local laboratory ranges.
2. If a laboratory measurement is present but there is no local laboratory range, that measurement will be presented as not done.

The most common shifts from normal at baseline to low values at the end of study in ≥ 10% of patients were for alanine transferase, blood urea nitrogen, and creatinine. Less than 10% of patients had shifts from normal at baseline to high values at the end of the study.

The following table presents the patients with laboratory toxicity grades ≥ 3 after baseline. Toxicity grades are based on the Division of AIDS Table for Grading Severity of Adult and Pediatric Adverse Events as of December 20014 (Grade 1: Mild, Grade 3: Moderate, Grade 3: Severe, Grade 4: Potentially Life-threatening).

Table 46. Patients With Laboratory Toxicity Grades ≥ 3 After Baseline. OXP3003

Patient Number	Laboratory Test (Units)	Oxy Pediatric Liquid Dose	Normal Local Laboratory Range	Baseline	Toxicity Grade at Baseline	End of Treatment	Toxicity Grade at End of Treatment
LOW							
53002	Hemoglobin (g/L)	Placebo	130 to 160	104	1	87	3
49007	Hemoglobin (g/L)	0.1 mg/kg	115 to 155	126	0	80	3
50004	Hemoglobin (g/L)	0.1 mg/kg	120 to 160	71	3	71	3
17002	Hemoglobin (g/L)	0.2 mg/kg	115 to 155	99	2	79	3
17005	Hemoglobin (g/L)	0.2 mg/kg	130 to 160	94	2	86c 76	3 3
26007	Hemoglobin (g/L)	0.2 mg/kg	115 to 155	148	0	65	3
45001	Hemoglobin (g/L)	0.2 mg/kg	120 to 150	83	3	86	3
49002	Hemoglobin (g/L)	0.2 mg/kg	130 to 160	143	10	86	3
HIGH							
49006	Lymphocytes Absolute (x10^6/L)[a]	Placebo		572	2	444	3
36002	Alanine Transferase (SGPT) (U/L)[b]	0.1 mg/kg	< 45	172	2	719	4
36002	Aspartate Transferase (SGOT) (U/L)[b]	0.1 mg/kg	< 40	269	3	577	4

(Source: OXP3003's report, Table 23, page 75)
[a] No normal local laboratory range given.
[b] Same patient.
[c]Lab value taken at an unplanned visit.
1. Patients who had a missing baseline value are not included in the listing.
2. The toxicity grading is defined by the Division of AIDS Table For Grading Severity of Adult and Pediatric Adverse Events as of December, 2004.
3. If a laboratory measurement is present but outside of the grade 1-4 range, that measurement will be coded as Grade level 0.

A decrease in hemoglobin values from toxicity grade 0 to grade 4 was observed in one patient (26007) in the 0.2 mg/kg treatment group. Increases in ALT and AST levels from toxicity grades 2 and 3, respectively, to grade 4 were observed in one patient (36002) in the 0.1 mg/kg treatment group.

7.4.2.2 Study OTR3001

Mean values, mean changes, and maximum increases and decreases in individual selected laboratory values for the safety population (all ages) are contained in the table below, derived from Table 14.3.4.1.1 from the study's report.

Table 47. Summary of Selected Laboratory Data – Mean and Mean Changes from Baseline. Study OTR3001.

Laboratory Test (Units)	Age Group		Total (N=155)
	6 to < 12 Years (N=27)	≥ 12 to ≤ 16 Years (N=128)	
Hematology			
Red Blood Cells (10^12/L)			
n*	21	102	123
Baseline Mean (SD)	3.54 (0.730)	3.73 (0.731)	3.70 (0.732)
End of Study Mean (SD)	3.663 (0.701)	3.99 (0.723)	3.93 (0.727)
Change from Baseline			
Mean (SD)	-0.01 (0.373)	0.28 (0.490)	0.23 (0.484)
Min, Max	-1.09, 0.54	-0.94, 1.44	-1.09, 1.44
Hemoglobin (g/L)			
n*	21	102	123
Baseline Mean (SD)	101.2 (18.92)	109.9 (19.55)	108.4 (19.65)
End of Study Mean (SD)	104.6 (17.67)	115.6 (18.06)	113.8 (18.39)
Change from Baseline			
Mean (SD)	0.1 (11.10)	5.9 (12.93)	5.9 (12.93)
Min, Max	-31, 18	-30, 37	-31, 37
Hematocrit (fraction)			
n*	21	102	123
Baseline Mean (SD)	0.30 (0.057)	0.33 (0.060)	0.33 (0.060)
End of Study Mean (SD)	0.32 (0.055)	0.35 (0.054)	0.35 (0.056)
Change from Baseline			
Mean (SD)	0.00 (0.033)	0.02 (0.043)	0.02 (0.042)
Min, Max	-0.07, 0.05	-0.08, 0.13	-0.08, 0.13
Platelet (10^9/L)			
n*	20	99	119
Baseline Mean (SD)	248.2 (159.72)	281.4 (136.90)	275.6 (141.17)
End of Study Mean (SD)	291.7 (154.05)	318.8 (133.11))	314.5 (136.38)
Change from Baseline			
Mean (SD)	11.0 (215.77)	26.0 (146.73)	23.5 (159.40)
Min, Max	-553, 421	-383, 342	-553, 421
White Blood Cells (10^9/L)			

Laboratory Test (Units)	Age Group		Total (N=155)
	6 to < 12 Years (N=27)	≥ 12 to ≤ 16 Years (N=128)	
n*	20	102	122
Baseline Mean (SD)	6.91 (4.564)	7.82 (3.456)	7.66 (3.673)
End of Study Mean (SD)	6.22 (2.987)	6.39 (2.624)	6.37 (2.673)
Change from Baseline			
Mean (SD)	-1.03 (4.041)	-1.50 (3.177)	-1.42 (3.320)
Min, Max	-11.2, 4.8	-9.0, 7.6	-11.2, 7.6
Neutrophils Absolute (10^6/L)			
n*	21	100	121
Baseline Mean (SD)	4038 (3619)	5291 (3100)	5069 (3220)
End of Study Mean (SD)	3267 (2078)	3847 (2005)	3752 (2022)
Change from Baseline			
Mean (SD)	-753.3 (3426.10)	-1493.9 (	-1365.4 (
Min, Max	-9760, 4500	-15270, 4510	-15270, 4510
Blood Chemistry			
(SGOT) Aspartate Transferase (U/L)			
n*	20	107	127
Baseline Mean (SD)	39.2 (27.82)	39.2 (32.32)	39.2 (31.54)
End of Study Mean (SD)	45.3 (47.51)	24.2 (17.32)	27.6 (25.75)
Change from Baseline			
Mean (SD)	8.9 (55.58)	-15.1 (36.85)	-11.4 (41.05)
Min, Max	-71, 215	-250, 133	-250, 215
(SGPT) Alanine Transferase (U/L)			
n*	20	107	127
Baseline Mean (SD)	40.0 (42.43)	35.3 (32.55)	36.1 (34.21)
End of Study Mean (SD)	58.0 (82.77)	28.0 (48.11)	32.8 (55.91)
Change from Baseline			
Mean (SD)	25.1 (78.81)	-5.8 (55.88)	-1.0 (60.76)
Min, Max	-66, 298	-256, 374	-256, 374
Total Bilirubin (umol/L)			
n*	20	106	126
Baseline Mean (SD)	10.0 (13.42)	6.6 (7.70)	7.2 (8.91)
End of Study Mean (SD)	8.7 (9.02)	7.3 (15.66)	7.5 (14.77)
Change from Baseline			
Mean (SD)	-1.5 (9.50)	-0.6 (4.20)	-0.8 (5.35)
Min, Max	-33, 18	-17, 15	-33, 18
Blood Urea Nitrogen (mmol/L)			
n*	20	107	127

Laboratory Test (Units)	Age Group		Total (N=155)
	6 to < 12 Years (N=27)	≥ 12 to ≤ 16 Years (N=128)	
Baseline Mean (SD)	3.47 (1.270)	3.74 (1.368)	3.70 (1.352)
End of Study Mean (SD)	3.72 (1.936)	3.71 (1.355)	3.71 (1.456)
Change from Baseline			
Mean (SD)	0.13 (1.475)	0.00 (1.368)	0.02 (1.380)
Min, Max	-2.2, 3.9	-3.9, 3.9	-3.9, 3.9
Blood Glucose (mmol/L)			
n*	19	106	125
Baseline Mean (SD)	5.68 (1.068)	5.39 (0.899)	5.44 (0.930)
End of Study Mean (SD)	5.19 (1.351)	5.47 (1.974)	5.42 (1.888)
Change from Baseline			
Mean (SD)	-0.24 (1.460)	0.05 (1.923)	0.01 (1.858)
Min, Max	-2.4, 4.5	-2.5, 14.4	-2.5, 14.4
Total Protein (g/L)			
n*	20	107	127
Baseline Mean (SD)	65.7 (6.44)	63.0 (7.85)	63.0 (7.85)
End of Study Mean (SD)	67.8 (8.50)	69.4 (6.81)	69.1 (7.10)
Change from Baseline			
Mean (SD)	0.9 (6.99)	6.4 (9.06)	5.5 (8.98)
Min, Max	-15, 10	-22, 26	-22, 26
Creatinine (umol/L)			
n*	20	107	127
Baseline Mean (SD)	34.8 (7.24)	51.1 (13.15)	48.5 (13.75)
End of Study Mean (SD)	38.5 (14.31)	53.1 (13.10)	50.8 (14.31)
Change from Baseline			
Mean (SD)	2.5 (11.02)	1.3 (7.70)	1.5 (8.27)
Min, Max	-10, 42)	-20, 22	-20, 42

* Patients are counted in the table if they have both a baseline and post-baseline value.
N = number of patients in population groups and total; n = number of patients with data. SD = standard deviation.

Overall, the majority of patients stayed within the normal range for hematologic and blood chemistry parameter values during the study. Laboratory values with toxicity grades ≥ grade 3 occurred in 24 patients; these included low hemoglobin and platelets, and elevated blood glucose, bilirubin, ALT, and AST. The most frequent laboratory abnormality was low hemoglobin in 13 of these 24 patients. Eight of these 13 patients were black and had a medical history of sickle cell disease or thalassemia, 1 of these 13 patients was white and had a medical history of aplastic anemia, and 4 of these 13 patients were white and had a medical history of neoplasm. In other words, the majority of outlier values were related to the baseline medical conditions and related treatments. In general, no unexpected safety concerns were observed in the clinical laboratory data.

The following table shows hematologic parameter values that shifted from normal at baseline to low at the end of the study for the safety population.

Table 48. Shifts from Normal to Low From Baseline to End of Study for Hematologic Parameter Values. OTR3001

Laboratory Parameter[a]	Age groups: 6 to <12 Years (N = 27) n/NN[b] (%)	Age groups: ≥12 to ≤16 Years (N = 128) n/NN[b] (%)	Total (N = 155) n/NN[b] (%)
Bands (fraction)	1/20 (5.0)	2/97 (2.1)	3/117 (2.6)
Basophils absolute (10^6/L)	0/21 (0.0)	1/101 (1.0)	1/122 (0.8)
Eosinophils absolute (10^6/L)	1/21 (4.8)	2/101 (2.0)	3/122 (2.5)
Eosinophil (manual differential) (%)	0/7 (0.0)	1/12 (8.3)	1/19 (5.3)
Hematocrit (fraction)	2/21 (9.5)	5/102 (4.9)	7/123 (5.7)
Hemoglobin (g/L)	1/21 (4.8)	5/102 (4.9)	6/123 (4.9)
Lymphocytes (fraction)	0/9 (0.0)	5/68 (7.4)	5/77 (6.5)
Lymphocytes absolute (10^6/L)	1/21 (4.8)	5/100 (5.0)	6/121 (5.0)
Lymphocyte (manual differential) (%)	0/7 (0.0)	2/12 (16.7)	2/19 (10.5)
Monocytes (fraction)	0/9 (0.0)	5/68 (7.4)	5/77 (6.5)
Monocytes absolute (10^6/L)	2/21 (9.5)	8/100 (8.0)	10/121 (8.3)
Monocyte (manual differential) (%)	0/7 (0.0)	2/12 (16.7)	2/19 (10.5)
Neutrophils (fraction)	1/9 (11.1)	2/68 (2.9)	3/77 (3.9)
Neutrophils absolute (10^6/L)	1/21 (4.8)	5/100 (5.0)	6/121 (5.0)
Neutrophils (manual differential) (%)	1/7 (14.3)	3/12 (25.0)	4/19 (21.1)
Platelet (10^9/L)	1/20 (5.0)	2/99 (2.0)	3/119 (2.5)
Red blood cells (10^{12}/L)	1/21 (4.8)	6/102 (5.9)	7/123 (5.7)
White blood cells (10^9/L)	1/21 (4.8)	11/102 (10.8)	12/123 (9.8)

(Source: OTR3001's study report, Table 35, page 126)
Note: N = number of patients in population groups and total
[a]Units reflected as SI units.
[b] NN = Number of patients with normal laboratory test results at baseline and laboratory test results available at the end of study; n = Number of patients with observed cases. Percentages are based on NN.

The following table shows hematologic parameter values that shifted from normal at baseline to high at the end of the study for the safety population.

Table 49. Shifts From Normal to High From Baseline to End of Study for Hematologic Parameter Values. OTR3001

Laboratory Parameter[a]	Age Group: 6 to <12 Years (N = 27) n/NN[b] (%)	Age Group: •12 to "16 Years (N = 128) n/NN[b] (%)	Total (N = 155) n/NN[b] (%)
Bands (fraction)	0/20 (0.0)	1/97 (1.0)	1/117 (0.9)
Basophil (manual differential) (%)	1/7 (14.3)	0/12 (0.0)	1/19 (5.3)
Eosinophils (fraction)	2/9 (22.2)	8/69 (11.6)	10/78 (12.8)
Eosinophils absolute (10^6/L)	0/21 (0.0)	2/101 (2.0)	2/122 (1.6)
Eosinophil (manual differential) (%)	0/7 (0.0)	1/12 (8.3)	1/19 (5.3)
Hematocrit (fraction)	0/21 (0.0)	1/102 (1.0)	1/123 (0.8)
Hemoglobin (g/L)	0/21 (0.0)	2/102 (2.0)	2/123 (1.6)
Lymphocytes (fraction)	1/9 (11.1)	2/68 (2.9)	3/77 (3.9)
Lymphocytes absolute (10^6/L)	0/21 (0.0)	1/100 (1.0)	1/121 (0.8)
Lymphocyte (manual differential) (%)	1/7 (14.3)	2/12 (16.7)	3/19 (15.8)
Monocytes absolute (10^6/L)	1/21 (4.8)	0/100 (0.0)	1/121 (0.8)
Monocyte (manual differential) (%)	1/7 (14.3)	4/12 (33.3)	5/19 (26.3)
Neutrophils (fraction)	0/9 (0.0)	6/68 (8.8)	6/77 (7.8)
Neutrophils absolute (10^6/L)	0/21 (0.0)	3/100 (3.0)	3/121 (2.5)
Neutrophils (manual differential) (%)	0/7 (0.0)	2/12 (16.7)	2/19 (10.5)
Platelet (10^9/L)	2/20 (10.0)	14/99 (14.1)	16/119 (13.4)
Red blood cells (10^{12}/L)	0/21 (0.0)	2/102 (2.0)	2/123 (1.6)
White blood cells (10^9/L)	0/21 (0.0)	2/102 (2.0)	2/123 (1.6)

(Source: OTR3001's study report, Table 36, page 127)
Note: N = number of patients in population groups and total
[a]Units reflected as SI units.
[b] NN = Number of patients with normal laboratory test results at baseline and laboratory test results available at the end of study; n = Number of patients with observed cases. Percentages are based on NN.

