PURDUE PHARMA L.P.

NDA 206830 Avridi™ (Immediate-Release Oxycodone Hydrochloride) Tablets

Advisory Committee Briefing Materials

For

Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee

On

September 10, 2015

ADVISORY COMMITTEE BRIEFING MATERIALS:

AVAILABLE FOR PUBLIC RELEASE

EXECUTIVE OVERVIEW

Immediate-release (IR) single-entity oxycodone is among the most commonly prescribed Schedule II opioids for the management of acute and chronic moderate to severe pain. Data on oxycodone utilization over time, duration of IR single-entity oxycodone use, and distribution of the number of tablets per day indicate that the use of IR single-entity oxycodone products for analgesia is extensive, widespread, and continues to grow.

Due to the high prescription rates, IR single-entity oxycodone products are likely to be found in many households in the United States, thus providing an increased risk for diversion, misuse, and abuse. The high prevalence of abuse of IR single-entity oxycodone by injecting and snorting, as shown in epidemiologic data, have a substantially increased risk of serious negative health outcomes relative to oral administration.

Avridi ™ (OCI) is a new IR single-entity oxycodone product designed with abuse-deterrent properties intended to deter IV and IN abuse as well as providing a similar safety and efficacy profile as currently available nonabuse-deterrent IR single-entity oxycodone products such as Roxicodone tablets, when taken as directed. The proposed indication for Avridi is for the management of acute and chronic moderate to severe pain where the use of an opioid analgesic is appropriate.

In accordance with FDA guidance to the industry on abuse-deterrent formulations (FDA Guidance to Industry: *Abuse-Deterrent Opioids- Evaluation and Labeling,* April 2015), Purdue has conducted comprehensive laboratory-based *in vitro* and clinical abuse potential studies. The *in vitro* studies show that, in contrast to Roxicodone, Avridi has physicochemical properties (gelling and local aversive effects) that present barriers to physical and chemical manipulations to deter abuse by the IV and IN routes. The clinical abuse potential study in recreational opioid users showed that IN administration of crushed Avridi is associated with significantly higher nasopharyngeal irritation and other local aversive effects, resulting in significantly lower drug liking in contrast to Roxicodone and placebo.

In accordance with the Section 505(b)(2) pathway for approval of a new drug application, the clinical development program for Avridi tablets relied on clinical studies that evaluated the bioequivalence of Avridi and the reference listed drug, Roxicodone, to establish therapeutic equivalence. A clinical study involving fasted subjects showed that Avridi is bioequivalent to Roxicodone with regard to rate and extent of absorption, and thus therapeutically equivalent, ie, as safe and effective as Roxicodone.

In the clinical study in which subjects were fed a high fat, high calorie meal, Avridi is bioequivalent to Roxicodone in terms of extent of absorption but is associated with lower peak oxycodone concentrations and a delay in time to reach peak oxycodone concentrations. In light of these results and to ensure that administration of Avridi produces oxycodone concentrations that are in the range of those resulting from administration of Roxicodone, the full prescribing information will instruct that Avridi should be administered in the fasted state. In addition, Purdue proposes targeted education, including specific dosing information aimed at pharmacists. The risk evaluation and mitigation program will monitor safety as well as misuse/abuse.

To evaluate whether patient noncompliance with the dosing instructions could lead to potential safety concerns, pharmacokinetic modeling of 3 Avridi dosing scenarios were performed, reflecting the "real world" use of IR single-entity oxycodone. For all dosing scenarios, the projected maximum oxycodone exposures from administration of Avridi with and without food were comparable to those defined by equivalent Roxicodone regimens. Therefore, it is appears that for those patients who do not follow the dosing instructions and take Avridi without regard to food, the safety risk is likely not to be clinically significant.

In conclusion, Avridi has a favorable benefit: risk profile at least as good as Roxicodone and available generic IR single-entity oxycodone products. Purdue's proposed risk evaluation and mitigation plans should ensure that the anticipated positive benefit:risk profile is maintained after approval.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AE	adverse event
AERS	adverse event reporting system
API	active pharmaceutical ingredient
ASI-MV	Addiction Severity Index-Multimedia Version
AUC	area under the plasma concentration-time curve
AUCinf	area under the plasma concentration-time curve extrapolated to infinity
AUCt	area under the plasma concentration-time curve from hour 0 to the last measurable plasma concentration
AUE	area under the effect curve
BE	bioequivalence
BMI	body mass index
CI	confidence interval
Cmax	maximum observed plasma concentration
CSR	clinical study report
CYP	cytochrome P450
DEQ	Drug Effects Questionnaire
ECG	Electrocardiogram
Emax	maximum (peak) effect
Emin	minimum effect
ER	extended-release
ER/LA	extended-release/long-acting
FDA	Food and Drug Administration
h	hour
IN	intranasal
IR	immediate-release
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MPC	maximum pupil constriction
NDA	new drug application
NPDS	National Poison Data System
OAS	Opioid Attractiveness Scale
OCI	Avridi™ (immediate-release oxycodone HCl) tablets
ORF	reformulated OxyContin®
PAOC	pupillometry area over the effect curve
PD	pharmacodynamic
PK	pharmacokinetic(s)

q	every
RADARS	Researched Abuse, Diversion and Addiction-Related Surveillance
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAMHSA	Substance Abuse and Mental Health Services Administration
SD	standard deviation
SDV	subjective drug value
SE	single-entity
SLS	sodium lauryl sulfate
SRAI	subject-rated assessment of irritation
t1/2	apparent terminal phase half-life
TEAE	treatment-emergent adverse event
Tmax	time to maximum observed plasma concentration
US	United States
VAS	visual analog scale
VPS	Value of Product Scale
WHO	World Health Organization

1 PRODUCT RATIONALE

Pain is a common problem in the United States, with an estimated 90 million Americans per year reporting pain, based on data from national surveillance surveys (Blackwell, 2014). Of these, approximately 66 million people report chronic pain due to arthritis and other long-term illnesses, and 35 million report transient pain due to conditions such as injury or surgery, with some patients reporting both chronic and acute pain. Opioid analgesics are one effective option for treating this high-prevalence condition and are recommended for the management of moderate to severe pain. For that reason, immediate-release (IR) opioid analgesics are dispensed to approximately 75 million and extended-release (ER) opioid analgesics to approximately 4 million patients in the United States (US) per year (FDA 2012a).

Oxycodone is marketed in the US for use as an analgesic as single-entity (IR and ER) and IR combination products (eg, oxycodone in combination with acetaminophen, aspirin, or ibuprofen). Use of IR oxycodone-containing products for analgesia in the US is widespread, with approximately 15.6 million prescriptions for IR single-entity oxycodone annually, and there has been a marked increase in the number of prescriptions and amount dispensed of IR single-entity oxycodone products since 2010 (IMS Health 2011-2013). The majority of use is acute, with 86% of commercially insured and 75% of Medicaid insured patients receiving prescriptions for < 30 days. A large number of patients are prescribed IR single-entity oxycodone for long-term treatment, including at higher doses, although long-term use represents a small proportion of overall use, with 6.5% and 13.2% of commercially insured and Medicaid insured patients, respectively, receiving treatment for ≥ 90 days (Truven Marketscan Commercial and Medicaid Claims, data on file). Long-term use can consist of an IR single-entity opioid as the sole opioid or in conjunction with an ER opioid product. In this latter situation, the IR opioid is typically used as needed to treat breakthrough pain. Thus, IR single-entity oxycodone, like other IR opioids, is prescribed in different distinct situations depending on the pain condition being treated.

Though effective at treating pain when used appropriately, opioids can be abused, and the abuse of opioids has resulted in a substantial public health burden in the United States. In 2013, an estimated 1.9 million people reported dependence or abuse of opioids (SAMHSA, 2014). The abuse of opioids contributes to substantial societal costs, estimated at approximately $58 billion in 2011 (Kirson, 2014), with annual direct incremental healthcare cost increases of over $10,000 for opioid abusers compared to nonabusers (Rice 2014; Rossiter 2014). In recent years, multiple efforts to reduce opioid abuse have been implemented, including prescription monitoring programs (PMPs), the extended-release/long-acting (ER/LA) opioid class risk evaluation and mitigation strategies (REMS), continuing education courses on safe opioid prescribing, patient education through Medication Guides, law enforcement efforts, insurance company prescription vigilance, and development of opioid formulations with abuse-deterrent properties (OADPs) (Raffa 2010; Romach 2013; Schaeffer 2012, Harris 2014). Studies assessing the impact of abuse-deterrent opioids have shown reductions in abuse of opioids with abuse-deterrent properties (Cicero 2015, Butler 2013, Severtson 2013, Havens 2014, Coplan 2013, Sessler 2014). The combination of the introduction of some abuse-deterrent opioids with other abuse-reduction efforts have demonstrated some success in moderating the trend in increasing prescription opioid abuse that was noted beginning in the late 1990's (LaRochelle 2015). In recent years, reports of opioid abuse have leveled off and possibly started to reverse (Dart 2015). Even so, approximately 4.5 million individuals aged 12 and older

reported past month nonmedical use of opioids in 2013, and 1.5 million reported initiating nonmedical use of these drugs, suggesting that more effort is needed to address the public health problem of opioid abuse (SAMHSA 2014).