The following table shows blood chemistry parameter values that shifted from normal at baseline to low at the end of the study for the safety population.

Table 50. Shift from Normal to Low From Baseline to End of Study for Blood Chemistry Parameter Values. OTR3001

Laboratory Parameter[a]	Age Groups: 6 to <12 Years (N = 27) n/NN[b] (%)	Age Groups: •12 to ”16 Years (N = 128) n/NN[b] (%)	Total (N = 155) n/NN[b] (%)
Albumin (g/L)	0/20 (0.0)	2/107 (1.9)	2/127 (1.6)
Alkaline phosphatase (U/L)	1/19 (5.3)	2/106 (1.9)	3/125 (2.4)
Blood urea nitrogen (mmol/L)	3/20 (15.0)	2/107 (1.9)	5/127 (3.9)
Calcium (mmol/L)	0/20 (0.0)	5/107 (4.7)	5/127 (3.9)
Chloride (mmol/L)	2/20 (10.0)	1/107 (0.9)	3/127 (2.4)
Bicarbonate/carbon dioxide (mmol/L)	1/20 (5.0)	6/107 (5.6)	7/127 (5.5)
Creatinine (–mol/L)	2/20 (10.0)	6/107 (5.6)	8/127 (6.3)
Blood glucose (mmol/L)	1/19 (5.3)	2/106 (1.9)	3/125 (2.4)
Lactic dehydrogenase (U/L)	0/20 (0.0)	1/107 (0.9)	1/127 (0.8)
Phosphorous/inorganic phosphate (mmol/L)	1/20 (5.0)	1/107 (0.9)	2/127 (1.6)
Potassium (mmol/L)	1/20 (5.0)	4/107 (3.7)	5/127 (3.9)
Total protein (g/L)	3/20 (15.0)	4/107 (3.7)	7/127 (5.5)
Sodium (mmol/L)	0/20 (0.0)	3/107 (2.8)	3/127 (2.4)
Uric acid (–mol/L)	0/20 (0.0)	1/107 (0.9)	1/127 (0.8)

(Source: OTR3001's study report, Table 37, page 128)
Note: N = number of patients in population groups and total
[a]Units reflected as SI units.
[b] NN = Number of patients with normal laboratory test results at baseline and laboratory test results available at the end of study; n = Number of patients with observed cases. Percentages are based on NN.

The following table shows blood chemistry parameter values that shifted from normal at baseline to high at the end of the study for the safety population.

Table 51. Shift from Normal to High From Baseline to End of Study for Blood Chemistry Parameter Values. OTR3001

Laboratory Parameter[a]	Age Groups: 6 to <12 Years (N = 27) n/NN[b] (%)	Age Groups: •12 to ”16 Years (N = 128) n/NN[b] (%)	Total (N = 155) n/NN[b] (%)
Alanine transferase (SGPT) (U/L)	4/20 (20.0)	7/107 (6.5)	11/127 (8.7)
Aspartate transferase (SGOT) (U/L)	3/20 (15.0)	4/107 (3.7)	7/127 (5.5)
Total bilirubin (–mol/L)	1/20 (5.0)	2/106 (1.9)	3/126 (2.4)
Blood urea nitrogen (mmol/L)	1/20 (5.0)	0/107 (0.0)	1/127 (0.8)
Calcium (mmol/L)	1/20 (5.0)	4/107 (3.7)	5/127 (3.9)
Bicarbonate/carbon dioxide (mmol/L)	0/20 (0.0)	1/107 (0.9)	1/127 (0.8)
Creatinine (–mol/L)	2/20 (10.0)	0/107 (0.0)	2/127 (1.6)
Blood glucose (mmol/L)	3/19 (15.8)	16/106 (15.1)	19/125 (15.2)
Lactic dehydrogenase (U/L)	0/20 (0.0)	6/107 (5.6)	6/127 (4.7)
Phosphorous/inorganic phosphate (mmol/L)	2/20 (10.0)	3/107 (2.8)	5/127 (3.9)
Total Protein (g/L)	1/20 (5.0)	0/107 (0.0)	1/127 (0.8)
Uric Acid (–mol/L)	1/20 (5.0)	0/107 (0.0)	1/127 (0.8)

(Source: OTR3001's study report, Table 37, page 128)
Note: N = number of patients in population groups and total
[a]Units reflected as SI units.
[b] NN = Number of patients with normal laboratory test results at baseline and laboratory test results available at the end of study; n = Number of patients with observed cases. Percentages are based on NN.

The following table displays a listing of patients with laboratory toxicity grades higher than grade 3 after baseline in the safety population. Toxicity grades are based on the Division of AIDS Table for Grading Severity of Adult and Pediatric Adverse Events as of December 20014 (Grade 1: Mild, Grade 3: Moderate, Grade 3: Severe, Grade 4: Potentially Life-threatening).

Table 52. Listing of Patients With Laboratory Toxicity Grades of ≥3 After Baseline

Patient Number (Sex, Age [years], Race)[a]	Laboratory Test (Unit)[b]	Starting Dose (mg)	Visit	Value*	Low	High	Toxicity Grade[c]
0105001 (M,13,W)	Hemoglobin (g/L)	10	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	78 L 86 L	116 116	148 148	3 3
	Platelet (10^9/L)	10	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	31 L 36 L	140 140	440 440	3 3
0533001 (F,14,W)	Platelet (10^9/L)	10	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	36 L 18 L	140 140	440 440	3 4
0507003 (M,16,W)	Alanine Transferase (SGPT) (U/L)	10	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	40 414 H	0 0	55 55	0 3
0507004 (F,13,W)	Platelet (10^9/L)	10	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	405 36 L	140 140	440 440	0 3
	Neutrophils absolute (10^6/L)	10	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	4950 220 L	1120 1120	7800 7800	0 4
	Phosphorus/inorg. phosphate (mmol/L)	10	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	1.52 0.74 L	0.81 0.81	1.71 1.71	0 3
0507005 (F,16,W)	Lymphocytes absolute (10^6/L)	10	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	1650 290 L	1120 1120	7800 7800	0 4
0507006 (F,10,W)	Alanine Transferase (SGPT) (U/L)	10	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	17 315 H	0 0	40 40	0 3
	Aspartate Transferase (SGOT) (U/L)	10	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	19 234 H	0 0	40 40	0 3
0801001 (F,12,W)	Hemoglobin (g/L)	20	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	111 L 88 L	116 116	148 148	0 3
0047001 (F,16,W)	Lymphocytes absolute (10^6/L)	20	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	670 L 370 L	1100 1100	5900 5900	0 3
0026002 (F,11,B)	Hemoglobin (g/L)	10	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	69 L 83 L	116 116	148 148	4 3
0071002 (M,8,W)	Phosphorus/inorg. phosphate (mmol/L)	10	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	1.03 0.74 L	0.9 0.9	2 2	1 3
0071004 (F,11,W)	Hemoglobin (g/L)	20	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	78 L 80 L	116 116	148 148	3 3
	Neutrophils absolute (10^6/L)	20	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	1289 L 70 L	1500 1500	7800 7800	1 4
0006001 (F,15,W)	Blood glucose (mmol/L)	10	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	4.3 18.7 H	3.6 3.6	5.5 5.5	0 3
0006014 (M,16,W)	Platelet (10^9/L)	50	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	190 28 L	140 140	440 440	0 3
	White Blood Cells (10^9/L)	50	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	4.93 1.18 L	4 4	12.5 12.5	0 3
	Neutrophils absolute (10^6/L)	50	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	3160 50 L	1500 1500	7800 7800	0 4
0051002 (F,14,B)	Hemoglobin (g/L)	10	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	73 L 84 L	116 116	148 148	3 3
0014001 (M,16,B)	Hemoglobin (g/L)	10	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	74 L 87 L	116 116	148 148	3 3
	Total bilibrubin (umol/L)	10	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	106 H 150 H	2 2	21 21	4 4
0014002 (M,15,W)	Lymphocytes absolute (10^6/L)	10	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	450 L 580 L	1100 1100	5900 5900	3 2
0014004 (F,14,B)	Hemoglobin (g/L)	15	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	88 L 81 L	116 116	148 148	3 3
0027001	Neutrophils absolute	20	Visit 1 (Screening/Day)	3200	1500	7800	0

Patient Number (Sex, Age [years], Race)[a]	Laboratory Test (Unit)[b]	Starting Dose (mg)	Visit	Value*	Low	High	Toxicity Grade[c]
(M,10,W)	(10^6/L)		Visit 3/EOS or Early DC (Week 4)	600 L	1500	7800	3
0080001 (F,14,B)	Hemoglobin (g/L)	20	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	80 L 82 L	116 116	148 148	3 3
	Total bilibrubin (umol/L)	20	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	53 H 60 H	2 2	21 21	3 3
0036002 (F,14,W)	Hemoglobin (g/L)	10	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	87 L 86 L	116 116	148 148	3 3
0016002 (M,9,B)	Hemoglobin (g/L)	10	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	104 L 89 L	116 116	148 148	1 3
0008004 (F,11,B)	Hemoglobin (g/L)	15	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	73 L 76 L	116 116	148 148	3 3
9007001 (F,14,B)	Blood glucose (mmol/L)	30	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	5.7 H 16.5 H	3,6 3.6	5.5 5.5	0 3
	Hemoglobin (g/L)	30	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	42 L 79 L	116 116	148 148	4 3
0009005 (F,11,W)	Hemoglobin (g/L)	10	Visit 1 (Screening/Day) Visit 3/EOS or Early DC (Week 4)	97 L 86 L	116 116	148 148	2 3

(Source: OTR3001's study report, Table 39, page 130-132)
Abbreviations: DC = discontinuation; EOS = end of study; F = female; Inorg.=inorganic; M = male.
* L = Value is below the laboratory normal range, H = Value is above the laboratory normal range.
[a]Race: W = White, B = Black or African American, N = Native Hawaiian or other Pacific Islander, A = Asian, I = American Indian or Alaska Native, O= Other
[b]Units reflected as SI units.
[c]The toxicity grading is defined by the Division of AIDS table for grading the severity of adult and pediatric adverse events as of December, 2004.

Twenty-four (15.5%) patients had a Grade 3 or above toxicity in Study OTR3001. Although this seems proportionally high, the population enrolled in this study at baseline had significant medical conditions such as malignancies and related chemotherapy, sickle cell, etc.

7.4.2.3 Study OXP1005

Mean values, mean changes, and maximum increases and decreases in individual selected laboratory values for the safety population (all ages) are contained in the table below.

Table 53. Summary of Selected Laboratory Data – Mean and Mean Changes from Baseline. Study OXP3003.

Laboratory Tests (Units)	Oxy Pediatric Liquid 1mg/mL			Total
	0.05 mg/kg (N=26)	0.1 mg/kg (N=17)	0.2 mg/kg (N= 17)	(N = 60)
Hematology				
Red Blood Cells (10^12/L)				
n	23	16	17	56
Baseline Mean (SD)	4.32 (0.82)	4.47 (0.53)	4.44 (0.79)	4.40 (0.73)
End of Study Mean (SD)	4.28 (0.61)	4.37 (0.55)	4.52 (0.82)	4.37 (0.66)
Change from Baseline				
Mean (SD)	-0.05 (0.66)	-0.11 (0.45)	0.07 (0.45)	-0.03 (0.54)
Min, Max	-1.35, 1.48	-0.94, 0.57	-0.64, 0.83	-1.35, 1.48
Hemoglobin (g/L)				
n	24	16	17	57
Baseline Mean (SD)	135.2 (24.81)	125.3 (17.45)	125.8 (22.56)	129.6 (22.42)
End of Study Mean (SD)	131.5 (23.41)	123.1 (20.38)	127.1 (23.21)	127.8 (22.42)
Change from Baseline				
Mean (SD)	-3.7 (20.85)	-2.2 (11.65)	1.4 (12.53)	-1.7 (16.26)
Min, Max	-42, 47	-23, 19	-16, 21	-42, 47
Hematocrit (fraction)				
n	24	16	17	57
Baseline Mean (SD)	0.39 (0.103)	0.37 (0.055)	0.37 (0.073)	0.38 (0.082)
End of Study Mean (SD)	0.39 (0.072)	0.37 (0.063)	0.38 (0.080)	0.38 (0.072)
Change from Baseline				
Mean (SD)	0.00 (0.085)	-0.00 (0.036)	0.01 (0.042)	0.00 (0.062)
Min, Max	-0.12, 0.28	-0.06, 0.06	-0.05, 0.08	-0.12, 0.28
Platelet (10^9/L)				
n	24	16	17	57
Baseline Mean (SD)	254.3 (95.91)	278.2 (153.86)	256.8 (115.86)	261.7 (118.59)
End of Study Mean (SD)	274.2 (103.46)	216.0 (79.14)	260.8 (86.36)	253.8 (93.84)
Change from Baseline				
Mean (SD)	19.9 (44.83)	-62.2 (160.68)	4.0 (82.66)	-7.9 (104.45)
Min, Max	-64, 113	-336, 289	-159, 176	-336, 289
White Blood Cells (10^9/L)				