While there are some opioid analgesics with abuse-deterrent properties, having additional opioids with abuse-deterrent properties is an important way to reduce abuse of prescription opioids and their public health impact while preserving analgesic benefits for patients (Hays 2003; Raffa 2010). The FDA has stated that it "considers the development of these products a high public health priority," and in April 2015 issued a final Guidance to Industry titled, *Abuse-Deterrent Opioids- Evaluation and Labeling*, for the development of these formulations.

While ER opioids have been the primary focus for the development of formulations with properties intended to deter abuse, IR opioids with abuse-deterrent properties are also needed in order to have a sustained and meaningful impact on opioid abuse in the general population. To develop an IR single-entity oxycodone formulation with abuse-deterrent properties, it is important to consider routes of abuse. Administration by intranasal (IN) and intravenous (IV) routes is typically more prevalent in experienced abusers (Butler 2010; Hays 2003; Hays 2004; Katz 2011), although many individuals start with oral abuse and progress from oral to chewing, snorting, and injecting (Hays 2003). Among individuals entering substance abuse treatment programs, IN and IV abuse of IR single-entity oxycodone is common (NAVIPPRO ASI-MV, Section 5).

The IN and IV routes of abuse have a significantly increased risk of morbidity and mortality relative to oral intact administration, including overdose, addiction and death , blood-borne bacterial and viral infection (including HIV), and nasal/palatal necrosis and perforation (Katz 2011; Surratt 2011). As a result, IN and IV routes remain important targets in the development of formulations with properties intended to deter abuse.

Although there have been other attempts to develop IR oxycodone formulations designed to deter abuse, none at present have label claims around expected deterrence of abuse. OXAYDO™ (formerly Oxecta™) is an approved IR oxycodone product formulated with excipients designed to deter IN and IV abuse; however, labeling for this product only includes study descriptions, not claims around anticipated abuse-deterrent properties. This product has only two doses (5 and 7.5 mg tablets) and has had a limited number of prescriptions since its approval (<1000) in 2011 (IMS Health NPA 2014). The impact of its introduction on IR oxycodone abuse is challenging to assess, in part due to the limited number of prescriptions and paucity of publicly available product-specific postmarket data. Of note, labeling for this product indicates that administration of the product with food causes a delay in time to maximum observed plasma concentrations (Tmax) from 1.25 to 3.00 hours.

There is an important public health priority for the development of an IR oxycodone product with abuse-deterrent properties to reduce the risk of abuse. Avridi is formulated with multiple tablet strengths (5 mg, 10 mg, 15 mg, 20 mg, and 30 mg) to provide prescribers the flexibility to individualize the dose specific to their patients' needs, designed with aversive and gelling agents to deter abuse via the IN and IV routes, and has been rigorously tested to assess its abuse-deterrent properties. Avridi tablets will provide an appropriate alternative to nonabuse-deterrent IR single-

entity oxycodone products, while still providing a treatment option for patients with moderate to severe pain when the use of an opioid analgesic is appropriate.

2 AVRIDI CLINICAL DEVELOPMENT PROGRAM

The clinical development program for Avridi tablets was conducted to support a Section 505(b)(2) new drug application according to the recommendations of the FDA Draft Guidance for Industry: *Applications Covered by Section 505(b)(2)*, October 1999. The clinical studies determined the therapeutic equivalence (ie, the safety and effectiveness of Avridi) by demonstrating bioequivalence to the reference listed drug IR oxycodone, Roxicodone. Based on the 505(b)(2) application and relying on the approved safety and effectiveness of Roxicodone, no additional safety or efficacy studies were required.

The primary development goal for Avridi was to reduce the IV and IN abuse potential of IR oxycodone. This was accomplished by including a combination of gelling agents that deter IV abuse by producing a viscous gel when a whole or crushed tablet is dissolved in aqueous media, and inclusion of an aversive agent (sodium lauryl sulfate) that deters IN abuse by producing temporary aversive effects when the crushed tablet is administered by the IN route. The laboratory-based *in vitro* manipulation and extraction studies (Category 1) and clinical abuse potential study (Category 3) conducted to demonstrate Avridi's abuse-deterrent properties are consistent with FDA's guidance on the evaluation of abuse-deterrent opioids (FDA Guidance to Industry: *Abuse-Deterrent Opioids – Evaluation and Labeling,* April 2015). These studies are presented in Section 5.

The clinical development program for Avridi tablets comprised 5 clinical pharmacology trials designed to assess bioequivalence to the reference listed drug, Roxicodone, assess Avridi's abuse-deterrent properties, and sodium lauryl sulfate's safety and tolerability.

- Study OCI1001, a pilot study, evaluated multiple formulations with different levels of excipients to optimize the formulation in terms of pharmacokinetics (PK) and abuse potential. The final Avridi formulation was not included.
- Study OCI1002 evaluated the bioequivalence (BE), safety, and tolerability of Avridi tablets vs those of the reference listed drug, Roxicodone tablets, in fasted healthy subjects.
- Study OCI1003 evaluated the BE, safety, and tolerability of Avridi tablets vs those of the reference listed drug, Roxicodone tablets, after a high fat meal in healthy subjects.
- Study OCI1005 evaluated the abuse potential, pharmacodynamics (PD), and PK of IN administration of crushed Avridi tablets vs those of IN administration of crushed Roxicodone tablets, IN administration of placebo powder, and oral administration of intact Avridi tablets in opioid abusers who were not physically dependent.
- Study OCI1008 evaluated the safety and tolerability of placebo tablets containing sodium lauryl sulfate vs those of placebo tablets not containing sodium lauryl sulfate after oral administration in healthy subjects.

The study populations consisted of healthy male and female subjects. The abuse potential study enrolled healthy subjects with relevant opioid experience.

Exposure to study drug is presented by individual study in Table 1.

Table 1 Overview of Exposure to Avridi, Roxicodone, and Placebo

	Number of subjects					
Study	**Avridi (OCI)**		**Roxicodone**		**Placebo**	
	Intact tablet oral admin	**Crushed tablet IN admin**	**Intact tablet oral admin**	**Crushed tablet IN admin**	**Tablet**	**IN Powder**
1001 [a,b] Formulation Finding	49[c]	71 [d]	48	0	0	42
1002 Fasted BE	52 (received single 15-mg dose with; naltrexone blockade)	0	53 (received single 15-mg doses with naltrexone blockade)	0	0	0
1003 Fed BE	53 (received single 15-mg doses with naltrexone blockade)	0	55 (received single 15-mg doses with naltrexone blockade)	0	0	0
1005[a] IN Abuse Potential	36 (received a single 30-mg dose)	35 (received a single 30-mg dose)	0	35 (received a single 30-mg dose)	35 (received a single dose)	36
1008[e] Safety and Tolerability of SLS	0	0	0	0	24 (placebo with SLS) 24 (placebo without SLS)	0

BE = bioequivalence; IN = intranasal; SLS=sodium lauryl sulfate.
[a] Data are from the treatment phase
[b] This was a formulation finding study; the final formulation was not studied.
c Multiple OCI formulations were administered. There were a total of 337 single-dose exposures to oral intact OCI among the 49 subjects.
[d] Multiple OCI formulations were administered There were a total of 191 single-dose exposures to intranasal OCI among the 71 subjects.
[e] Only placebo tablets were administered. Subjects received 4 tablets, 4 x daily for 7 days.

2.1 Overview of Efficacy

Consistent with a 505(b)(2) application, the Avridi clinical development program relied on BE studies to demonstrate therapeutic equivalence and did not include efficacy studies. The active component of Avridi tablets, oxycodone, was shown to be bioequivalent to that of the marketed IR oxycodone product, Roxicodone, in the fasted state. However, in the fed state, the onset of absorption is delayed, resulting in a lower Cmax and a longer Tmax. Therefore, it is likely that in some instances, individuals who take Avridi tablets with food may experience a delay in analgesia. The gelling agents intended to reduce IV abuse and the aversive agent intended to reduce IN abuse do not alter the mechanism of action of oxycodone.

2.2 Overview of Safety

No serious adverse events (SAEs) or deaths were reported in any of the 5 clinical studies. Across all 5 studies, 3 subjects discontinued because of adverse events (AEs) (1 after administration of Avridi and 2 after administration of Roxicodone). Aside from the intended aversive nasal/oropharyngeal effects associated with crushed Avridi administered by the IN route, no new or unexpected AEs were reported by any subject in the 5 clinical studies in the Avridi clinical development program.

The majority of treatment emergent AEs reported in the clinical studies were mild or moderate in severity. In the clinical abuse potential study (study OCI1005), consistent with the subjective reports of IN effects, nasal treatment-emergent adverse events including nasal discomfort, nasal congestion, and rhinorrhea, and treatment-emergent adverse events of lacrimation and throat irritation were more common after IN administration of crushed Avridi compared with IN crushed Roxicodone. These nasal/oropharyngeal AEs were considered highly unpleasant and led to substantial decrease in drug liking. None of these TEAEs was considered serious, and none led to injury of the nasal mucosa. These AEs are consistent with the intended abuse-deterrent properties of the formulation.

Potential Risks Associated with Off-Label Use in the Fed State Followed by Re-dosing Earlier Than the Recommended Interval

As proposed in the full prescribing information for Avridi tablets, the product should only be taken in the fasted state, one hour prior to or two hours following a meal. There is a delayed peak concentration of oxycodone following the administration of Avridi in the fed state. If a patient takes Avridi with food, it is possible that the onset of analgesia is delayed (since Tmax is delayed) and the patient might then take a second dose at less than the minimum prescribed dosing interval of 4 hours, despite labeling. This second dose could result in higher than intended exposures to oxycodone, and this possibility is a potential safety concern. While these concerns are somewhat mitigated by the lower peak concentrations in the fed state, extensive PK modeling of oxycodone concentrations following the administration of Avridi in multiple dosing scenarios was performed to evaluate this potential risk (see Section 4). Results of PK modeling suggest that maximum oxycodone exposures associated with administration of Avridi remain within the range of oxycodone exposures observed when Roxicodone is taken as prescribed at the recommended dosing interval of every 4 to 6 hours.

Sodium Lauryl Sulfate Safety

Sodium lauryl sulfate, an excipient in Avridi tablets, has relatively low acute oral and dermal toxicity but is irritating to the skin, mucous membrane, and eye at high doses and has also been reported to be a respiratory tract irritant resulting in inhibition of respiration. Sodium lauryl sulfate is not a skin sensitizer and has tested negative in a battery of genotoxicity assays, including the Ames test, mammalian bone marrow chromosome aberration tests, mammalian erythrocyte micronucleus tests, and rodent dominant lethal mutation assays. Repeated dose oral toxicity studies in animals have demonstrated findings consistent only with surfactant-mediated irritant effects (gastric irritation) and body weight reduction at high doses (US EPA 2009, Ciuchta 1978, Final Report 1983). Findings for the rat and dog support the lack of toxicity of sodium lauryl sulfate or structurally related surfactants following long-term (chronic) administration with the exception of reduced body weights and/or hepatocellular hypertrophy/elevated liver enzymes at high doses. Importantly, no evidence of genotoxicity, reproductive or selective developmental toxicity, or a neoplastic or preneoplastic response was observed in the animal species studied.

To further assess the potential impact of sodium lauryl sulfate at exposures higher than those generally expected in clinical situations, Study OCI1008 evaluated the tolerability and safety of orally administered intact placebo (no oxycodone) tablets that contained sodium lauryl sulfate at the level included in Avridi tablets vs those of intact placebo tablets that did not contain sodium lauryl sulfate in 48 healthy male and female subjects. In each treatment, 4 tablets were administered 4 times daily for 7 days.No treatment-emergent AEs were experienced by more than 1 subject, and all of the reported treatment-emergent AEs were mild.

3 CLINICAL PHARMACOLOGY

3.1 Mechanism of Action

Oxycodone hydrochloride (HCl) is a pure opioid agonist and is relatively selective for the μ receptor, although it can interact with other opioid receptors at higher doses. The principal therapeutic action of oxycodone is analgesia. Like all pure opioid agonists, there is no ceiling effect to analgesia as seen with partial agonists or nonopioid analgesics.

Avridi is an IR single-entity tablet formulation of oxycodone HCl with abuse-deterrent properties, indicated for the management of acute and chronic moderate to severe pain where the use of an opioid analgesic is appropriate.

The main effects of oxycodone are mediated via opioid receptors in cell membranes of presynaptic nerve endings in the central nervous system (Kokki 2012). Oxycodone binds to and is an agonist at μ, κ, and δ opioid receptors that are coupled to G-proteins throughout the central, peripheral, and autonomic nervous systems. The pharmacologic effects of oxycodone result from the activity of these G-proteins coupled to opioid receptors in the cell membranes of presynaptic nerve endings. The binding of oxycodone to the receptors causes hyperpolarization of the nerve cell. There is a decrease in cyclic adenosine monophosphate resulting from inhibition of the adenyl cyclase system, as well as decreases in ionic calcium to the cell and increases in potassium flow. Nerve stimulation is decreased as a result of reduction in release of neurotransmitters (Ordonez 2007. Kokki 2012, Kalso 2005). Although oxycodone undergoes extensive hepatic metabolism to noroxycodone and oxymorphone via cytochrome P450 (CYP) enzymes, CYP3A4 and CYP2D6, the central opioid effects are attributed to oxycodone, not to metabolites (Riley 2008, Kalso 2005).

3.2 Pharmacokinetics

Three studies in healthy subjects were conducted to evaluate the PK of oxycodone following the administration of OCI tablets, including 2 studies using the final formulation, ie, Avridi.

A formulation finding study (study OCI1001) was conducted to evaluate the pharmacokinetics of oxycodone following the administration of IR oxycodone tablets formulated with varying levels of the abuse-deterrent excipients to optimize the formulation. The Avridi formulation was not tested. The results of this study are not presented in this document.

Two BE studies comparing Avridi to the reference listed drug, Roxicodone, were conducted in healthy subjects dosed in the fasted state (study OCI1002) and dosed following consumption of a standard FDA-defined high-fat, high calorie meal (study OCI1003). These studies were consistent with current FDA 505(b)(2) guidance noting that therapeutic equivalence may be established for products by comparing the systemic exposure of the proposed product to the reference listed drug (FDA 1999).

3.2.1 Study OCI1002 Fasting Bioequivalence

This was a single-center, randomized, open-label, 2-period, 2-sequence, single-dose, 2- way crossover study in healthy adult male and female subjects in the fasted state. The primary objective of this pivotal trial was to demonstrate that Avridi 15-mg tablets are bioequivalent to Roxicodone 15-mg tablets in the fasted state.

Each subject was administered the following treatments according to the randomization schedule:

- Avridi 15-mg tablet in the fasted state
- Roxicodone 15-mg tablet in the fasted state

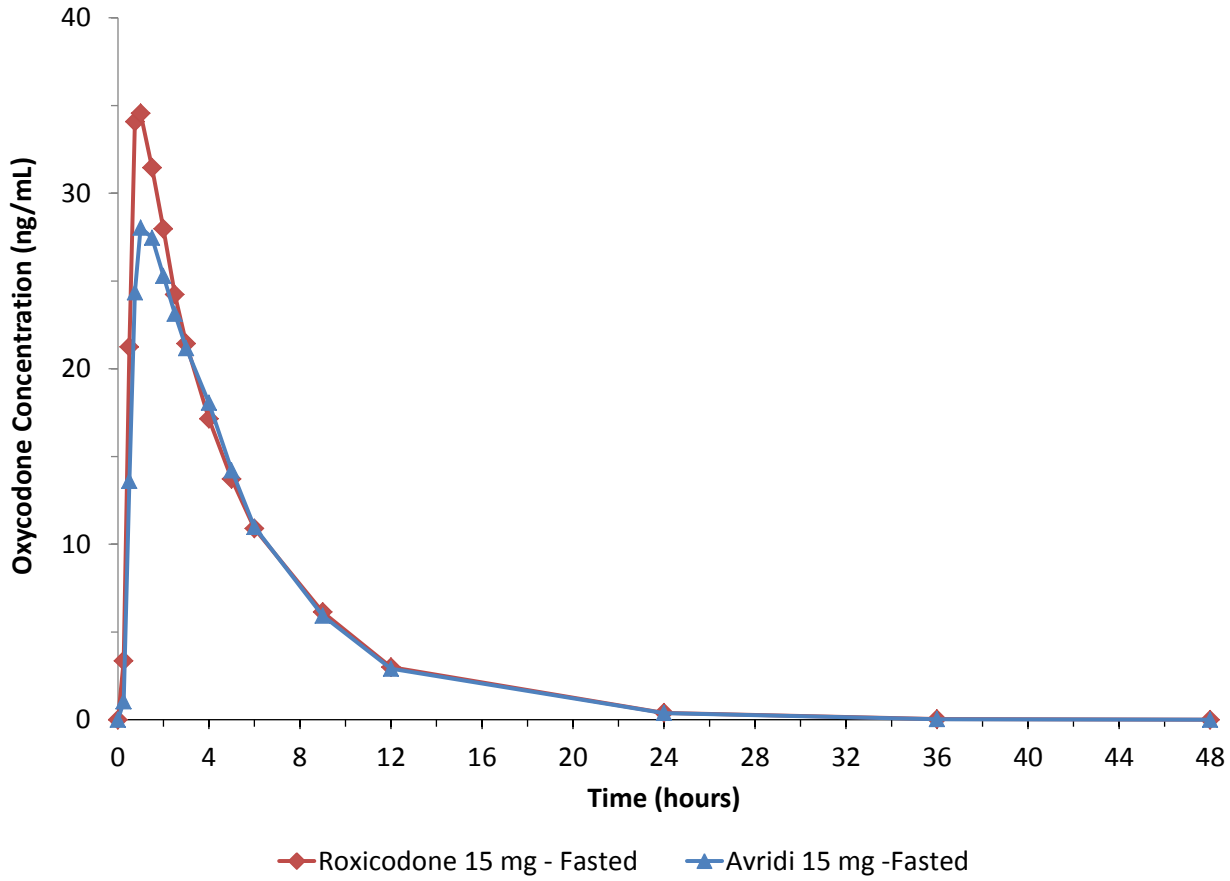
Study drug was administered with 240 mL of water. Treatments were preceded by an overnight fast (ie, at least 10 hours) from food, not including water, and were followed by a 4-hour fast. There was a minimum 7-day washout period between study drug administrations. Naltrexone HCl 50-mg tablet was administered at -12, 0, 12 and 24 hours, relative to study drug administration, to minimize opioid-related AEs. A naloxone HCl challenge test was performed prior to the first dose of naltrexone HCl to screen out subjects who have been chronically using opioids. Vital signs were collected. Blood samples for determining oxycodone plasma concentrations were obtained for each subject at selected time points after study drug administration during each of the treatment periods.