Laboratory Tests (Units)	Oxy Pediatric Liquid 1mg/mL			
	0.05 mg/kg (N=26)	0.1 mg/kg (N=17)	0.2 mg/kg (N= 17)	Total (N = 60)
n	23	16	17	56
Baseline Mean (SD)	13.01 (4.85)	12.40 (4.17)	11.80 (3.70)	12.47 (4.29)
End of Study Mean (SD)	11.10 (3.49)	11.61 (3.97)	11.01 (3.49)	11.22 (3.58)
Change from Baseline				
Mean (SD)	-1.91 (3.204)	-0.79 (2.53)	-0.80 (2.63)	-1.25 (2.86)
Min, Max	-7.1, 3.5	-5.6, 3.1	-5.1, 5.0	-7.1, 5.0
Neutrophils Absolute (10^6/L)				
n	16	14	13	43
Baseline Mean (SD)	81856 (3580)	8130 (4833)	8699 (3632)	8323 (3955)
End of Study Mean (SD)	5714 (3032)	5689 (3132)	6415 (2839)	5918 (2955)
Change from Baseline				
Mean (SD)	-2472 (2917)	-2441 (4031)	-2285 (2456)	-2405 (3130)
Min, Max	-6888, 3959	-12779, 3639	-7914, 1385	-12779, 3959
Blood Chemistry				
(SGOT) Aspartate Transferase (U/L)				
n	22	15	16	53
Baseline Mean (SD)	73.6 (59.23)	96.3 (70.12)	77.9 (27.51)	81.4 (55.25)
End of Study Mean (SD)	71.9 (133.05)	52.9 (21.50)	57.5 (35.74)	62.2 (87.83)
Change from Baseline				
Mean (SD)	-1.8 (141.81)	-43.5 (65.40)	-20.4 (43.70)	-19.2 (100.61)
Min, Max	-201, 575	-227, 17	-83, 113	-227, 575
(SGPT) Alanine Transferase (U/L)				
n	22	15	16	53
Baseline Mean (SD)	25.5 (12.78)	26.9 (7.32)	24.6 (8.94)	25.6 (10.21)
End of Study Mean (SD)	31.2 (55.51)	27.1 (14.30)	26.0 (12.88)	28.5 (36.78)
Change from Baseline				
Mean (SD)	5.7 (53.92)	0.2 (12.93)	1.4 (13.14)	2.8 (35.71)
Min, Max	-30, 240	-14, 43	-12, 42	-30, 240
Total Bilirubin (umol/L)				
n	21	15	15	51
Baseline Mean (SD)	50.64 (60.32)	11.16 (6.64)	14.01 (5.62)	28.25 (42.84)
End of Study Mean (SD)	50.64 (60.32)	11.49 (8.86)	13.97 (9.07)	28.32 (54.38)
Change from Baseline				
Mean (SD)	-0.06 (36.94)	0.33 (10.02)	-0.03 (8.08)	0.06 (24.33)
Min, Max	-80.4, 132.0	-12.0, 32.0	-17.1, 15.4	-80.4, 132.0
Blood Urea Nitrogen (mmol/L)				
n	22	16	17	55

Laboratory Tests (Units)	Oxy Pediatric Liquid 1mg/mL			
	0.05 mg/kg (N=26)	0.1 mg/kg (N=17)	0.2 mg/kg (N= 17)	Total (N = 60)
Baseline Mean (SD)	4.16 (2.78)	4.39 (1.775)	4.67 (1.743)	4.39 (2.196)
End of Study Mean (SD)	4.09 (3.07)	4.25 (2.059)	3.50 (1.276)	3.96 (2.327)
Change from Baseline				
Mean (SD)	-0.08 (2.03)	-0.14 (1.943)	-1.17 (1.634)	-0.43 (1.923)
Min, Max	-6.2, 3.0	-3.9, 4.3	-3.6, 1.4	-6.2, 4.3
Creatinine (umol/L)				
n	24	16	17	57
Baseline Mean (SD)	43.47 (26.47)	29.49 (10.29)	28.27 (11.33)	35.01 (20.15)
End of Study Mean (SD)	36.49 (14.19)	27.05 (6.55)	27.14 (11.36)	31.05 (12.37)
Change from Baseline				
Mean (SD)	-6.99 (15.67)	-2.44 (6.93)	-1.12 (10.39)	-3.96 (12.31)
Min, Max	-56.0, 12.4	-14.1, 8.8	-22.2, 15.0	-56.0, 15.0

(Source: derived from OXP1005's report, Table 14.3.4.1)
Patients are only presented in the table if they have both a baseline and post-baseline value.
Baseline is defined as the last reported result before first study medication intake.
A creatinine result of 45 MMOL/L for patient 0037008 seems erroneous; unit should probably have been UMOL/L.
For patient 0047001, the hematocrit value of 2.7% in the database should have been 27% as recorded on the CRF.
Patient 0047012 has an incorrect platelet value of 2.51 x 10^9/L. The correct value would have been 251 x 10^9/L.

The following table presents data for all clinical laboratory hematologic and blood chemistry values that shifted from normal at baseline to abnormal at end of the study for the safety population.

Table 54. Shift Table for Hematologic and Blood Chemistry Parameters From Normal at Baseline to Low/High at End of Study. OXP1005

All Patients	Oxy Pediatric Liquid 1 mg/mL		
	0.05 mg/kg (N = 26)	0.1 mg/kg (N = 17)	0.2 mg/kg (N = 17)
Hematology[1] (Low/High)	13/2	5/0	4/8
Blood Chemistry[1] Liver (Low/High)	0/4	0/2	4/5
Blood Chemistry[1] Renal (Low/High)	3/2	1/1	3/0

(Source: OXP1005's study report, derived from Table 19, page 73)
[1]Hematology includes red blood cell, hemoglobin, hematocrit, platelet, white blood cells; blood chemistry liver includes aspartate transferase, alanine transferase, total bilirubin; Blood chemistry renal includes blood urea nitrogen and creatinine.
13/2 = normal to low (13) / normal to high (2)

The following table presents patient with laboratory toxicity grades ≥ 3 after baseline. Toxicity grades are based on the Division of AIDS Table for Grading Severity of Adult and Pediatric Adverse Events as of December 20014 (Grade 1: Mild, Grade 3: Moderate, Grade 3: Severe, Grade 4: Potentially Life-threatening).

Table 55. Patients With Laboratory Toxicity Grades ≥ 3 After Baseline. OXP1005

Patient Number	Laboratory Test (Units)	Oxy Pediatric Liquid Dose	Normal Local Laboratory Range	Time Point	Value	Toxicity Grade at End of Treatment
LOW						
37003	Hemoglobin (g/L)	0.05 mg/kg	105 to 135	Baseline	77	3
				EOS	83	3
34005	Hemoglobin (g/L)	0.05 mg/kg	115 to 135	Baseline	116	0
				Unplanned (Error)	0.107	4
				EOS	102	1
37004	Hemoglobin (g/L)	0.1 mg/kg	100 to 135	Baseline	103	1
				Unplanned (error)	103	1
				EOS	80	3
HIGH						
34001	Aspartate Transferase (SGOT) (U/L)[b]	0.05 mg/kg	17 to 59	Baseline	84	1
				Unplanned (error)	37	0
				EOS	659	4

(Source: OXP1005's study report, derived from Table 19, page 73)
The toxicity grading is defined by the Division Of AIDS Table For Grading Severity Of Adult And Pediatric Adverse Events as of December, 2004.
If a laboratory measurement is present but outside of the grade 1-4 range, that measurement will be coded as grade level 0.
Patient 34005 had a hemoglobin toxicity grade 4 due to an incorrectly applied lab unit (mg/dL instead of g/dL).

One patient (34001) in the 0.05 mg/kg group had an increase in AST values from grade 1 at baseline to grade 4. There were no contributing factors noted on the study report. AST levels returned to normal after the study. One patient (37004) in the 0.1 mg/kg group had a decrease in hemoglobin values from grade 1 at baseline to grade 3. There were no contributing factors noted. Levels returned to normal after the study.

7.4.3 Vital Signs

7.4.3.1 Study OXP3003

7.4.3.1.1 Blood Pressure, Pulse, and Respiratory Rate

The following table presents the mean changes in blood pressure, pulse, and respiratory rate from baseline to the end of study.

Table 56. Summary of Vital Signs Mean and Mean Changes from Baseline: Safety Population. Study OXP3003

Laboratory Tests (Units)	Placebo (N=19	Oxy Pediatric Liquid 1mg/mL 0.1 mg/kg (N=24)	Oxy Pediatric Liquid 1mg/mL 0.2 mg/kg (N= 22)	Total (N = 65)
Blood Pressure and Pulse				
Systolic Blood Pressure (mm Hg)				
n	18	23	22	63
Baseline Mean (SD)	115.4 (16.04)	115.7 (15.81)	110.3 (14.94)	113.7 (15.53)
End of Study Mean (SD)	119.1 (12.55)	115.7 (14.73)	114.0 (14.92)	116.1 (14.13)
Change from Baseline				
Mean (SD)	3.6 (15.53)	-0.0 (14.44)	3.7 (16.50)	2.3 (15.35)
Min, Max	-29, 30	-49, 19	-26, 47	-49, 47
Diastolic Blood Pressure (mmHg)				
n	18	23	22	63
Baseline Mean (SD)	65.4 (12.61)	62.0 (10.59)	62.3 (10.59)	63.1 (11.12)
End of Study Mean (SD)	69.6 (10.61)	64.0 (9.05)	62.5 (11.55)	65.1 (10.66)
Change from Baseline				
Mean (SD)	4.1 (9.05)	2.0 (10.01)	0.2 (10.55)	2.0 (9.91)
Min, Max	-17, 22	-27, 15	-16, 24	-27, 24
Temperature (Centigrade)				
n	16	22	22	60
Baseline Mean (SD)	37.10 (0.438)	37.27 (0.555)	37.18 (0.733)	37.19 (0.595)
End of Study Mean (SD)	37.09 (0.464)	37.07 (0.847)	37.05 (0.512)	37.07 (0.635)
Change from Baseline				
Mean (SD)	-0.01 (0.630)	-0.20 (0.916)	-0.12 (0.698)	-0.12 (0.761)
Min, Max	-1.5, 1.0	-2.2, 1.9	-1.4, 1.9	-2.2, 1.9

Laboratory Tests (Units)	Placebo (N=19	Oxy Pediatric Liquid 1mg/mL 0.1 mg/kg (N=24)	Oxy Pediatric Liquid 1mg/mL 0.2 mg/kg (N= 22)	Total (N = 65)
Respiratory Rate (Breaths per Minute)				
n	18	23	22	63
Baseline Mean (SD)	19.9 (3.80)	22.3 (6.38)	22.1 (4.44)	21.5 (5.11)
End of Study Mean (SD)	22.3 (4.52)	22.8 (7.38)	21.2 (3.22)	22.1 (5.38)
Change from Baseline				
Mean (SD)	2.3 (4.49)	0.5 (4.46)	-0.9 (4.25)	0.5 (4.51)
Min, Max	-4, 17	-6, 10	-9, 8	-9, 17

(Source: Derived from OXP3003's report Table 14.3.5.2, pages 587-588)

Mean changes in systolic blood pressure were comparable in the Oxy Pediatric Liquid 0.2 mg/kg and placebo groups. Mean changes in diastolic blood pressure and pulse were less in the study drug treatment groups than in the placebo group from baseline to end of study. AEs attributed to the increase in blood pressure were reported for 1 patient (26015) in the placebo group and 1 subject in the Oxy Pediatric Liquid 0.2 mg/kg (17003) treatment group.

The following table presents a summary of respiratory rates for all patients.

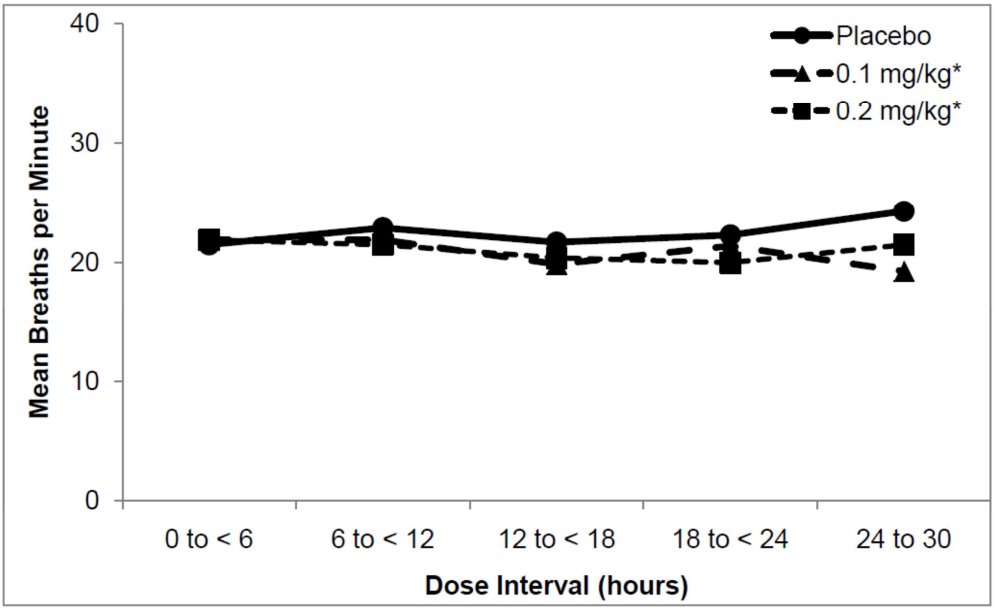
Table 57. Summary of Respiratory Rates. OXP3003

Dose Interval All Patients	Placebo (N = 19)	Oxy Pediatric Liquid 1mg/mL 0.1mg/kg (N = 24)	Oxy Pediatric Liquid 1mg/mL 0.2mg/kg N = 22)	*P* value[1]
Overall (1h Postdose Evals. Incl. 0 to <6 h)				
Mean (SD) bpm	21.4 (4.51)	22.3 (5.24)	21.1 (3.34)	
Median	21.0	21.4	21.0	
Min, Max	13, 29	14, 36	16, 31	
95% Confidence Interval	(19.2, 23.6)	(20.0, 24.5)	(19.6, 22.6)	.452/.548
Overall (6h Postdose Evals. Excl 0 to < 6h)	**n=16**	**n=21**	**n=21**	
Mean (SD) bpm	22.6 (4.80)	21.1 (4.18)	20.8 (3.98)	
Median	22.3	20.0	19.3	
Min, Max	16, 32	15, 31	15, 32	
95% Confidence Interval	(20.0, 25.1)	(19.2, 23.0)	(19.0, 22.6)	.138/.862
Overall (6h Postdose Evals. Incl. 0 to < 6h)	**N=18**	**n=23**	**n=21**	
Mean (SD) bpm	22.6 (4.33)	21.6 (4.32)	20.9 (4.20)	
Median	22.4	20.8	19.0	
Min, Max	15, 32	16, 31	15, 34	
95% Confidence Interval	(20.4, 24.7)	(19.7, 23.5)	(19.0, 22.8)	.085/.915

1 P-values bsed on asymptotic Jonckheere-Terpstra test and were provided by the Sponsor.
(Source: OXP3003's report, Table 25, page 77)

The following figure presents a summary of mean respiratory rate data by dose interval for all patients.