Bioequivalence of the Avridi 15-mg tablets (test) to the Roxicodone 15-mg tablets (reference) was assessed. For area under the plasma concentration-time curve from hour 0 to the last measurable plasma concentration (AUCt), area under the plasma concentration-time curve extrapolated to infinity (AUCinf), and Cmax, a mixed-model analysis of variance (SAS PROC MIXED) was used to compare (test vs reference) logarithmic-transformed (base e) values from the test and reference treatments with fixed effects for treatment, period, and sequence, and a random effect of subject nested within sequence. The 90% confidence intervals (CIs) were estimated for the ratios (test/reference) of exponentiated least squares (LS) means. As per FDA guidelines, bioequivalence (test vs reference) was established if the 90% CIs for these parameters were contained within the range of 80% to 125%.

Results:

Fifty-three subjects (17M/36F) with ages ranging from 18 to 55 years (mean: 32.6 years) were randomized and 52 subjects (98.1%) completed the study. One subject (1.9%) discontinued due to AE (Roxicodone treatment, case of alcohol abuse; not related to study drug).

Mean oxycodone plasma concentrations vs time by treatment are presented in Figure 1.



Source: OCI1002 CSR Figure 14.2.1

Figure 1 Mean Oxycodone Plasma Concentration vs Time Profiles for Avridi 15 mg and Roxicodone 15 mg, Administered in the Fasted State

Median Tmax was 1 hour and mean apparent terminal phase half-life (t1/2) was approximately 3.8 hours for both treatments.

The 90% CIs for the geometric LS means ratios of Cmax, AUCt, and AUCinf for oxycodone in the comparison of Avridi with Roxicodone were within the predefined range of 80% to 125%, indicating bioequivalence of oxycodone following the administration of Avridi 15 mg vs Roxicodone 15 mg in healthy subjects under fasted conditions (based on LS means, Table 2).

Table 2 Pharmacokinetic Metrics of Oxycodone Hydrochloride in the Fasted State

	LS Geometric Means[a]				
Metric (unit)	Avridi 15 mg	Roxicodone 15 mg	CV (%)	LS Mean Ratio (%) (Avridi/Roxicodone)[b]	90% CI of Ratio[c]
AUCt (h*ng/mL)	165	177	8.79	93.6	90.9, 96.4
AUCinf (h*ng/mL)	167	178	8.50	93.6	91.0, 96.3
Cmax (ng/mL)	32.3	37.4	19.6	86.3	81.0, 92.1

Source: OCI1002 CSR Table 14.2.3.
Note: A linear mixed model analysis of variance (SAS PROC MIXED) on the natural logarithms (ln) of the PK metrics was performed with treatment, sequence, and period as fixed effects and subject within sequence as a random effect.
[a] LS mean from analysis of variance. Natural-log (ln) metric means were calculated by transforming the ln means back to linear scale, ie, geometric means.
[b] Ratio of LS means (expressed as a percentage). The ln-transformed ratio was transformed back to linear scale to obtain the ratio of geometric LS means.
[c] The 90% CI for ratio of metric means (expressed as a percentage). The ln-transformed confidence limits were transformed back to linear scale.

Conclusion:

Avridi 15-mg tablets are bioequivalent to Roxicodone 15-mg tablets following administration of a single oral dose in healthy subjects under fasted conditions, in accordance with FDA guidelines on bioequivalence.

3.2.2 Study OCI1003 Fed Bioequivalence

This was a single-center, randomized, open-label, 2-period, 2-sequence, single-dose, 2-way crossover study in healthy adult male and female subjects in the fed state. The primary objective was to determine whether Avridi 15-mg tablets are bioequivalent to Roxicodone 15-mg tablets in the fed state. This study was conducted according to the FDA Guidance for Industry: *Food Effect Bioavailability and Fed Bioequivalence Studies*, December 2002).

Each subject was administered the following treatments according to the randomization schedule:

- Avridi 15-mg tablet in the fed state
- Roxicodone 15-mg tablet in the fed state

Following a 10-hour overnight fast, subjects were fed an FDA-defined "standard meal," (ie, a high-fat breakfast consisting of 2 pieces of toast with butter, 2 eggs fried in butter, 8 oz. of whole milk, 2 strips of bacon, and 4 oz. of hashed brown potatoes (Total calories: 900-1000, approx. 150 protein calories, 250 carbohydrate calories, and 500-600 fat calories) 30 minutes prior to administration of either Avridi 15-mg tablets or Roxicodone 15-mg tablets with 240 mL of water. No food was allowed for at least 4 hours postdose.

There was a minimum 7-day washout period between study drug administrations. Naltrexone HCl 50-mg tablet was administered at -12, 0, 12 and 24 hours, relative to study drug administration to minimize opioid-related AEs. A naloxone HCl challenge test was performed prior to the first dose of naltrexone HCl to screen out subjects who have been chronically using opioids.

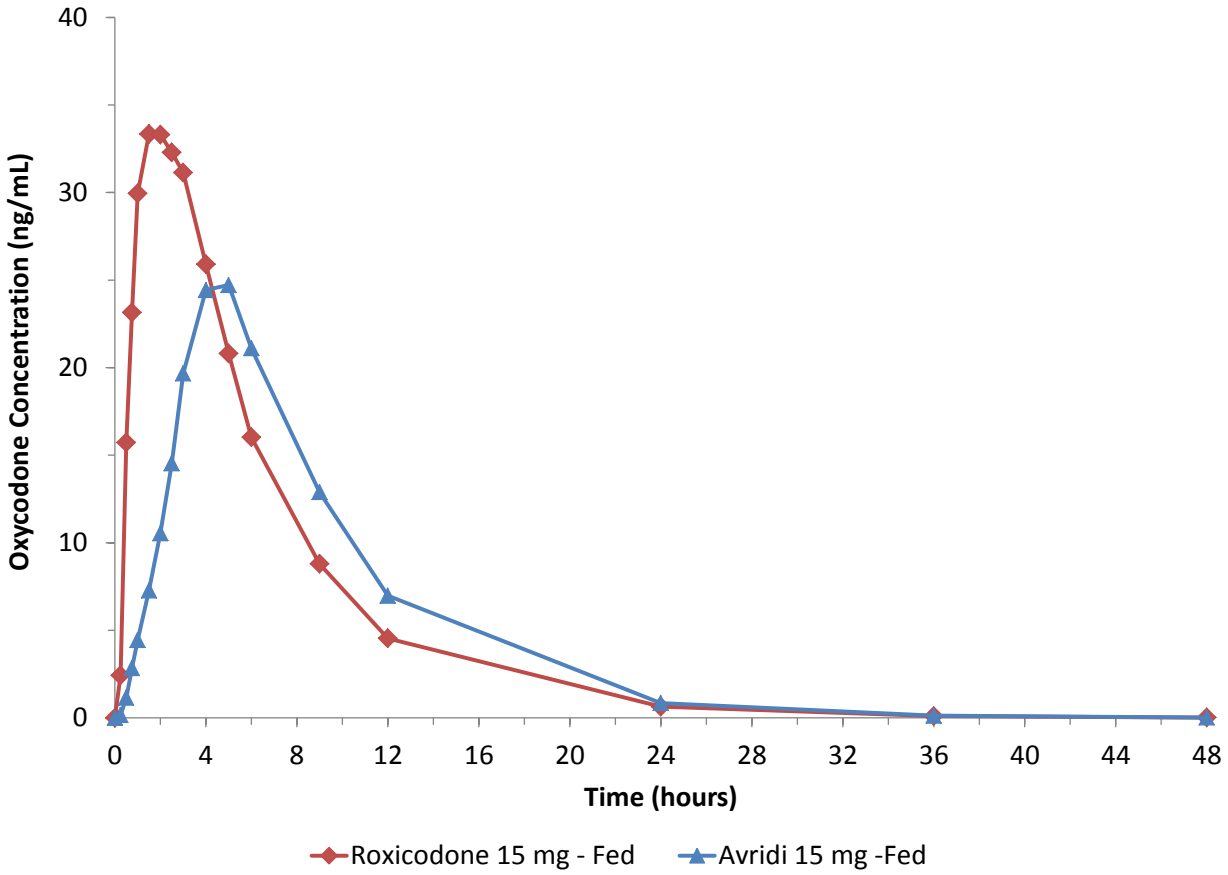
Vital signs were taken at specific time points and blood samples for determining oxycodone plasma concentrations were obtained for each subject after study drug administration during each of the treatment periods.

Bioequivalence of the Avridi 15-mg tablets (test) to the Roxicodone 15-mg tablets (reference) was assessed. For AUCt, AUCinf, and Cmax, a mixed-model analysis of variance (SAS PROC MIXED) was used to compare (test vs reference) logarithmic-transformed (base e) values from the test and reference treatments with fixed effects for treatment, period, and sequence, and a random effect of subject nested within sequence. The 90% CIs were estimated for the ratios (test/reference) of exponentiated LS means. As per FDA guidelines, bioequivalence (test vs reference) was established if the 90% CIs for these parameters were contained within the range of 80% to 125%.

Results:

Fifty-five subjects (25M/30F) with ages ranging from 20 to 53 years (mean: 33.7 years) were randomized and 53 subjects (96.4%) completed the study. Two subjects (3.6%) discontinued, 1 due to AE (Roxicodone treatment, moderate vomiting; not related to study drug) and 1 due to subject's choice.

Mean oxycodone plasma concentrations vs time by treatment are presented in Figure 2.



Source: OCI1003 CSR Figure 14.2.1

Figure 2 Mean Oxycodone Plasma Concentration vs Time Profiles for Avridi 15 mg and Roxicodone 15 mg, Administered in the Fed State

Median Tmax was 4.0 and 1.5 hours for Avridi and Roxicodone, respectively, and mean t1/2 was approximately 4 hours for both treatments.

The 90% CIs for the geometric LS means ratios of AUCt and AUCinf for oxycodone in the comparison of Avridi with Roxicodone were within the bioequivalence range of 80% to 125%; however, the 90% CI for the geometric LS means ratio of Cmax was outside the bioequivalence bounds with values of 68.4% to 77.0%, with a 27% lower peak exposure of oxycodone following the administration of Avridi vs Roxicodone in healthy subjects under fed conditions (based on the LS means, Table 3).

Table 3 Pharmacokinetic Metrics of Oxycodone Hydrochloride in the Fed State

	LS Geometric Means[a]				
Metric (unit)	Avridi 15 mg	Roxicodone 15 mg	CV (%)	LS Mean Ratio (%) (Avridi/Roxicodone)[b]	90% CI of Ratio[c]
AUCt (h*ng/mL)	218	234	7.74	93.4	91.1, 95.9
AUCinf (h*ng/mL)	220	235	7.69	93.5	91.1, 95.9
Cmax (ng/mL)	28.9	39.8	18.0	72.6	68.4, 77.0

Source: OCI1003 CSR Table 14.2.3.
Note: A linear mixed model analysis of variance (SAS PROC MIXED) on the natural logarithms (ln) of the PK metrics was performed with treatment, sequence, and period as fixed effects and subject within sequence as a random effect.
[a] LS mean from analysis of variance. Natural-log (ln) metric means were calculated by transforming the ln means back to linear scale, ie, geometric means.
[b] Ratio of LS means (expressed as a percentage). The ln-transformed ratio was transformed back to linear scale to obtain the ratio of geometric LS means.
[c] The 90% CI for ratio of metric means (expressed as a percentage). The ln-transformed confidence limits were transformed back to linear scale.

Conclusion:

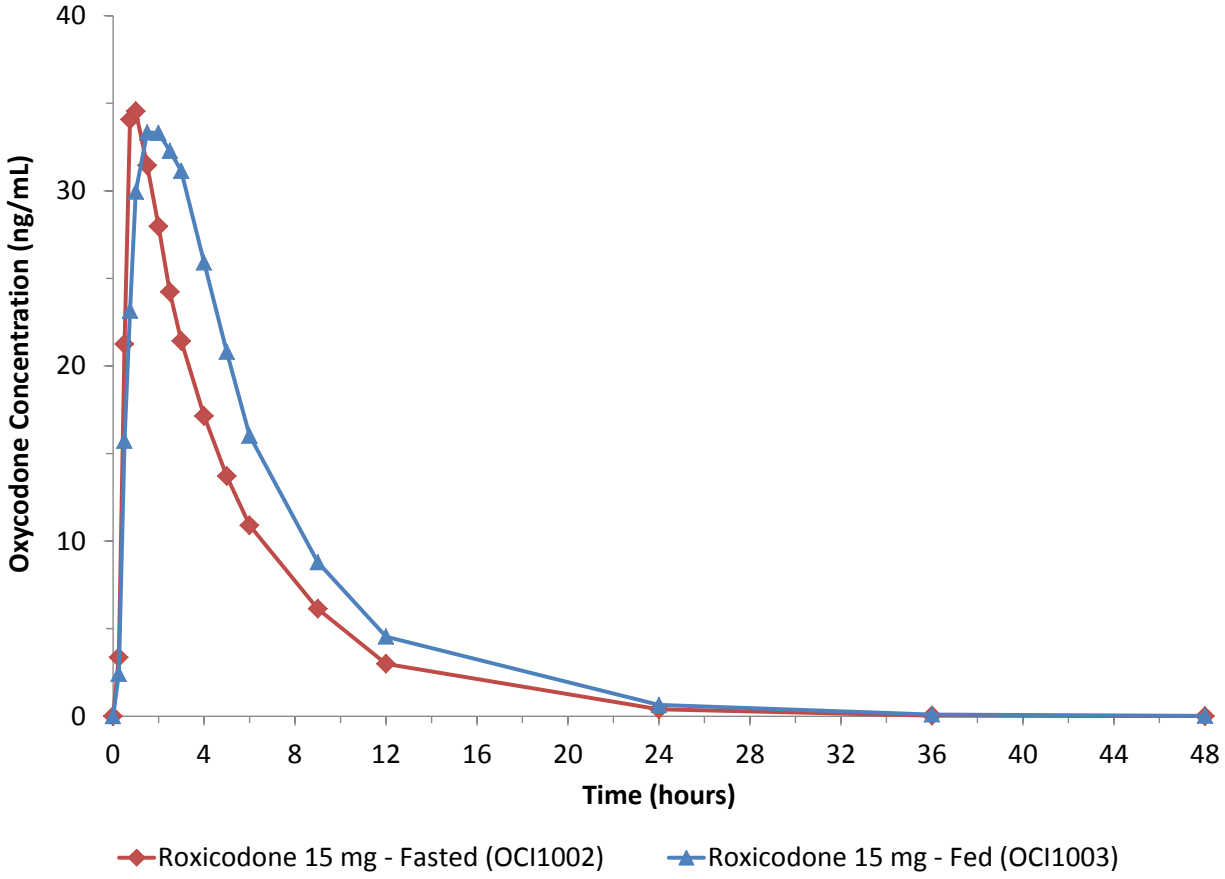
The AUCt and AUCinf for oxycodone are bioequivalent following the administration of Avridi 15-mg tablets compared with Roxicodone 15-mg tablets in healthy subjects under fed conditions.

The Cmax for oxycodone is not bioequivalent following the administration of Avridi 15-mg tablets compared with Roxicodone 15-mg tablets in healthy subjects under fed conditions. Following the administration of Avridi 15-mg tablets, Cmax values are 27% lower than those for Roxicodone 15-mg tablets in healthy subjects under fed conditions.

The median Tmax is delayed approximately 2.5 hours following the administration of Avridi 15-mg tablets compared with the administration of Roxicodone 15-mg tablets.