Figure 10. Summary of Mean Respiratory Rate Data by Dose Interval. OXP3003



(Source: OXP3003's study report, Figure 8, page 78)
*Oxy Pediatric Liquid 1mg/mL

There was no statistically significant change in mean respiratory rate for the safety population between active and placebo treatments across the 1 hour and 6 hour postdose evaluations and the mean respiratory rates were within the normal range. Two, 2 patients in the 5 to < 12 year age group (patients 36004 and 49007) had minimum rates of 10 breaths per minute (bpm) and 2 patients (36002 and 12001) had minimum rates of 12 bpm. In the 12 to ≤ 16 year age group, 3 patients (26023, 26018, and 49006) had a minimum rates of 9, 11, and 12 bpm, respectively.

In summary, there was no significant difference in mean hemoglobin-oxygen saturation values between active treatment and placebo groups and across dose intervals.

7.4.3.2 Hemoglobin-Oxygen Saturation

A summary of the number and percent of patients experiencing hemoglobin oxygen desaturation is presented on the table below.

Table 58. Hemoglobin-Oxygen Saturation Scores ≤ 90% Postbaseline. OXP3003

Dose Interval	Placebo (N = 19) n(%)	Oxy Pediatric Liquid 1mg/mL 0.1mg/kg (N = 24) n(%)	Oxy Pediatric Liquid 1mg/mL 0.2mg/kg (N = 22) n(%)
All patients			
0 to < 6 hours	1 (5.3)	0	2 (9.1)
6 to < 12 hours	2 (10.5)	0	2 (9.1)
12 to < 18 hours	1 (5.3)	0	1 (4.5)
18 to < 24 hours	2 (10.5)	0	3 (13.6)
24 to < 30 hours	0	0	1 (4.5)
Overall	3 (15.8)	0	5 (22.7)

(Source: OXP3003's report, Table 27, page 80)

Eight (12.3%) out of 65 patients had hemoglobin oxygen saturation values ≤ 90% at some time during dosing. Three of these patients were in the placebo group and 5 patients in the 0.2 mg/kg dose group. Two of the 8 patients (26006 and 35008) had values ≤ 90 % at baseline. Six patients who started the study with hemoglobin-oxygen saturation values greater than 90% had values ≤ 90% on at least 1 occasion post-baseline.

In summary, hemoglobin-oxygen saturation values were similar across treatment groups throughout the dose intervals. Eight patients experienced desaturation at some point during the study: 3 in the placebo group and 5 in the 0.2 mg/kg treatment group.

7.4.3.2 Study OTR3001

7.4.3.2.1 Blood Pressure and Pulse

The mean worst increase and worst decreases in blood pressure and pulse for the younger age cohort is summarized in the table below.

Table 59. Mean Worst Increase and Worst Decreases in Blood Pressure and Pulse: Ages 6 to <12 years. OTR3001

Vital Sign Parameter (Unit) Time Point	<3 Hours Post-dose[a]		≥3 Hours Post-dose[b]	
	Value	Change from Baseline	Value	Change from Baseline
Pulse rate (beats/min)				
Baseline				
n	26	-	0	-
Baseline Mean (SD)	98.19 (20.321)	-		-
Median	94.00	-		-
Min, Max	57.0, 142.0	-		-
Max. Post-baseline Value				
n	26	26	26	26
Baseline Mean (SD)	109.46 (20.269)	11.27 (17.064)	113.23 (20.962)	15.04 (18.780)
Median	107.50	8.00	110.50	16.00
Min, Max	72.0, 161.0	-14.0, 53.0	67.0, 156.0	-33.0, 74.0
Min. Post-baseline Value				
n	26	26	26	26
Baseline Mean (SD)	98.27 (17.194)	0.08 (14.718)	91.69 (15.753)	-6.50 (13.363)
Median	98.50	-1.00	87.00	-6.50
Min, Max	70.0, 137.0	-22.0, 36.0	67.0, 131.0	-33.0, 25.0
Systolic blood pressure (mmHg)				
Baseline				
n	26	-	0	-
Baseline Mean (SD)	110.19 (11.510)	-		-
Median	108.50	-		-
Min, Max	88.0, 139.0	-		-
Max. Post-baseline Value				
n	26	26	26	26
Baseline Mean (SD)	115.08 (9.520)	4.88 (6.470)	115.00)	7.50 (10.704)
Median	113.50	3.50	70.00	7.00
Min, Max	97.0, 139.0	-7.0, 17.0	104.0, 145.0	-10.0, 40.0
Min. Post-baseline Value				
n	26	26	26	26
Baseline Mean (SD)	104.92 (11.356)	-5.27 (6.809)	104.15 (9.797)	-6.04 (11.029)

Vital Sign Parameter (Unit) Time Point	<3 Hours Post-dose[a]		≥3 Hours Post-dose[b]	
	Value	Change from Baseline	Value	Change from Baseline
Median	103.50	-3.00	105.50	-5.50
Min, Max	77.0, 134.0	-21.0, 5.0	89.0, 133.0	-38.0, 17.0
Diastolic blood pressure (mmHg)				
Baseline				
n	26	-	0	-
Baseline Mean (SD)	65.38 (10.752)	-		-
Median	65.00	-		-
Min, Max	48.0, 91.0	-		-
Max. Post-baseline Value				
n	26	26	26	26
Baseline Mean (SD)	70.81 (8.343)	5.42 (8.358)	70.58 (10.841)	5.19 (10.598)
Median	68.50	5.00	70.00	4.00
Min, Max	60.0, 90.0	-11.0, 19.0	41.0, 94.0	-14.0, 32.0
Min. Post-baseline Value				
n	26	26	26	26
Baseline Mean (SD)	59.50 (10.001)	-5.88 (8.815)	57.42 (9.313)	-7.96 (11.837)
Median	59.50	-4.00	57.50	-3.50
Min, Max	45.0, 85.0	-21.0, 12.0	41.0, 78.0	- 40.0, 14.0

(Source: Derived from Table 40 of OTR3001's report, pages 135-137)

The mean worst increase and worst decreases in blood pressure and pulse for the younger age cohort is summarized in the table below.

Table 60. Mean Worst Increase and Worst Decreases in Blood Pressure and Pulse: Ages 12 to ≤ 16 years. OTR3001

Vital Sign Parameter (Unit) Time Point	<3 Hours Post-dose[a]		≥3 Hours Post-dose[b]	
	Value	Change from Baseline	Value	Change from Baseline
Pulse rate (beats/min)				
Baseline				
n	126	-	0	-
Baseline Mean (SD)	89.30 (15.249)	-		-
Median	89.00	-		-
Min, Max	61.0, 138.0	-		-
Max. Post-baseline Value				
n	125	125	124	124
Baseline Mean (SD)	94.82 (17.018)	5.41 (12.808)	96.47 (17.861)	7.30 (15.985)
Median	93.00	3.00	97.00	6.00

Vital Sign Parameter (Unit) Time Point	<3 Hours Post-dose[a]		≥3 Hours Post-dose[b]	
	Value	Change from Baseline	Value	Change from Baseline
Min, Max	57.0, 141.0	-35.0, 53.0	58.0, 144.0	-32.0, 61.0
Min. Post-baseline Value				
n	125	125	124	124
Baseline Mean (SD)	85.26 (15.024)	-4.14 (10.433)	82.23 (14.614)	-6.94 (14.952)
Median	84.00	-4.00	81.00	-6.50
Min, Max	57.0, 126.0	-35.0, 41.0	50.0, 126.0	-47.0, 34.0
Systolic blood pressure (mmHg)				
Baseline				
n	126	-	0	-
Baseline Mean (SD)	112.95 (13.239)	-		-
Median	113.00	-		-
Min, Max	77.0, 144.0	-		-
Max. Post-baseline Value				
n	125	125	124	124
Baseline Mean (SD)	119.28 (13.370))	6.28 (9.310)	119.08 (12.512)	6.15 (12.050)
Median	118.00	3.00	118.00	6.00
Min, Max	85.0, 152.0	-19.0, 34.0	94.0, 162.0	-38.0, 46.0
Min. Post-baseline Value				
n	125	125	124	124
Baseline Mean (SD)	108.23 (11.909)	-4.77 (9.503)	106.33 (9.453)	-6.60 (12.932)
Median	108.00	-4.00	105.50	-6.00
Min, Max	79.0, 136.0	-42.0, 27.0	80.0, 129.0	-38.0, 17.0
Diastolic blood pressure (mmHg)				
Baseline				
n	126	-	0	-
Baseline Mean (SD)	64.98 (10.291)	-		-
Median	64.00	-		-
Min, Max	38.0, 95.0	-		-
Max. Post-baseline Value				
n	125	125	124	124
Baseline Mean (SD)	68.90 (9.130)	3.95 (8.024)	69.99 (10.389)	4.97 (11.372)
Median	69.00	4.00	69.00	4.50
Min, Max	48.0, 96.0	-19.0, 26.0	44.0, 95.0	-24.0, 33.0
Min. Post-baseline Value				
n	125	125	124	124
Baseline Mean (SD)	59.99 (8.442)	-4.95 (8.276)	58.35 (8.594)	-6.67 (10.238)
Median	60.00	-5.00	59.50	-6.00
Min, Max	70.0, 137.0	-29.0, 26.0	38.0, 81.0	-41.0, 19.0

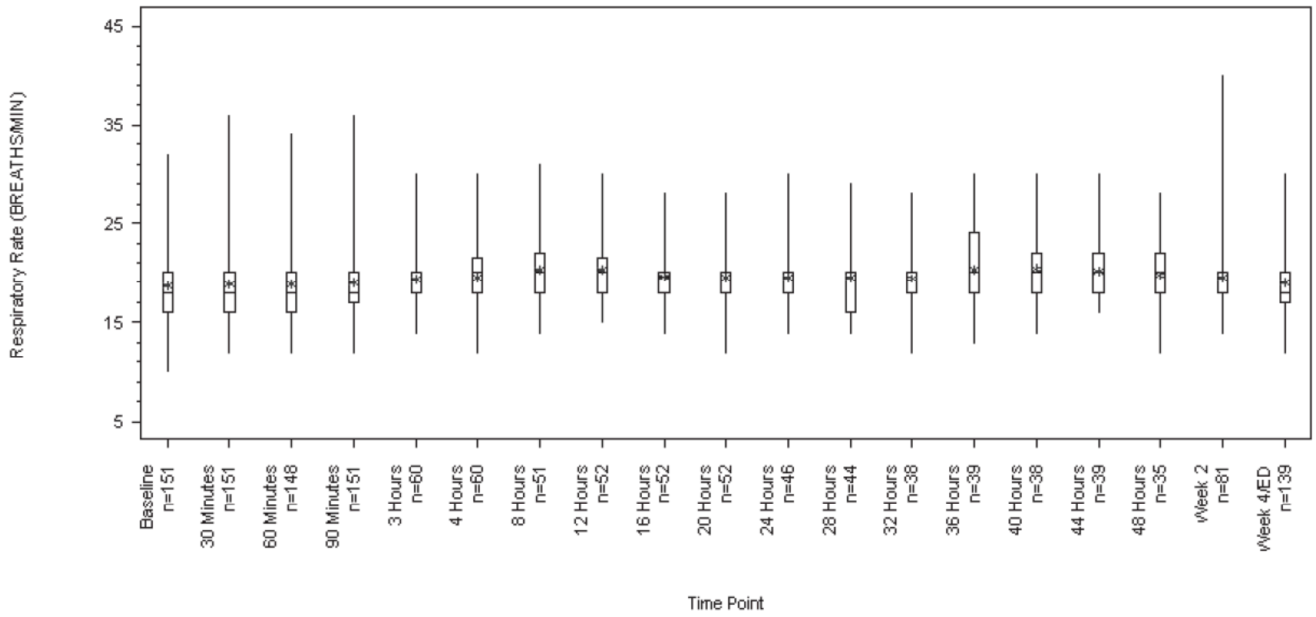
(Source: Derived from Table 40 of OTR3001's report, pages 135-137)

In summary, there were no clinically significant changes in systolic and diastolic blood pressure or pulse rate from baseline to the end of the study in any age group. Additionally, there were no TEAEs under the SOC of Investigations related to vital sign findings were reported.

7.4.3.2.2 Respiratory Rate

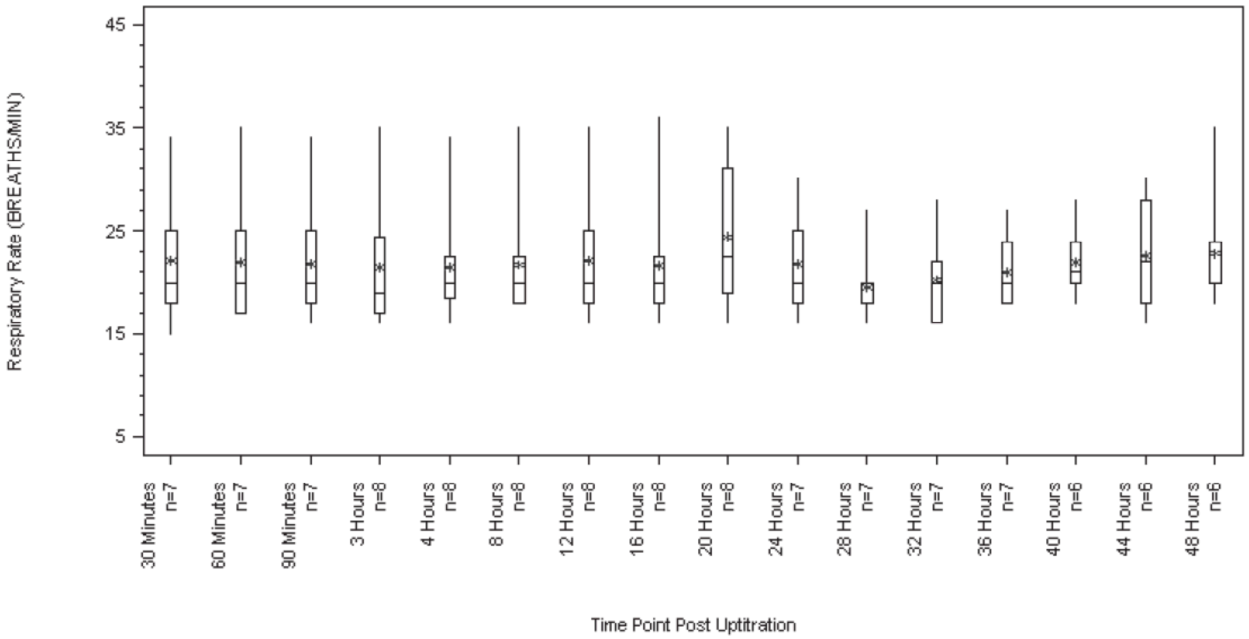
Box plots of respiratory rate over time for all scheduled timepoints and for post-uptitration only are provided in the figures below.