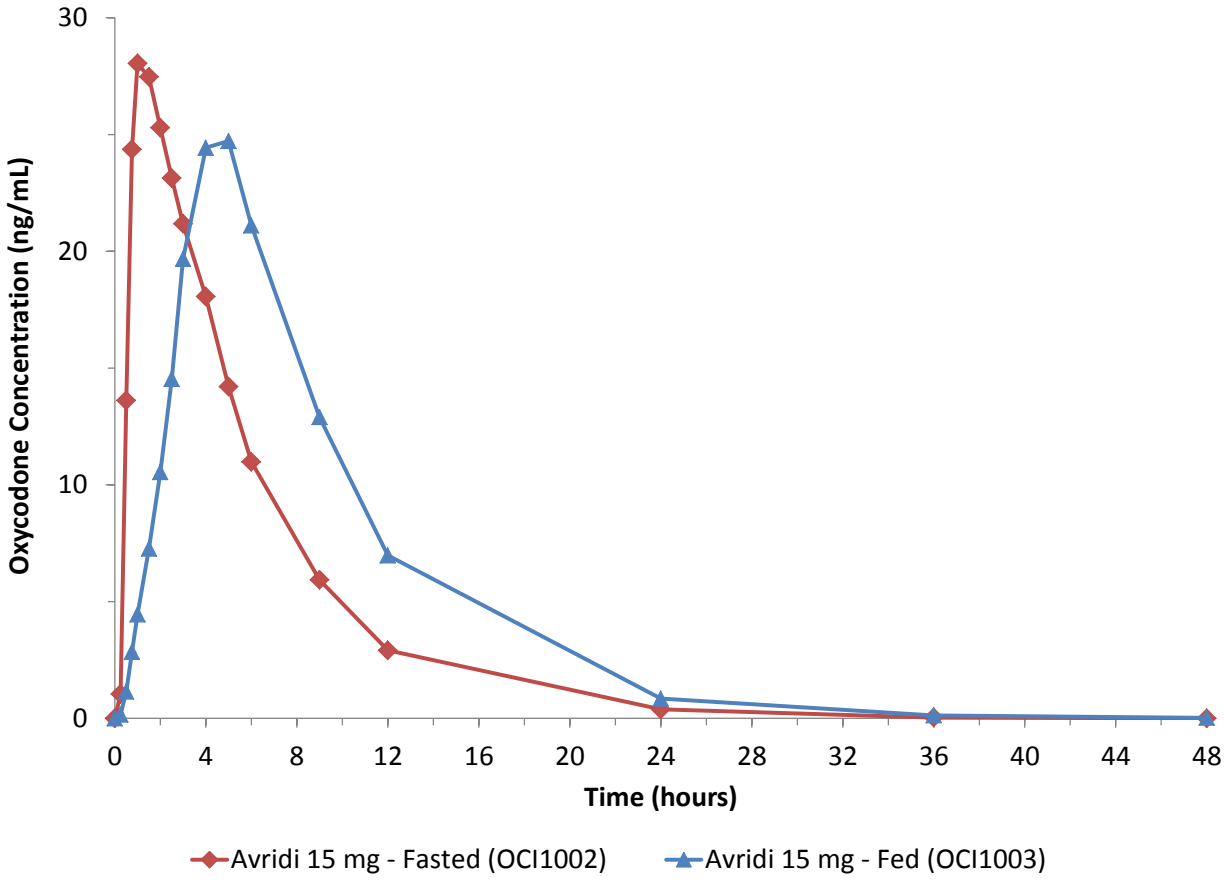
3.3 Effect of Food on Oxycodone Exposure Following Administration of Avridi and Roxicodone: Integrated Evaluation of Fasting and Fed Bioequivalence Study Results

Consistent with new drug applications covered by the 505(b)(2) route (FDA Draft Guidance for Industry: *Applications Covered in Section 505(b)(2)*, October 1999), the bioequivalence of Avridi tablets administered under fasting and fed conditions was assessed in separate studies (OCI1002 and OCI1003). Therefore, cross-study comparisons are required to examine the effect of food on oxycodone exposures following administration of Avridi compared with Roxicodone. Figure 3 and Figure 4 show the mean concentration vs time profiles for Roxicodone and Avridi, respectively, administered under both fasting (study OCI1002) and fed (study OCI1003) conditions. Table 4 presents the combined PK metrics and results of the BE analysis for the 2 studies.



Source: Derived from OCI1002 CSR Figure 14.2.1 and OCI1003 CSR Figure 14.2.1.

Figure 3 Cross-Study Comparison of Mean Oxycodone Concentration vs Time Profiles Following Administration of Roxicodone 15 mg Under Fasting and Fed Conditions



Source: Derived from OCI1002 CSR Figure 14.2.1 and OCI1003 CSR Figure 14.2.1.

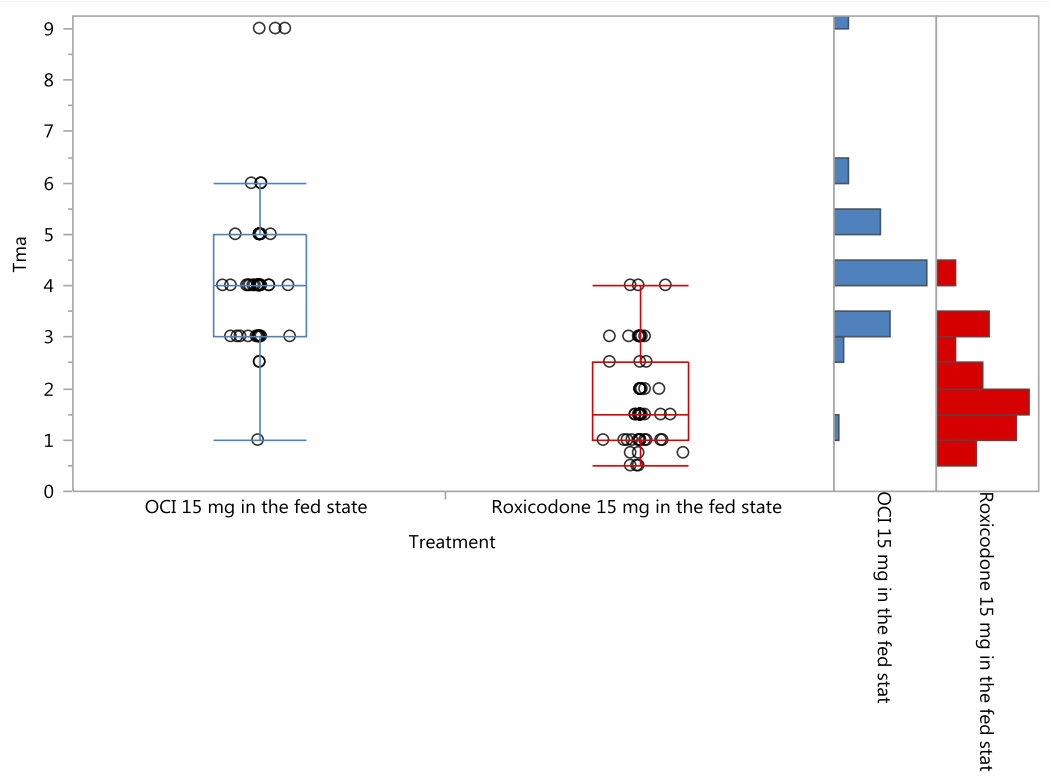
Figure 4 Cross-Study Comparison of Mean Oxycodone Concentration vs Time Profiles Following Administration of Avridi 15 mg Under Fasting and Fed Conditions

Table 4 Fasting and Fed Bioequivalence PK Metrics

Study	Treatments (Dose, dosage form, route)	Mean ± SD PK Metrics				Mean Ratio (90% CI)		
		Cmax (ng/mL)	Tmax(h) median (range)	AUCt (ng*h/mL)	AUCinf (ng*h/mL)	Cmax	AUCt	AUCinf
OCI1002 Fasting BE	Avridi 15 mg, po fasted	34.02 ± 11.23	1.03 (0.5, 5.0)	171.39 ± 45.73	172.84 ± 45.77	86.33 (80.96, 92.07)	93.60 (90.91, 96.36)	93.59 (91.00, 96.27)
	Roxicodone 15 mg, po fasted	38.77 ± 10.92	1.0 (0.5, 6.07)	182.86 ± 47.79	184.35 ± 47.64			
OCI1003 Fed BE	Avridi 15 mg, po fed	29.79 ± 7.18	4.0 (1.0, 9.05)	226.49 ± 60.54	227.96 ± 60.34	72.56 (68.38, 77.00)	93.44 (91.05, 95.89)	93.50 (91.13, 95.94)
	Roxicodone 15 mg, po fed	41.43 ± 11.74	1.50 (0.5, 4.05)	241.24 ± 61.35	242.75 ± 61.28			

Source: Adapted from module 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Method, Table 5
Abbreviations: BE= Bioequivalence; po=oral route.

Comparison of the fasting vs fed oxycodone concentration profiles for Roxicodone and Avridi indicates that food has a modest effect on the rate and extent of oxycodone exposure following Roxicodone administration. In contrast, administration of Avridi with a high fat meal was associated with reduction in the early rate of rise in oxycodone exposure. The potential magnitude of the reduced rate of oxycodone absorption after dosing of Avridi vs Roxicodone under fed conditions is reflected in the comparison of their respective distributions related to Tmax, shown in Figure 5.



Missing Rows 2704

Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
OCI 15 mg in the fed state	1.00	3.00	3.00	4.00	5.00	6.00	9.00
Roxicodone 15 mg in the fed stat	0.50	0.75	1.00	1.50	2.50	3.00	4.00

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
OCI 15 mg in the fed state	51	4.25	1.54	0.21619	3.8207	4.69
Roxicodone 15 mg in the fed stat	53	1.78	0.93	0.12790	1.5217	2.03

OCI=Avridi

Figure 5 Tmax Distributions for Roxicodone 15 mg and Avridi 15 mg, Administered Under Fed Conditions

In the fed bioequivalence study (OCI1003), a total of 54 subjects were dosed, 50 of whom received both Avridi and Roxicodone in crossover fashion, while 3 subjects received only Roxicodone and 1 received only Avridi. Among 53 healthy subjects who received Roxicodone in the fed state, Tmax ranged from 0.5 to 4.5 hours. The corresponding range among 51 subjects who received Avridi in the fed state was from 1.0 to 9.05 hours.

In the clinical setting of first administration, as needed (PRN) dosing, or PRN treatment in conjunction with an around-the-clock ER opioid, the reduction in the rate of rise in oxycodone concentrations after administration of Avridi with food may delay analgesia in some patients. Therefore, to ensure that administration of Avridi tablets produces oxycodone concentrations that

are within the range of those resulting from Roxicodone administration, Avridi should be administered in the fasted state. Proposed Avridi labeling and dosing instructions will advise patients to take Avridi on an empty stomach, at least one hour prior to or two hours after eating. Additionally, as included under instructions for patients in other oxycodone product labeling, Avridi's labeling will state:

1. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
2. Patients should be advised not to adjust the dose of Avridi without consulting the prescribing professional.

4 RELEVANT IR OXYCODONE PATIENT USE SCENARIOS FOR EVALUATION

4.1 IR Oxycodone Utilization Patterns

Approved IR oxycodone products are indicated for the management of acute and chronic moderate to severe pain where the use of an opioid analgesic is appropriate. As a result, IR oxycodone can be used PRN or as an around-the-clock treatment. IR opioids can also be used alone for acute pain of more than several days duration and for chronic pain, or in conjunction with ER opioids for breakthrough pain. Real-world utilization patterns for currently approved IR single-entity oxycodone are provided in Section 6.

Three common anticipated IR single-entity oxycodone utilization patterns are:

1) **PRN IR Oxycodone Use Scenarios**: IR Oxycodone administration PRN at 4- to 6-hour intervals in patients with acute pain or intermittent pain.

2) **Around-the-Clock IR Oxycodone Use Scenarios**: Around-the-clock IR oxycodone administration every 4 to 6 hours in patients with acute pain greater than several days duration or with chronic pain.

3) **PRN IR Oxycodone Use + Around-the-Clock ER Opioid Scenarios**: IR oxycodone administration PRN for breakthrough pain in patients also taking an around-the-clock ER opioid.

These patterns of use are important to consider in the context of Avridi's potential food effect. Proposed labeling states that Avridi should be taken on an empty stomach, one hour before or two hours after a meal. As the anticipated food effect may delay analgesia, some patients, despite labeling instructions, might take a second dose of Avridi before the end of the minimum prescribed dosing interval. This situation may be applicable for both patients newly initiating therapy or patients on long-term treatment, though patients unfamiliar with the formulation or taking the product PRN may be at greater risk of taking a second dose before the end of the minimum prescribed dosing interval.

To evaluate possible maximum oxycodone exposures associated with these utilization patterns, Purdue Pharma L.P. conducted a number of PK modeling projections of possible scenarios that could result following administration of Avridi tablets with food.

Interpretation of the consequences of various Avridi dosing scenarios based upon corresponding projected oxycodone concentration vs time profiles is challenging since there are not well-recognized and broadly applicable associations between oxycodone concentrations and safety and efficacy. Due to a variety of factors, it is not possible to cite a particular therapeutic range of oxycodone concentrations within which there is an expectation of efficacy and above which there is an expectation of tolerability and safety issues. Based on our thorough literature review and examination of the Roxicodone package insert, little useful data are available on IR single-entity oxycodone and measures of efficacy (onset, magnitude, and duration) or safety profile in relation to PK metrics.

The relationship between the plasma concentration of oxycodone and a patient's analgesic response is likely to depend upon a variety of factors, including age and other demographics, state of health, medical condition, pain type and intensity, and extent of previous opioid treatment. The minimum effective plasma concentration of oxycodone to achieve analgesia will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids, including patients who use long-term IR oxycodone to manage chronic pain, either alone, or for breakthrough pain in addition to an ER opioid analgesic. Thus, patients need to be treated with individualized titration of dosage to the desired effect. The minimum effective analgesic concentration of oxycodone for any individual patient may increase with repeated dosing due to an increase in pain and/or development of tolerance, a well-recognized and labeled characteristic of opioid analgesics.

Although these complexities exist, it is evident that for individual patients there is a relationship between plasma concentration and effect in terms of analgesia as well as other effects. In addition, the frequency, intensity, and duration of AEs tend to increase with increased exposure.

4.2 Safety Assessment of Avridi Dosing Scenarios Compared with Roxicodone Dosing Scenarios Using Oxycodone Exposure Comparisons

As an alternative to attempting to define a particular oxycodone concentration above which meaningful safety concerns arise, it is reasonable to consider the range of oxycodone concentrations produced by a particular recommended regimen of the reference treatment, Roxicodone. Projections based on the actual PK data collected following administration of 15-mg doses of Roxicodone in the fasting and fed BE studies described in Section3.2 reflect concentration profiles which can be reasonably assumed to be safe and effective when Roxicodone is administered to appropriate patients at 4- to 6-hour dosing intervals, consistent with existing Roxicodone labeling. It is reasonable to compare distributions of PK metrics, such as Cmax, from observed or validly projected Roxicodone dosing regimens, which are consistent with its labeled dosing instructions, with distributions of PK metrics arising from potential Avridi dosing scenarios. If projected maximum oxycodone exposures following a particular Avridi dosing scenario are comparable to, or less than, those defined by labeled Roxicodone regimens with the same dose strengths, then that Avridi dosing scenario is not likely to represent a clinically significant safety concern related to increased oxycodone exposure.

4.3 Pharmacokinetic Modeling Approaches Used to Project Oxycodone PK Metrics Associated with Various IR Oxycodone Utilization Patterns

The IR oxycodone reference listed drug, Roxicodone, has been shown to have dose-proportional total oxycodone exposure across the dose range of 5 to 30 mg [Roxicodone Package Insert 2009]. Cmax concentrations also increase approximately in proportion to dose across this range. PK projections for various dosing scenarios were explored using both noncompartmental methods (linear superposition) and compartmental methods (mathematical fitting of both mean and individual values). The 2 methods yielded generally similar results, and the validity of each rests on similar assumptions regarding linear oxycodone pharmacokinetics for the dosage forms under consideration.

The results presented below are based on linear superposition. This method was chosen because it can be applied more readily to various specific dosing situations and it preserves specific PK profile

shapes, rather than forcing mathematical fits to various exponential equations. This provides a measure of conservatism in that individual values, including Cmax concentrations, and observed time intervals between dosing and onset of significant oxycodone exposures, are preserved across the modeled dose scenarios.

To provide a further measure of conservatism, the specific time points in the modeled dosing scenarios were selected to preserve the individual contributions arising from each time point at which the original concentration data were collected in the 2 BE studies (Section 3.2). Thus, peak oxycodone exposures from a modeled dose contributed their full value when composite PK profiles were calculated using linear superposition.

4.4 PRN IR Oxycodone Use Scenarios: IR Oxycodone Administration PRN at 4- to 6-Hour Intervals in Patients With Acute Pain or Intermittent Pain

4.4.1 Description of Pattern Utilization

As noted in Section 6, most prescriptions for IR single-entity oxycodone are short in duration. Of commercially insured and Medicaid insured patients, 86% and 75% of the populations, respectively, received prescriptions of IR single-entity oxycodone for < 30 days. Patients likely to use IR single-entity oxycodone on a PRN basis include those with acute pain from injury or surgery or those with intermittent pain.

For example, a patient following outpatient surgery may eat a meal while his local anesthesia is still in effect. As the local anesthesia wears off, he may develop more severe pain and choose to take a dose of Avridi despite instructions about not taking the medication with food. Subsequently, if there is a notable delay in analgesia, he may choose to take another dose early, despite instructions not to do so.