Figure 11. Box Plot of Respiratory Rate Over Time (Scheduled Time Points). OTR3001



The box displays median and 25%-75% quartiles. The lines extend to minimum and maximum values. The mean is indicated by an asterisk.
The time points 3 hours and 48 hours are only assessed for inpatients.
ED=early discontinuation
(Source: OTR3001's study report, Figure 3, page 139)

Figure 12. Box Plot of Respiratory Rate Over Time (Post Uptitration). OTR3001



The box displays median and 25%-75% quartiles. The lines extend to minimum and maximum values. The mean is indicated by an asterisk.
The time points 3 hours and 48 hours are only assessed for inpatients. For patients with multiple uptitrations, multiple values may contribute to the statistics at any time point.
(Source: OTR3001's study report, Figure 4, page 140)

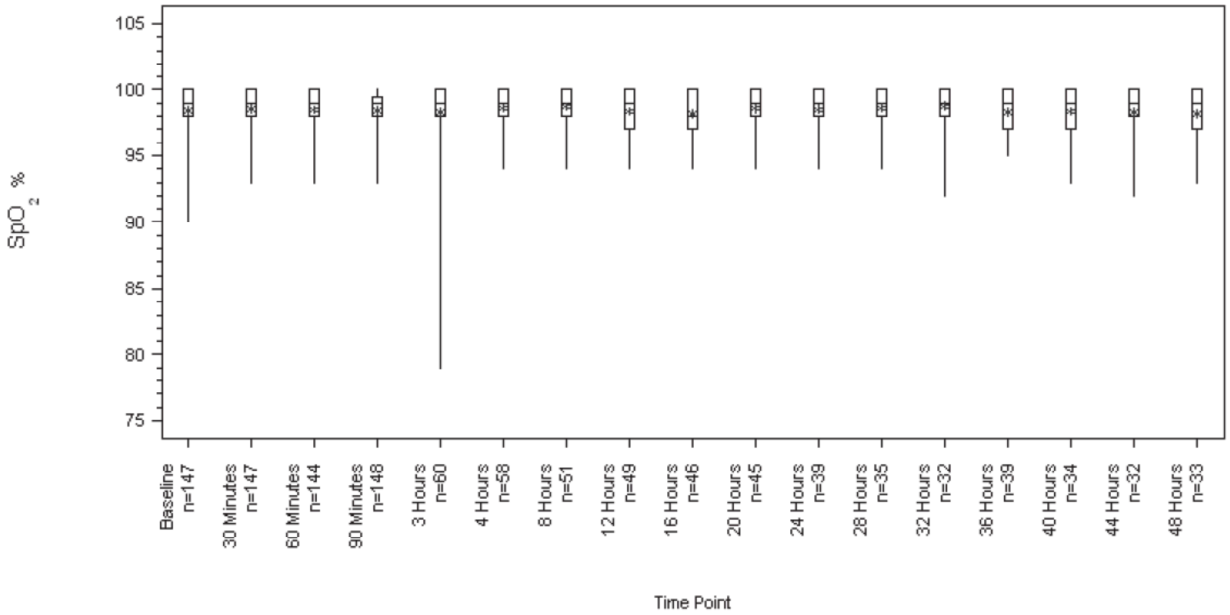
There were no patients with treatment-emergent clinically significant respiratory depression (defined as respiratory rate of ≤10 breaths per minute for patients aged over 12 years; ≤12 breaths per minute for patients aged 6 to < 12 years) in either age group or in the total safety population during the study.

7.4.3.2.3 Hemoglobin-Oxygen Saturation

There was 1 patient in the 6 to less than 12 years group and 1 patient in the 12 to 16 years group with treatment-emergent clinically significant hemoglobin-oxygen desaturations (defined as SpO_2 ≤ 90%), each of them with one episode, and each episode occurring 3 or more hours after either the first dose or uptitration. One of them was a 15 y/o female had a minimum SpO_2 of 88% 32 hours post-dose on day 5 of the study. She died on day 19 of hypoxia from her underlying neuroblastoma (patient 0513002 is discussed in section 7.3.1.1). The other one was an 11 y/o female with a minimum SpO_2 of 79% 3 hours post-dose 1 on day 1 of the study. Neither of these events resulted in a reduction of the dose or discontinuation of the study drug. There were 4 patients in the total population (2 in each age group) that experienced the TEAE of oxygen saturation decreased.

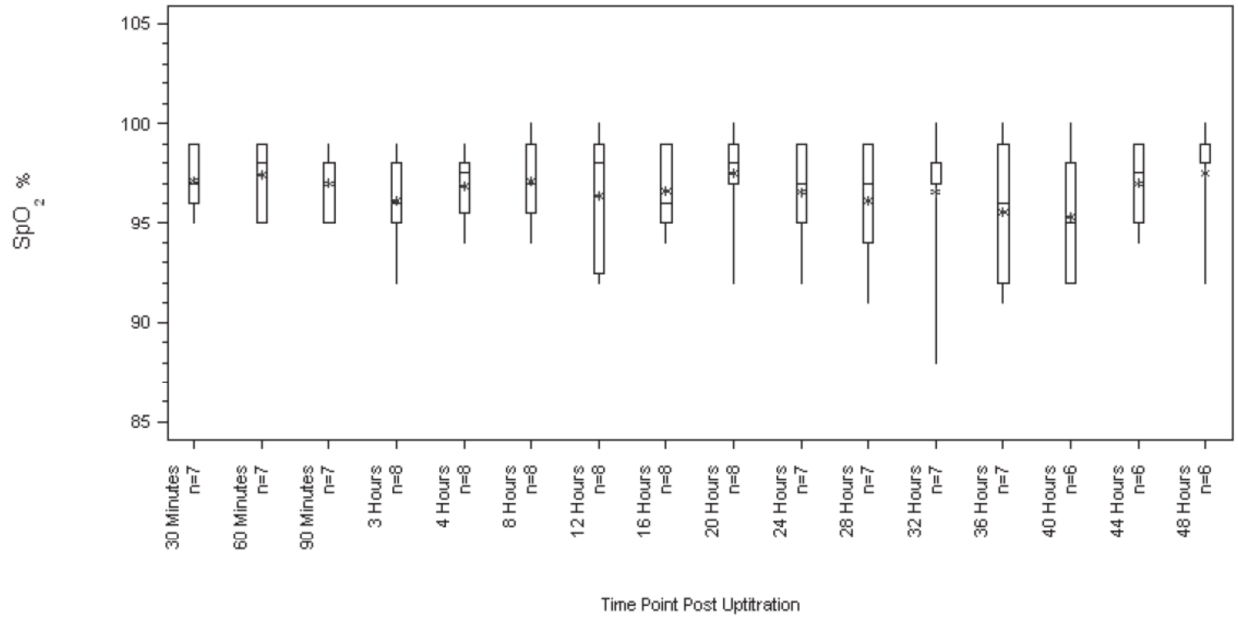
Box plots of SpO_2 over time for all scheduled time points and for post-uptitration only are provided below for the overall safety population.

Figure 13. Box Plot of SpO_2 Over Time (Scheduled Time Points). OTR3001



The box displays median and 25%-75% quartiles. The lines extend to minimum and maximum values. The mean is indicated by an asterisk.
The time points 3 hours and 48 hours are only assessed for inpatients.
(Source: OTR3001's study report, Figure 5, page 144)

Figure 14. Box Plot of SpO_2 Over Time (Post-Uptitration). OTR3001



The box displays median and 25%-75% quartiles. The lines extend to minimum and maximum values. The mean is indicated by an asterisk.
The time points 3 hours and 48 hours are only assessed for inpatients. For patients with multiple uptitrations, multiple values may contribute to the statistics at any time point.
(Source: OTR3001's study report, Figure 4, page 145)

7.4.3.3 Study OXP1005

7.4.3.3.1 Blood Pressure and Pulse

The table below summarizes the mean changes in blood pressure and pulse from baseline through the end of the study.

Table 61. Mean Changes from Baseline to End of Study in Blood Pressure and Pulse. OXP1005

Laboratory Tests (Units)	Oxy Pediatric Liquid 1mg/mL			
	0.05 mg/kg (N=26)	0.1 mg/kg (N=17)	0.2 mg/kg (N= 17)	Total (N = 60)
Hematology				
Systolic Blood Pressure (mm Hg)				
n	25	16	17	58
Baseline Mean (SD)	89.9 (19.82)	99.6 (18.71)	106.6 (14.07)	97.5 (19.09)
End of Study Mean (SD)	89.1 (15.82)	100.3 (14.26)	102.7 (11.21)	96.2 (15.29)
Change from Baseline				
Mean (SD)	-0.8 (16.21)	0.7 (13.36)	-3.9 (16.72)	-1.3 (15.47)
Min, Max	-41, 23	-20, 19	-44, 22	-44, 23
Diastolic Blood Pressure (mm Hg)				
n	25	15	17	57
Baseline Mean (SD)	53.4 (14.68)	56.3 (11.47)	57.0 (9.00)	55.2 (12.29)
End of Study Mean (SD)	52.6 (10.63)	60.0 (13.94)	59.6 (10.74)	56.7 (11.95)
Change from Baseline				
Mean (SD)	-0.8 (12.88)	3.7 (12.44)	2.6 (16.12)	1.4 (13.71)
Min, Max	-30, 18	-15, 26	-44, 27	-44, 27
Pulse (Beats per Minute)				
n	26	17	17	60
Baseline Mean (SD)	130.2 (20.25)	124.2 (16.45)	120.9 (18.08)	125.9 (18.75)
End of Study Mean (SD)	132.5 (19.17)	119.6 (20.48)	123.3 (14.45)	126.2 (18.93)
Change from Baseline				
Mean (SD)	2.3 (18.83)	-4.6 (18.46)	2.4 (12.15)	0.4 (17.11)
Min, Max	-24, 39	-53, 25	-27, 22	-53, 39

(Source: OXP1005's study report, Table 21, page 75)

The greatest mean change in systolic blood pressure was observed in the 0.2 mg/kg group (-3.9 decrease). The greatest mean changes in diastolic blood pressure (3.7 rise) and pulse (-4.6 decrease) were observed in the 0.1 mg/kg group.

7.4.3.3.2 Respiratory rates

The following table summarizes the respiratory rates for the safety population.

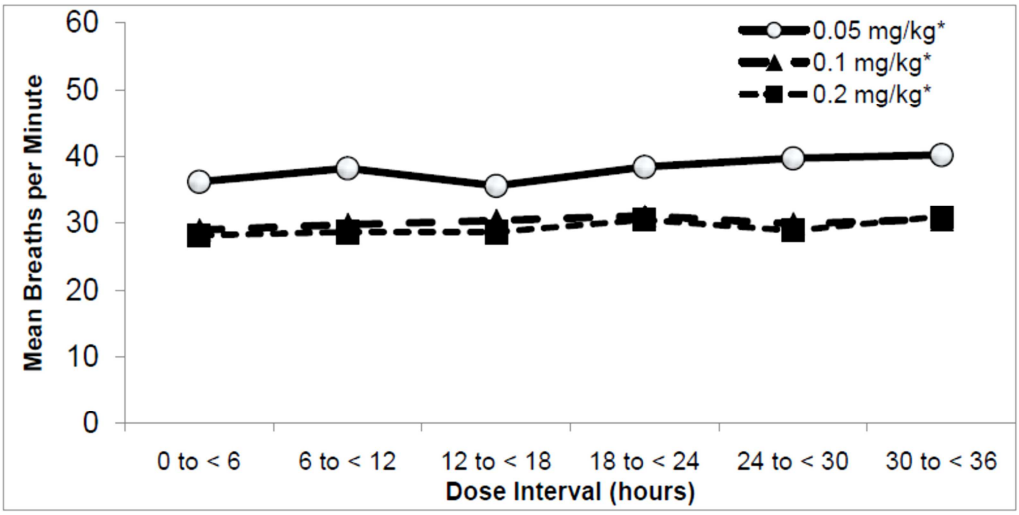
Table 62. Respiratory Rates (Breaths per Minute). OXP1005

Dose Interval All Patients	Oxy Pediatric Liquid 1mg/mL 0.05mg/kg (N = 26)	0.1mg/kg (N = 17)	0.2mg/kg N = 17)	*P* value[1]
Overall (1h Postdose Evals. Incl. 0 to <6 h)				
n	26	17	16	
Mean (SD) bpm	37.7 (13.11)	29.9 (6.32)	(26.6, 33.1)	
Median	34.8	28.7	26.4	
Min, Max	20, 67	22, 43	18, 45	
95% Confidence Interval	(32.4, 43.0)	(26.6, 33.1)	(24.6, 33.0)	.003
Overall (6h Postdose Evals. Excl 0 to < 6h)				
n	25	17	15	
Mean (SD) bpm	39.3 (12.33)	30.5 (5.86)	29.7 (9.53)	
Median	39.0	31.4	28.2	
Min, Max	19, 70	22, 41	17, 51	
95% Confidence Interval	(34.2, 44.4)	(27.4, 33.5)	(24.4, 34.9)	<.001
Overall (6h Postdose Evals. Incl. 0 to < 6h)				
n	25	17	17	
Mean (SD) bpm	38.4 (12.27)	30.2 (5.51)	29.8 (8.48)	
Median	37.5	30.5	27.7	
Min, Max	20, 70	22, 42	22, 42	
95% Confidence Interval	(33.3, 43.5)	(27.4, 33.1)	(25.5, 34.2)	.002

(Source: OXP1005's report, Table 22, page 76)
[1]P value is based on asymptotic J-T test, evaluating the hypothesis of no dose-response relationship (equality of treatments) vs the 1-sided alternative of non-(increasing/decreasing) dose-response. A significant P value means non-(increasing/decreasing) respiratory rate in higher dose groups compared to lower dose groups.
Note: Confidence intervals are presented for descriptive purposes only. Only 2 patients received optional Dose 7.

The following figure presents mean respiratory rate data by dose interval.

Figure 15. Respiratory Rates by Dose Intervals. OXP1005



(Source: OXP1005's study report, Figure 8, page 76
*Oxy Pediatric Liquid 1mg/mL

As seen above, a dose response was observed for mean respiratory rates across all dose intervals, with higher respiratory rates associated with the lowest dose (0.05 mg/kg). This could be because the neonate group (birth to 30 days) were exclusively administered the 0.5 mg/kg dose, and younger patients have higher baseline respiratory rates.

One patient (38008, discussed in more detail in Sections 7.3.2.1.3 and 7.3.3.3) was a 13-day-old white male who experienced a respiratory event (obstructive apnea neonate and tachypnea) 16 minutes postdose. The study drug was stopped permanently and the patient fully recovered after deep suctioning of thick nasal secretions, manual bag ventilation and re-intubation.

7.4.3.3.3 Hemoglobin-Oxygen Saturation

The following table summarizes hemoglobin-oxygen saturation scores.

Table 63. Hemoglobin-Oxygen Saturation. OXP1005

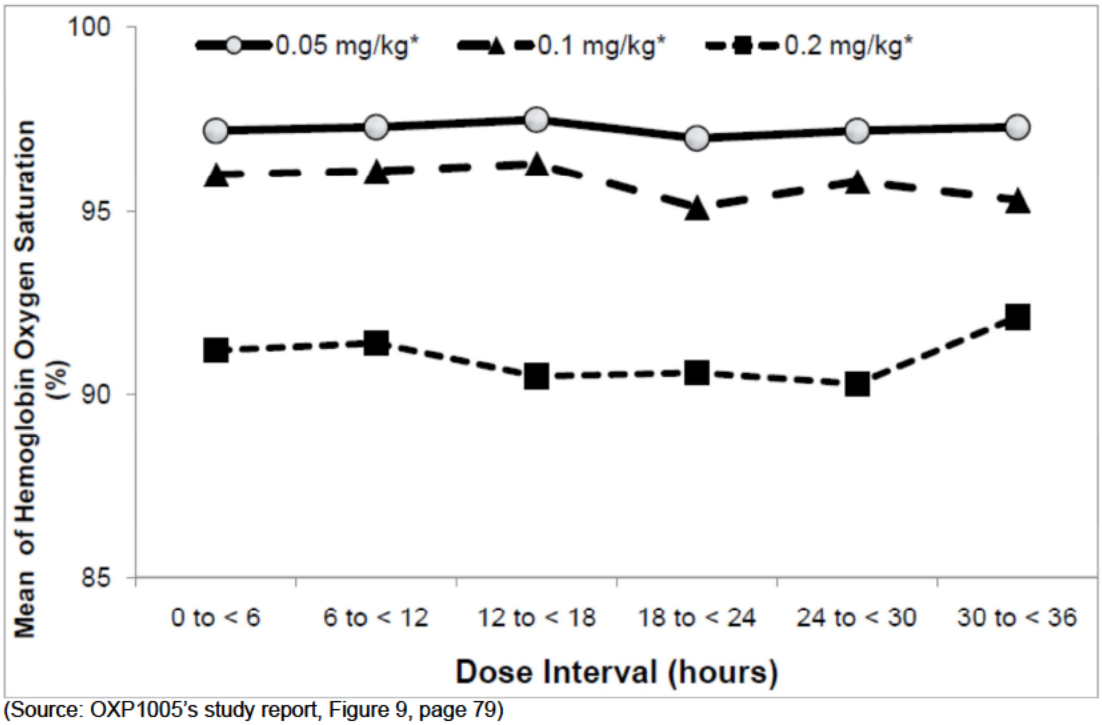
Dose Interval All Patients	Oxy Pediatric Liquid 1mg/mL 0.05mg/kg (N = 26)	0.1mg/kg (N = 17)	0.2mg/kg N = 17)	*P* value[1]
Overall (1h Postdose Evals. Incl. 0 to <6 h)				
n	26	17	16	
Mean (SD) bpm	97.3 (2.06)	97.3 (2.06)	90.0 (8.38)	
Median	97.5	97.5	95.0	
Min, Max	90, 100	80, 100	76, 98	
95% Confidence Interval	(96.5, 98.2)	(93.3, 98.5)	(85.5, 94.5)	<.001
Overall (6h Postdose Evals. Excl 0 to < 6h)				
n	25	17	15	
Mean (SD) bpm	97.2 (2.11)	96.0 (4.71)	91.1 (7.83)	
Median	97.3	97.0	94.8	
Min, Max	89, 100	82, 100	79, 99	
95% Confidence Interval	(96.3, 98.1)	(93.6, 98.4)	(86.8, 95.4)	.003
Overall (6h Postdose Evals. Incl. 0 to < 6h)				
n	25	17	17	
Mean (SD) bpm	97.3 (2.00)	96.1 (4.58)	90.6 (8.63)	
Median	97.3	97.3	95.3	
Min, Max	90, 100	82, 99	78, 100	
95% Confidence Interval	(96.5, 98.1)	(93.7, 98.4)	(86.2, 95.1)	.004

(Source: OTR1005's study report, Table 23, page 78)
P value is based on asymptotic J-T test. The test seeks to evaluate the hypothesis of no dose-response relationship (equality of treatments) vs the 1-sided alternative of non-increasing dose-response.
A significant P value means non-increasing oxygen saturation in higher dose groups compared to lower dose group.

There was a statistically significant decrease in oxygen saturation values in the 0.2 mg/kg group when compared to the other two dose groups. However, patients receiving this dose in the 31 days to less than 6 months of age had low oxygen saturation values (mean between 84% and 87%) at all dose intervals.

The following figure summarizes mean hemoglobin-oxygen saturation scores by dose interval.

Figure 16. Hemoglobin-Oxygen Saturation by Treatment Group Over Dose Intervals. OXP1005



(Source: OXP1005's study report, Figure 9, page 79)
*Oxy Pediatric Liquid 1mg/mL

The following table presents patients with SPO_2 saturation ≤90%.

Table 64. SPO_2 Saturation Scores ≤ 90% Post-Baseline. OXP1005

Dose Interval	Oxy Pediatric Liquid 1mg/mL			Total (N=60) n(%)
	0.05mg/kg (n = 26) n(%)	0.1mg/kg (n = 17) n(%)	0.2mg/kg (n = 17) n(%)	
All patients				
0 to < 6 hours	1 (3.8)	2 (11.8)	7 (41.2)	10 (16.7)
6 to < 12 hours	0	3 (17.6)	5 (29.4)	8 (13.3)
12 to < 18 hours	1 (3.8)	2 (11.8)	5 (29.4)	8 (13.3)
18 to < 24 hours	2 (7.7)	3 (17.6)	6 (35.3)	11 (18.3)
24 to < 30 hours	2 (7.7)	2 (11.8)	6 (35.3)	10 (16.7)
30 to < 36 hours	1 (3.8)	2 (11.8)	5 (29.4)	8 (13.3)
36 to < 42 hours	0	0	0	0
Overall	3 (11.5)	4 (23.5)	8 (47.1)	15 (25.0)

(Source: OXP1005's study report, Table 24, page 79)
Note: Results displayed are the number and percentage of patients at each time interval with a hemoglobin-oxygen saturation score ≤ 90%..

Fifteen (25%) out of the 60 patients in the safety population experienced SPO2 desaturation values of ≤ 90% during Study OXP1005. However, it should be noted that 8 of these patients started the study with SpO2 values already ≤ 90% and these values remained below this cutoff until the end of the study. Seven patients who started the study with hemoglobin-oxygen saturation values > 90% had values ≤ 90% on at least 1 occasion post-baseline.

7.4.4 Electrocardiograms (ECGs)

No electrocardiogram data was submitted for evaluation.

7.4.5 Special Safety Studies/Clinical Trials

No human special safety studies were conducted to support this NDA.

7.4.6 Immunogenicity

No human immunogenicity studies were conducted to support this NDA.

7.5 Other Safety Explorations

7.5.1 Somnolence

7.5.1.1 OXP3003

The table below presents a summary of average somnolence scores in the safety population.

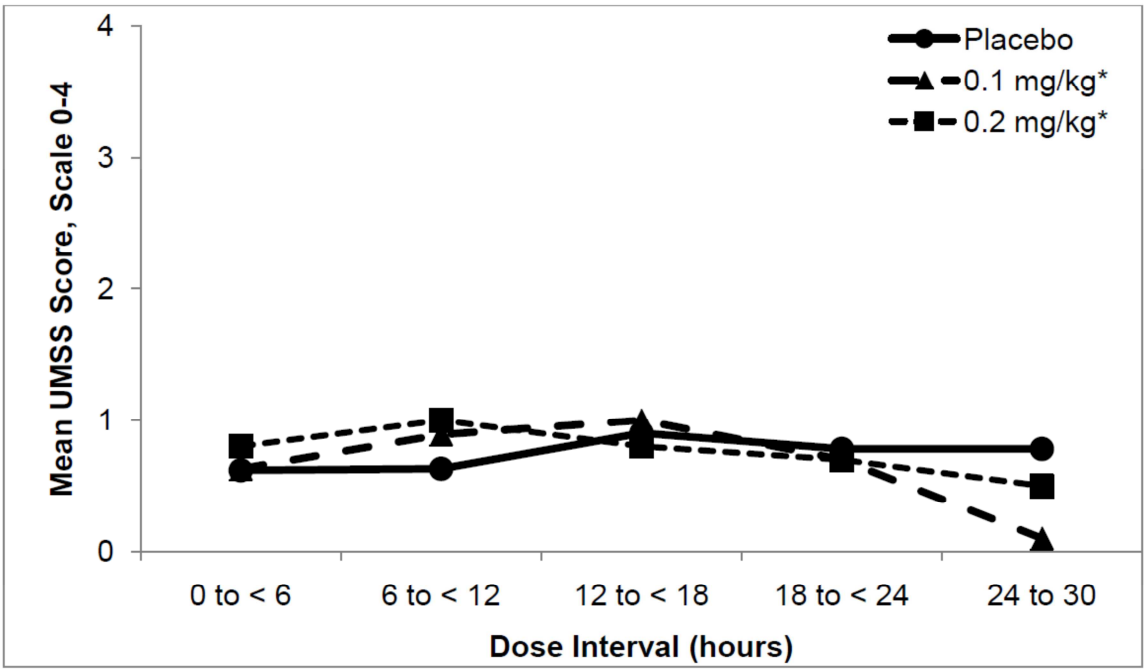
Table 65. Summary of Average Somnolence Scores. OXP3003

Dose Interval All Patients	Placebo (N = 19)	Oxy Pediatric Liquid 1mg/mL 0.1mg/kg (N = 24)	Oxy Pediatric Liquid 1mg/mL 0.2mg/kg N = 22)	*P* value[1]
Overall (1h Postdose Evals. Incl. 0 to <6 h)	**n=19**	**n=24**	**n=21**	
Mean (SD)	0.7 (0.38)	0.8 (0.71)	0.8 (0.65)	
Median	0.8	0.8	0.8	
Min, Max	0, 1	0, 3	0, 3	
95% Confidence Interval	(0.5,0.9)	(0.5,1.1)	(0.5,1.1)	.522
Overall (6h Postdose Evals. Excl 0 to < 6h)	**n=16**	**n=21**	**n=21**	
Mean (SD)	0.7 (0.38)	0.7 (0.66)	0.8 (0.70)	
Median	0.7	0.7	0.7	
Min, Max	0, 1	0, 3	0, 3	
95% Confidence Interval	(0.5,0.9)	(0.4,1.0)	(0.4,1.1)	.636
Overall (6h Postdose Evals. Incl. 0 to < 6h)	**N=18**	**n=23**	**n=21**	
Mean (SD)	0.7 (0.35)	0.7 (0.57)	0.8 (0.64)	
Median	0.8	0.6	0.6	
Min, Max	0, 2	0, 2	0, 3	
95% Confidence Interval	(0.6,0.9)	(0.5,1.0)	(0.5,1.1)	.524

(Source: OXP3003's study report, Table 29, page 82)
[1]P value is based on asymptotic Jonckheere-Terpstra test.
Note: Somnolence Scores: 0 = Awake/alert, 1=Minimally sedated, 2=Moderately sedated, 3=Deeply sedated, 4=Unarousable.

As seen in above, the mean somnolence scores were low (below 1) for all patients in the active and placebo treatment groups.

Figure 17. Somnolence Scores by Treatment Group over Dose Intervals. OXP3003



(Source: OXP3003's study report, Table 29, page 82).
*Oxy Pediatric Liquid 1mg/mL

There were 8 (13.3%) patients who experienced somnolence scores of ≥ 3 following the first dose or following multiple dosing. One patient (17002), who began the study with a somnolence score of 0, had a single score of 4 one hour after the second dose, but the scores ranged from 0 to 1 for the remainder of the study. Two patients (36002 [discussed in Sections 7.3.2.1.1, 7.3.3.1, 7.4.2.1, and 7.4.3.1.1] and 17004 [discussed in Section 7.3.2.1.1]) began the study with a score of 3, and had scores ranging from 2 to 3 during the first dose interval and for the remainder of the study. Three patients (36003, 26009, and 17003) began the study with scores < 3, then had a score of 3 at some time during the 0 to <6 hour dose interval. Two of these (26009 and 17003) had scores of < 3 for the remainder of the study. Two patients (26024 and 30001) had predose scores <3 and scores were less than 3 following the first dose interval, but had a single score of 3 during the rest of the study.

In summary, the mean somnolence scores for the 1 hour and 6 hour post-dose evaluations overall were low (less than 1), with no significant difference between dose groups. One patient had a somnolence score of 4.0.

7.5.1.2 OTR3001

There were no patients with treatment-emergent clinically significant somnolence events. There was 1 (3.7%) patient in the younger cohort and there were 2 (1.6%) patients in the older cohort with somnolence scores 3 (deeply sedated) at any point during treatment. No patient had a somnolence score of 4 (unarousable) at any point during the study.

7.5.1.3 OXP1005

The table below presents a summary of average somnolence scores in the safety population.

Table 66. Somnolence Scores. OXP1005

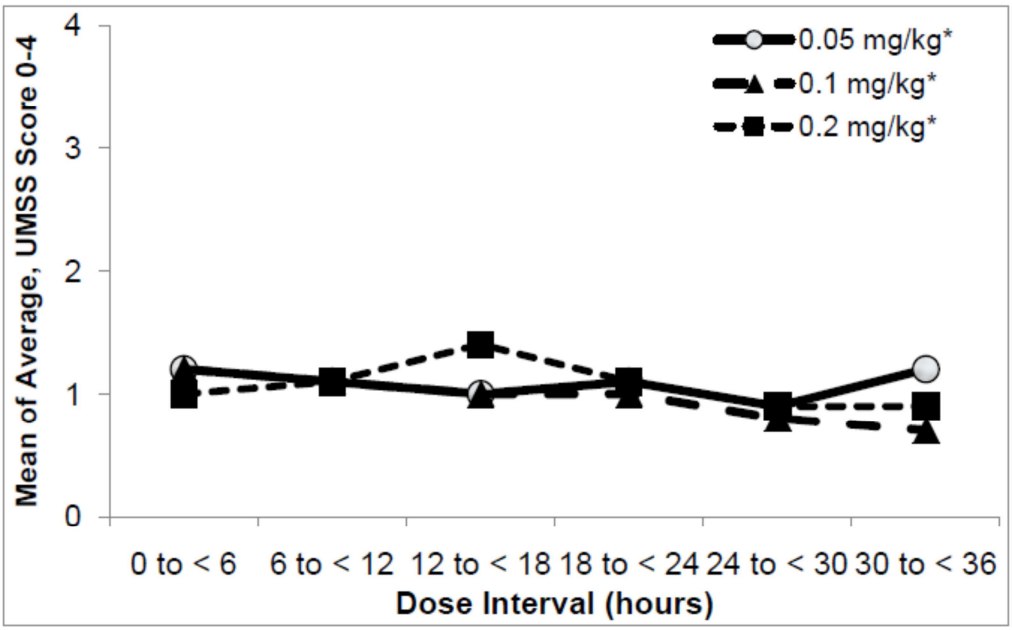
	Oxy Pediatric Liquid 1mg/mL			
Dose Interval All Patients	**0.05mg/kg (N = 26)**	**0.1mg/kg (N = 17)**	**0.2mg/kg N = 17)**	***P* value[1]**
Overall (1h Postdose Evals. Incl. 0 to <6 h)				
n	26	17	17	
Mean (SD)	1.2 (0.59)	1.0 (0.52)	1.2 (0.62)	
Median	1.2	0.8	1.2	
Min, Max	0, 2	0, 2	0, 2	
95% Confidence Interval	(1.0,1.4)	(0.8,1.3)	(0.8,1.5)	0.648
Overall (6h Postdose Evals. Excl 0 to < 6h)				
n	25	17	15	
Mean (SD)	0.9 (0.66)	0.9 (0.72)	1.0 (0.61)	
Median	0.8	0.8	1.0	
Min, Max	0, 3	0, 3	0, 2	
95% Confidence Interval	(0.6,1.2)	(0.5,1.2)	(0.7,1.4)	0.344
Overall (6h Postdose Evals. Incl. 0 to < 6h)				
n	25	17	17	
Mean (SD)	1.0 (0.61)	0.9 (0.55)	1.0 (0.65)	
Median	1.0	0.8	0.8	
Min, Max	0, 3	0, 2	0, 2	
95% Confidence Interval	(0.7, 1.2)	(0.6, 1.2)	(0.6, 1.3)	0.627

c
Confidence intervals are presented for descriptive purposes only. Only 2 patients received optional dose 7.
Somnolence Scores: 0 = awake/alert; 1 = sleepy/responds appropriately; 2 = somnolent/arouses to light stimuli; 3 = deep sleep/arouses to deeper physical stimuli; and 4 = unarousable to stimuli.

Mean somnolence scores for all patients across all dosing intervals at 1h post-dose evaluations (including 0 to < 6h) ranged from 1.0 to 1.2 (sleepy/responds appropriately), and at 6 h post-dose evaluations (including 0 to < 6 h) ranged from 0.9 to 1.0.

The figure below presents a mean of average somnolence scores by dose interval.

Figure 18. Somnolence scores by Dose Intervals. OXP1005



(Source: OXP1005's study report, Figure 10, page 82)
*Oxy Pediatric Liquid 1mg/mL

Three (5%) out of the 60 of the patients who came into the study with somnolence scores of 1 to 2 during the first 6 hours increased to a score of 3 by the end of the study. Twelve (20% patients came into the study with somnolence scores from 0 to 2, later increased to 3 at some time during the study at least once but later returned to score of 0 to 2 at the end of the study.

In summary, mean somnolence scores for all patients across all dosing intervals remained low and were similar among the 3 pediatric age groups: at 1h postdose evaluations (including 0 to < 6h) ranged from 1.0 to 1.2 (sleepy/responds appropriately), and at 6 h postdose evaluations (including 0 to < 6 h) ranged from 0.9 to 1.0.

7.5.1 Dose Dependency for Adverse Events

Only in Study OXP3003 were subjects randomized to a fixed dose for the duration of the study. Although it only had a relatively small number of subjects and it was of short duration, this is the only study that can provide some controlled data regarding the study drug dose dependency for AEs. The table included in Section 7.4.1.1, titled "TEAEs Occurring in ≥2 Patients", displays the most common AEs sorted by dose. The preferred term pyrexia was the most common AE and occurred almost three times more commonly in patients randomized to Oxy Pediatric Liquid 0.2 mg/kg than in those randomized to 0.1mg/kg or placebo, although the incidence was similar between placebo and 0.1mg/kd dose. The only other preferred term that stands out when comparing placebo, Oxy Pediatric Liquid 0.1 mg/kg and 0.2mg/kg, is constipation, which did not occur on any patients in the placebo or 0.1mg/kg groups but occurred in 2 (9.81%). Again, although Study OXP3001 provides us with controlled data, the small number of enrolled patients limits any conclusions derived from this analysis.

7.5.2 Time Dependency for Adverse Events

Because of the significant study design (acute vs. chronic use, baseline medical conditions) and age differences in the patients participating in these studies, it is difficult to make a time dependence analysis for adverse events. However, we can look at the AE data from Study OTR3002 (the extension study for patients who had completed OTR3001) and compare it with the core study (OTR3001) in order to gain some insights into how long-term exposure (i.e., months) to OxyContin compares against 2-4 week use in regards to adverse events. One limitation of this approach is that only 23 subjects were enrolled in OTR3002. Another limitation is that, because it recruits from patients who completed OTR3001, the population for OTR3002 is enriched for patients who are relatively tolerant of the test drug. Nevertheless, I have constructed the following table which shows the most common AEs in both studies.

Table 67. Comparison of Common TEAEs in Studies OTR3001 and OTR3002

System Organ Class Preferred Term	OTR3001		OTR3002	
	6 to <12 Years (N=27) n (%)	≥12 to ≥16 Years (N=128) n (%)	6 to <12 Years (N=9) n (%)	≥12 to ≥16 Years (N=23) n (%)
Any TEAEs	**19 (70.4)**	**89 (69.5)**	**8 (88.9)**	**8 (57.1)**
Gastrointestinal disorders	**12 (44.4)**	**51 (39.8)**	**3 (33.3)**	**2 (14.3)**
Vomiting	6 (22.2)	28 (21.9)	2 (22.2)	2 (14.3)
Nausea	3 (11.1)	20 (15.6)	1 (11.1)	1 (7.1)
Constipation	4 (14.8)	12 (9.4)	1 (11.1)	1 (7.1)
Diarrhoea	3 (11.1)	5 (3.9)	0	1 (7.1)
General disorders and administration site conditions	**9 (33.3)**	**28 (21.9)**	**5 (55.6)**	**5 (35.7)**
Pyrexia	6 (22.2)	12 (9.4)	3 (33.3)	2 (14.3)
Nervous system disorders	**3 (11.1)**	**36 (28.1)**	**2 (22.2))**	**1 (7.1)**
Headache	3 (11.1)	19 (14.8)	1 (11.1)	1 (7.1)
Dizziness	0	12 (9.4)	0	0
Skin and subcutaneous tissue disorders	**4 (14.8)**	**22 (17.2)**	**2 (22.2)**	**3 (21.4)**
Pruritus	3 (11.1)	7 (5.5)	1 (11.1)	0

(Source: Constructed from OTR3002's study report Table 14.3.1.1.2 and OTR3001's study report Table 25)
Note: Patients who experienced 2 or more adverse events within the same SOC or preferred term were counted only once.

The most frequently observed TEAEs during the core and extensions studies combined were in the SOCs of gastrointestinal disorders (vomiting, 6 patients, 26.1%; nausea, 5 patients, 21.7%; constipation, 4 patients, 17.4%; and diarrhoea, 4 patients, 17.4%), general disorders and administration site conditions (pyrexia, 6 patients, 26.1%, and fatigue, 3 patients, 13.0%), nervous system disorders (headache, 5 patients, 21.7%, and somnolence, 4 patients, 17.4%), and skin and subcutaneous tissue disorders (pruritus, 3 patients, 13.0%). No other SOCs had TEAEs that were reported by ≥ 10% of patients.

Of the TEAEs observed in the core and extension studies combined, the most frequently reported TEAEs considered by the investigators to be treatment-related included: gastrointestinal disorders (including constipation, 4 patients, 17.4%; nausea, 3 patients, 13.0%; vomiting, 3 patients, 13.0%; and diarrhoea, 2 patients, 8.7%), general disorders and administration site conditions (including fatigue, 3 patients, 13.0%), and nervous system disorders (including headache, 4 patients, 17.4% and somnolence, 3 patients, 13.0%). Most of the TEAEs were considered mild or moderate in intensity; only 3 patients (13.0%) experienced TEAEs that were considered by the investigators to be severe in intensity, of which 1 (4.3%) experienced a TEAE of fatigue that was considered related to treatment.

7.5.3 Drug-Demographic Interactions

Please see Dr. Srikanth C. Nallani's Clinical Pharmacology Review.

7.5.4 Drug-Disease Interactions

No new data was submitted.

7.5.5 Drug-Drug Interactions

No new data was submitted

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No new human carcinogenicity studies were submitted with this NDA.

7.6.2 Human Reproduction and Pregnancy Data

No new human reproduction/pregnancy data was submitted with this NDA.

7.6.3 Pediatrics and Assessment of Effects on Growth

No assessments of the effects on growth for the test drug were conducted.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Although drug accountability and assessments for drug diversion were conducted, no formal evaluations were done to address these issues.

7.7 Additional Submissions / Safety Issues

Not applicable.

8 Postmarket Experience

8.1 Introduction and Background

Purdue has submitted a pediatric postmarketing experience report for OxyContin, spanning from the original approval of the product in 1995 through June 30, 2014. As previously discussed, a reformulated, abuse-deterrent, OxyContin was approved in 2010 and the original version was discontinued later that year. Thus, this report covers two similar but different products, with potentially different safety profiles, particularly in regards to how it affects certain pediatric subpopulations (e.g., adolescents and substance misuse and abuse). At the present time, (b) (4)

Because the current OxyContin label does not recommend its use in patients younger than 18 years of age the vast majority of the adverse events (AEs) contained within the international drug safety database result from off-label use (e.g., drug abuse, intentional overuse), medication errors, and accidental and in-utero exposures to the drug.

In addition to covering two different OxyContin formulations, one major limitation of this postmarketing experience report is that cases received from the RADARS (Researched Abuse, Diversion and Addiction-Related Surveillance) system and entered into the worldwide safety contained minimal data, preventing any practical assessment of the medical relevance of any given occurrence. The RADARS system was designed by Purdue in 2002 to track and analyze patterns of opioid drug abuse, not to track individual cases. RADARS operations were transferred from the Sponsor to Rocky Mountain Poison and Drug Center (RMPDC) in 2006. Since that transfer, Purdue no longer receives or has access to individual cases from the Poison Control Center's Study, or from any other component of the System.

The search of the worldwide safety database (Argus) performed does not include "Not Complete Information" cases. That is, it excludes potential adverse event reports lacking at least 1 of the 4 for core elements required (i.e., patient, reporter, suspect product, and AE).

8.2 Results

The search for this postmarketing experience report of the international drug safety database identified a total of 2,411 pediatric cases (1,727 serious, 684 non-serious) involving 5,069 AEs (2,924 serious, 2,145 non-serious) as summarized on the table below.

Table 68. Worldwide Postmarketing Cases by Seriousness and Reporter Source

Reporter Type	Serious	Non-Serious	Total
Health care provider	867	462	1,329
Non-health care provider	860	222	1,082
Total	**1,727**	**684**	**2,411**

(Source: OxyContin Pediatric Postmarketing Experience report, page 3)

The breakdown by country of incidence, report source, age group, and gender of these 2,411 postmarketing cases is provided below.

Table 69. Worldwide Postmarketing Cases; Breakdown by Country of Incidence, Report Source, Age Group, and Gender

Worldwide Safety Database Breakdown	Number of Cases (N=2,411)
Country of Incidence (COI)	
United States	2,320
Canada	45
Australia	17
United Kingdom	8
Germany	4
France	4
Japan	4
Norway	3
China	2
Ireland	1
Denmark	1
Italy	1
Philippines	1
Total	2,411
Report Source	
Spontaneous	1,412
Post Marketing Study*	934
Literature	39
Regulatory Authority	19

Worldwide Safety Database Breakdown	Number of Cases (N=2,411)
Other	7
Total	**2,411**
Age Group	
Adolescent (13 to < 18 years)	1,609
Child (1 year to < 13 years)	651
Infant (1 month to < 1 year)	85
Neonate (< 1 month)	66
Total	**2,411**
Gender	
Male	1,156
Female	844
Unknown	411
Total	**2,411**

(Source: OxyContin Pediatric Postmarketing Experience report, constructed from various tables, pages 3-4). *Includes 931 RADARS® cases, 2 (non-company) postmarketing study cases, and 1 IPAP case.

The vast majority or 96% of the cases in the report are from the United States, 59% were spontaneous in nature, and 67% involved adolescent patients. The most common events in the pediatric postmarketing experience report varied with the age of the pediatric subjects. Drug abuse, overdose and dependence were the most common events in adolescents. Accidental exposures and medication errors were most common in children and infants. Fetal exposures and drug withdrawal syndrome were the most common events in neonates. The majority (88%) of the drug abuse cases in adolescents and the cases associated with a fatal outcome in both adolescent patients (91%) and children (80%) involved the original (non-abuse-deterrent) formulation of OxyContin.

As discussed earlier within this section, the 2,411 OxyContin cases involved a total of 5,069 AEs. The 5,069 AEs included 2,145 non-serious AEs, of which 929 were unlabeled, and 2,924 serious AEs, of which 646 were unlabeled. The most common SOCs were: Psychiatric Disorders (N=1,449), Injury, Poisoning and Procedural Complications (N=1,293), Nervous System Disorders (N=636), General Disorders and Administration Site Conditions (N=384), Social Circumstances (N=235), and Gastrointestinal Disorders (N=229).

The Sponsor presented a list with the most common MedDRA preferred terms with more than 50 occurrences. However, overlapping or similar preferred terms when separated this way may fail to make the threshold, giving us a very limited (and perhaps too optimistic) overview of real-world patient experiences. For example, dyspnoea (26), hypoxia (3), hypopnoea (5), respiratory depression (25), respiratory depth decreased

(1), respiration abnormal (3), respiratory disorder (6), tachypnoea (2) and hypoventilation (2) are preferred terms given to similar clinical events. Although these terms do not mean the exact same thing, they are closely related and if we were to apply a clinical lens when looking at them, the differences may become mostly semantic. Respiratory problems become even more apparent if we include the terms such as respiratory arrest (31), apnoea (10), or death (44). Of course, respiratory depression is a well-known opioid potential problem, particularly with relatively higher doses, but the point is that we would have missed this if we only relied on listing adverse events which exceeded 50 events. In fact, the Respiratory, thoracic, and mediastinal disorders SOC did not even make it into the most common SOCs for the reported preferred terms. The intent is just to point out the limits of this approach.

I have constructed the following table of the most common preferred terms (PTs) with a threshold of a minimum of 30 occurrences, in order to increase sensitivity.

Table 70. Summary of Pediatric AEs by Seriousness and Labeling from Marketing Through June 30, 2014 (per US Package Insert).

SOC MedDRA Preferred Term	Non-serious Listed	Non-serious Unlisted	Serious Listed	Serious Unlisted	Total Events
Eye disorders	**54**	**31**	**22**	**16**	**123**
Miosis	54	0	21	0	75
Gastrointestinal disorders	**182**	**13**	**33**	**1**	**229**
Nausea	45	0	13	0	58
Vomiting	110	0	16	0	126
General disorders and administration site conditions	**156**	**91**	**56**	**81**	**384**
Death	0	0	0	44	44
Drug withdrawal syndrome	25	0	14	0	39
Drug withdrawal syndrome neonatal	4	10	20	3	37
Malaise	42	4	8	0	54
Injury, poisoning and procedural complications	**139**	**448**	**161**	**706**	**1293**
Accidental exposure to product	6	278	14	85	383
Accidental exposure to product by child	1	80	28	21	130
Accidental overdose	1	0	118	1	120
Fetal exposure during pregnancy	15	2	15	8	40
Intentional overdose	11	0	37	1	49
Medication error	0	41	0	8	49
Overdose	91	0	323	3	417
Nervous system disorders	**336**	**36**	**177**	**87**	**636**
Coma	0	1	38	16	55
Lethargy	39	0	18	0	57
Loss of consciousness	1	3	22	15	41
Somnolence	182	0	33	0	215
Tremor	22	1	11	0	34
Psychiatric disorders	**180**	**74**	**1166**	**29**	**1449**
Drug abuse	2	1	568	0	571

SOC MedDRA Preferred Term	Non-serious Listed	Non-serious Unlisted	Serious Listed	Serious Unlisted	Total Events
Drug dependence	0	0	268	1	269
Euphoric mood	57	0	1	0	58
Social circumstances	**4**	**46**	**158**	**27**	**235**
Drug abuser	0	0	155	1	156
Legal problem	0	40	0	0	40

(Resource: Derived from Attachment 2 of the Pediatric Postmarketing Experience)
Individual cases may contain more than 1 PT per case.

It seems odd that a specific preferred term could have both, listed and unlisted non serious AEs or listed and unlisted serious AEs. For example, "Drug withdrawal syndrome neonatal" has serious listed, serious unlisted, non-serious listed, and non-serious unlisted reported AEs. One possible explanation for this is that the postmarketing report includes cases dating back to the original approval of OxyContin in 1995 and the label has gone through various revisions since. As a clear example of this, since the reformulated OxyContin was approved in 2010, there have been 8 label revisions. Therefore, it is possible that some of these AEs may have been unlabeled at the time they were reported and labeled at a later time as changes in the label occurred.

Similarly, there also seems to be a significant number of unlisted events. The most common preferred terms within these unlisted events are: accidental exposure (279), accidental exposure by child (80), death (44), medication error (41), and legal problems (40). It should be noted that the three most common unlisted AEs, as per this postmarketing report, are included in the current label for OxyContin.

As mentioned above, the most common SOC for the reported AEs was "Psychiatric disorders". By far, the most common PTs within this SOC were drug abuse (571), substance dependence (296), and drug dependence (269) – polysubstance dependence (7) is closely related to these. Drug abuser (156) is virtually indistinguishable from these PTs but was reported under a different SOC. Because adolescents are a group at increased risk of suicidal behavior and oxycodone is a centrally acting substance, I searched PTs within the Psychiatric disorders SOC that could be associated with this type of behavior: completed suicide (6), suicidal ideation (2), and suicidal attempt (7). Intentional overdose (49) was found under a different SOC but should be part of the suicidal behavior assessment. Intentional overdose alone is 2.0% of all cases included in this report. Mood altered (2), mood swings (2), depression (7), irritability (19), aggression (20), and agitation (25) can be all be symptoms associated with Mood disorders in children and adolescents. In general, the vast majority of the PTs in this SOC were related to substance abuse/misuse. The relative low count of suicidal/parasuicidal behaviors and mood disturbances is somewhat reassuring but may warrant some discussion within the label.

8.2.1. Adolescents (13 to 17 years of age)

A total of 1,609 cases in adolescents (13 to < 18 years) were identified in the worldwide drug safety database; 159 cases (10%) originated via the US news media.

Table 71. Most Common Postmarketing AEs in Adolescents

Preferred Term (PT)	No. of Cases in Adolescents (N=1,609)
Drug abuse	546 (33.9%)
Overdose	343 (21.3%)
Substance abuse	291 (18.1%)
Drug dependence	231 (14.4%)
Drug abuser	155 (9.6%)
Somnolence	114 (7.1%)
Accidental overdose	87 (5.4%)
Vomiting	81 (5%)
Euphoric mood	57 (3.5%)
Nausea	50 (3.1%)

(Source: OxyContin Pediatric Postmarketing report, page 5)
Individual cases my contain more than 1 PT per case

The most commonly reported adverse events in the adolescent age group involved drug or substance abuse/misuse, overdose and drug dependence. Most of the events of overdose were associated with reports of abuse, drug dependence and / or accidental exposures.

The reports of drug abuse (N=546), substance abuse (N=291), and drug abuser (N=155) involved a total of 969 unique cases. However, the vast majority of the cases involved the original formulation of OxyContin (N=853; 88%).

Approximately 31% (N=296) of the 969 unique cases involved the use, misuse of multiple licit / illicit drugs and/or alcohol.

A total of 342 of the 1,609 adolescent cases were associated with a fatal outcome. Most involved the original formulation of OxyContin (N=312; 91%). “With the exception of 24 cases (23 cases involving the PT of “death” (i.e. cause of death unknown, not reported), 12 of which were received via the RADARS system, and 1 case of diabetic ketoacidosis in a 17-year-old male taking an unknown brand of oxycodone for an unspecified indication (USA-2003-0010021)), all of the fatalities were associated with reports of drug abuse, substance abuse, and/or overdose (accidental, intentional). Seventy eight (78) of the fatalities (23%) involved the use of multiple licit / illicit drugs.”

8.2.2 Children (1 to 12 years of age)

A total of 651 cases in children were identified in the worldwide drug safety database and will be summarized in the table below.

Table 72. Most Common Postmarketing AEs in Children

Preferred Term (PT)	No. of Cases in Children (N=651)
Accidental exposure to product	335 (51.5%)
Accidental exposure to product by child	123 (18.9%)
Somnolence	93 (14.3%)
Overdose	59 (9.1%)
Vomiting	42 (6.5%)
Medication error	34 (5.2%)
Miosis	34 (5.2%)
Accidental overdose	32 (4.9%)
Lethargy	29 (4.5%)
Drug abuse	25 (3.8%)

(Source: OxyContin Pediatric Postmarketing report, page 6)
Individual cases my contain more than 1 PT per case

The most common events in children involved accidental exposures, medication errors, known opioid-related adverse events (e.g. vomiting, and lethargy), and signs and symptoms associated with overdose (e.g. somnolence, miosis). All of the overdose cases were associated with reports of accidental exposures, medication errors and/or drug abuse/misuse; or contained limited information (as to the details surrounding the event).

The number of medication errors (5.2%) is concerning but there is no explanation from the Sponsor and I have no data to further explore this high incidence of medication errors.

Eighty of the 651 cases in children were associated with a fatal outcome. “With the exception of 10 cases (9 cases involving the PT of “death” (i.e., cause of death unknown, not reported), 4 of which were received via the RADARS® system, and 1 case involving a 5-year-old female child with cerebral palsy who died of [suspected] aspiration pneumonitis and was found to have oxycodone and codeine in the cerebral spinal fluid, urine, cardiac and vitreous humor (USA-2006-0025849); all of the fatalities were associated with reports of accidental exposure (N=36) or overdose (N=33). Five (5) of the overdoses involved multiple drugs, 5 other cases involved child abuse / homicide, and 1 other case involved drug abuse.”

Sixty-four (80%) of all the fatal cases involved the original OxyContin formulation, including 2 cases in which the child chewed the OxyContin tablet (USA-2008-0036349 and USA-2008-0036350). None of the reformulated OxyContin cases (N=16; 20%) involved tampering with or chewing the tablet.

8.2.3 Infants (1 month old to less than 1 year old)

A total of 85 cases in infants were identified in the worldwide drug safety database and will be summarized in the table below.

Table 73. Most Common Postmarketing AEs in Infants

Preferred Term (PT)	No. of Cases in Infants (N=85)
Accidental exposure to product	27 (31.8%)
Foetal exposure during pregnancy	13 (15.3%)
Drug withdrawal syndrome neonatal	13 (15.3%)
Overdose	12 (14.1%)
Drug dependence	10 (11.8%)
Somnolence	7 (8.2%)
Accidental exposure to product by child	7 (8.2%)
Miosis	7 (8.2%)
Tremor	5 (5.9%)
Drug withdrawal syndrome	5 (5.9%)

(Source: OxyContin Pediatric Postmarketing report, page 6)
Individual cases my contain more than 1 PT per case

As seen in the table above, the most common events in infants involved accidental exposures, fetal exposures during pregnancy, neonatal drug withdrawal syndrome, overdose, and drug dependence (which in the context of this population, I presume it means from maternal exposure). All but 5 of the accidental exposure and overdose cases involved the original OxyContin formulation.

Fourteen of the 85 cases in infants were associated with a fatal outcome. “With the exception of 3 cases (2 cases involving the PT of “death“, i.e., cause of death unknown, not reported) and 1 case of sudden infant death syndrome (SIDS) in a 2-month-old female infant (USA-2011-0067602); all of the fatalities were associated with reports of accidental exposure or overdose.” Four of the overdose cases involved victims of homicide.

8.2.4 Neonates (birth to less than 1 month old)

A total of 66 cases in neonates were identified in the worldwide drug safety database and will be presented in the table below.

Table 74. Most Common Postmarketing AEs in Neonates

Preferred Term (PT)	No. of Cases in Neonates (N=66)
Drug withdrawal syndrome neonatal	23 (34.8%)
Foetal exposure during pregnancy	20 (30.3%)
Drug dependence	20 (30.3%)
Irritability	5 (7.6%)
Drug withdrawal syndrome	5 (7.6%)
Premature baby	5 (7.6%)
Crying	4 (6.1%)
Overdose	3 (4.5%)
Low birth weight baby	3 (4.5%)
Exposure during breast feeding	3 (4.5%)

(Source: OxyContin Pediatric Postmarketing report, page 8)
Individual cases my contain more than 1 PT per case

As seen above, the most common adverse events in neonates involved fetal exposures during pregnancy and the resulting drug-dependence and drug-withdrawal syndrome, along with associated events including irritability and crying.

Seven of the 66 cases in neonates were associated with a fatal outcome and will be discussed below:

- Three cases involved US news media reports of suspected homicide/intentional overdose (USA-2002-0001288, USA-2014-0112874, and USA-2007-0030694).
- One case involved an 8 ½ month old stillborn fetus exposed to oxycodone in utero (USA-2007-0026708). The report was received from a relative of the baby's mother. The coroner's report stated that the baby's drug screen was negative.
- One case involved a report of sudden infant death syndrome (SIDS) in a 1-day-old newborn whose mother used OxyContin during the pregnancy (USA-2011-0079878). This spontaneous report was received from an attorney in the context of an OxyContin litigation case. No medical history or concomitant medications were received. This event occurred in 2006 although the report was received in 2011. Additional information is being requested by the Sponsor.
- One case involved a newborn, born with gastroschisis, who died in the hospital after 4 days and whose mother was addicted to oxycodone (USA-2013-0101804). This spontaneous report was received from a US journalist. Per the media report, the mother was addicted to oxycodone while pregnant and was prescribed

methadone, although no further specifics were given. Additional information is being requested by the Sponsor.

- One case involved a premature female infant who tested positive for oxycodone and cocaine and expired after about a day of life (USA-2007-0027590). This spontaneous report was received via US news media. The baby was born 3 months prematurely. The mother and the baby tested positive for oxycodone and cocaine.

8.2.5 Discussion

The postmarketing reports contained within the international drug safety database largely comprise AEs resulting from off-label use (such as drug abuse and intentional misuse), medication errors, accidental exposures, and in-utero exposures.

The majorities of the pediatric cases originated domestically or in the United States (96%), were spontaneous (59%), and involved adolescent patients (67%). The most common AEs involved known opioid-related events (or consequences of known events) such as drug abuse, overdose, drug dependence, somnolence, nausea, vomiting, and lethargy. The most frequent events varied by age group. In adolescents, AE reports of drug abuse, overdose and substance dependence were the most common. In children and infants, accidental exposure and medication errors were the most commonly reported AEs. In neonates, the most commonly reported AEs were fetal exposures during pregnancy, drug dependence and neonatal withdrawal syndrome. The majority of the cases in all age groups were a consequence of drug abuse. The original formulation accounted for the majority of drug abuse cases in adolescents (88%) and in fatal cases (91% in adolescents and 80% in children). Although this may seem as reinforcing the abuse-deterrent claims of reformulated OxyContin, it could simply be due to the fact that out of two decades that OxyContin has been marketed in the United States, the reformulated version has been available less than 25% of that time.

In general, two things stand out in the review of the postmarketing data. The first is the relative high frequency of unexplained “medication errors”. Although a large number of AEs reported within the Psychiatric disorders SOC are related to substance abuse and misuse, when taken as a whole mood disturbances and related suicidal and parasuicidal behaviors are not insignificant, particularly in an adolescent population that is statistically at risk for such psychiatric problems. Therefore, I recommend that some language describing these should be added to the label.

9 Appendices

9.1 Literature Review/References

1. **Pediatric Analgesic Clinical Trial Designs, Measures, and Extrapolation: Report of an FDA Scientific Workshop** Charles B. Berde, *et al*. Pediatrics peds.2010-3591; published ahead of print January 16, 2012, doi:10.1542/peds.2010-3591

9.2 Labeling Recommendations

The following recommendations points are recommended for labeling consideration by the clinical team:

- (b) (4)
- Because OxyContin was exclusively studied in patients who were opioid-tolerant and the current label discusses the use of OxyContin in opioid-naïve adult patients, the pediatric indication should include specific language highlighting the indication is for opioid-tolerant pediatric patients (i.e., patients already receiving and tolerating a minimum of 20mg of OxyContin per day of its equivalent for at least 5 days.
- Guidance regarding the initial dosing of OxyContin should include the conversion table used during the conduct of Study OTR3001 (Table 13), modified to reflect the opioids most commonly used during the study (Table 14), as we have limited or no data on some of the opioids in the original conversion table.
- In contrast to the titration and dose adjustment language in adults (i.e., the dose can be increased by 25-50% of the total daily OxyContin dose), the titration language for pediatric patients should be consitent to the language in the protocol for OTR3001 (25% of the total daily dose).
- As discussed in the Postmarketing Experience results (Section 8.2), the majority of AEs reported fall in the Psychiatric disorders SOC. The vast majority of these are substance abuse/misuse-related. When taken as a whole, unlabeled preferred terms related to suicidal/parasuicidal behavior (completed suicide, intentional overdose, suicide attempt, suicidal ideation) and mood disorders (mood altered, irritability, aggression) seem to warrant inclusion in the Postmarketing experience of the label.

9.3 Advisory Committee Meeting

No Advisory Committee Meeting was held for this supplemental application.

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/s/

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05/15/2015

JOHN J FEENEY
05/18/2015