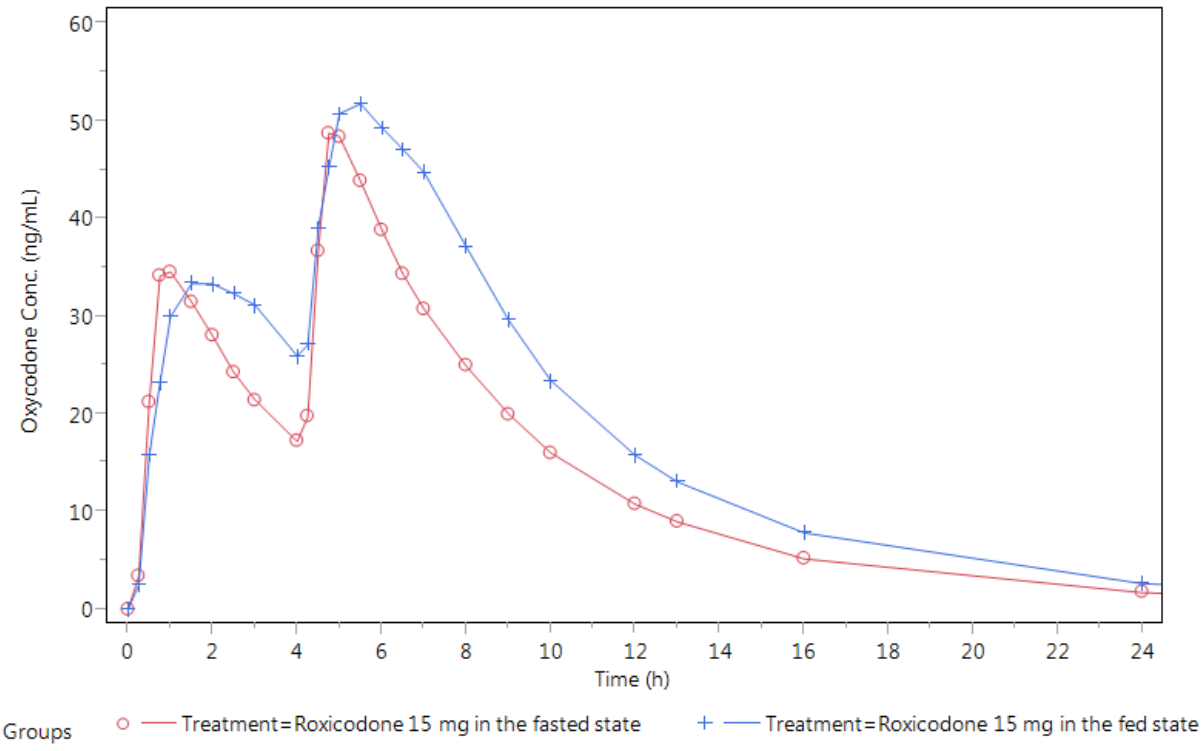
4.4.2 PK Projections Related to IR Oxycodone Administration at 4- to 6- Hour Intervals PRN (Management of Acute or Intermittent Pain)

The Dosing and Administration Section of Roxicodone tablets' full prescribing information (Roxicodone Package Insert 2009) contains the following description of regimens appropriate for administration to patients who are not already receiving opioid analgesics: "Patients who have not been receiving opioid analgesics should be started on ROXICODONE in a dosing range of 5 to 15 mg every 4 to 6 hours as needed for pain."

In the setting of IR oxycodone use at 4- to 6- hour intervals on a PRN basis, it is appropriate to model the administration of two 15-mg doses of Roxicodone administered at 4-hour intervals under both fasting and fed conditions to provide estimates of the ranges of concentrations that would be commonly observed and that are therapeutically acceptable for patients for whom IR oxycodone 15-mg doses are appropriate. The resulting oxycodone exposures projected for Roxicodone administration, consistent with its labeling, can then be compared with various potential Avridi dosing scenarios to determine the extent to which such Avridi dosing scenarios may raise the potential for clinically significant safety concerns.

Projected Oxycodone Exposures Following Administration of Two Roxicodone 15-mg Doses Administered 4 hours Apart Under Fasting and Fed Conditions

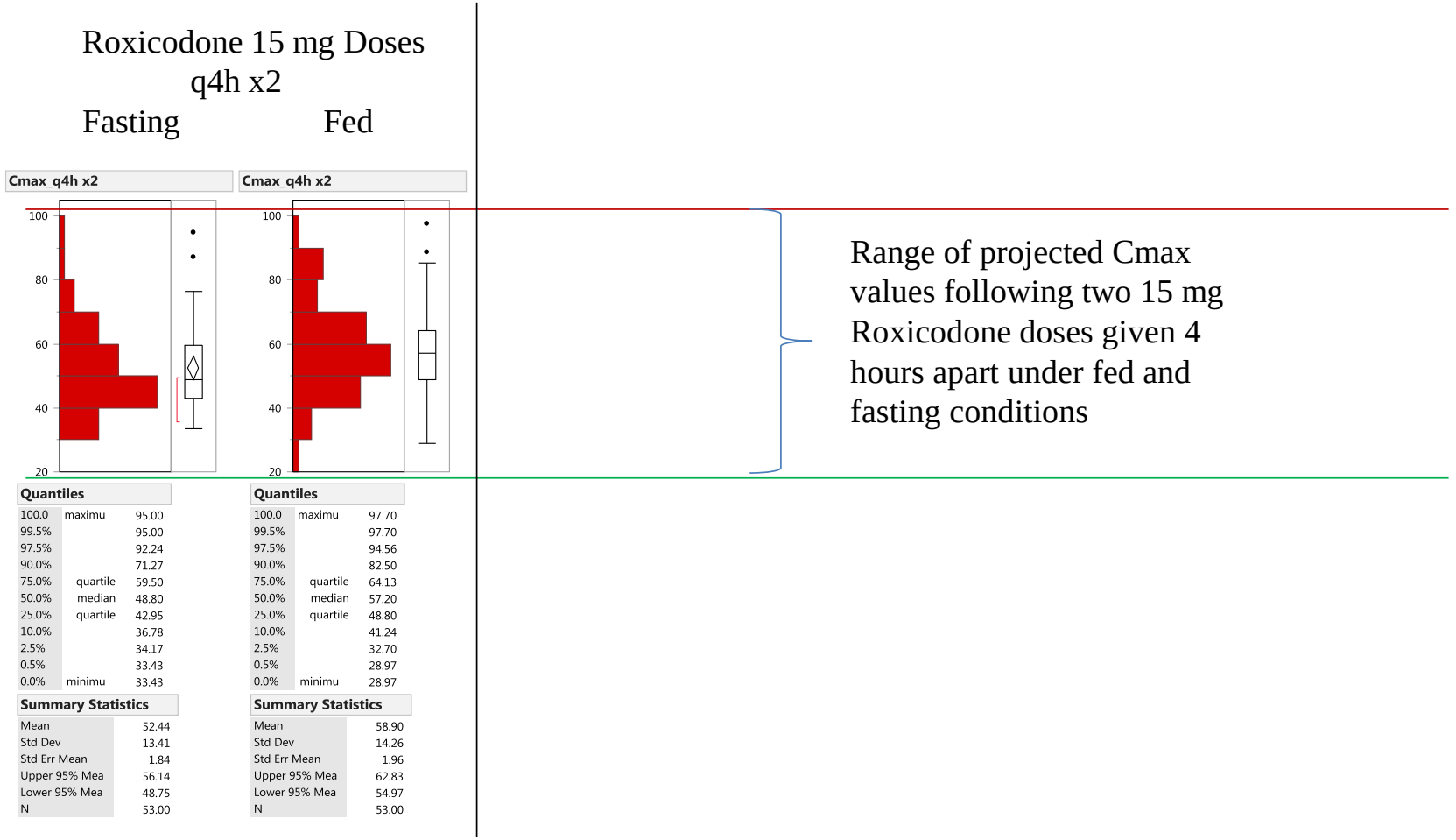
Using linear superposition, each individual subject's oxycodone concentration vs time profile observed following administration of a single Roxicodone 15-mg dose was used to project the oxycodone concentration profile that would accompany administration of two Roxicodone 15-mg doses separated by the minimum dosing interval of 4 hours (Roxicodone Package Insert 2009). The same procedure was used to model the profiles expected when Roxicodone is administered as two 15-mg doses separated by a 4-hour dosing interval in the 53 subjects who were dosed in the fasted state (study OCI1002) and in the 53 subjects who were dosed in the fed state (study OCI1003). The mean concentration profiles calculated using the individual oxycodone concentration vs time projections are shown in Figure 6.



Source: Derived from study data OCI1002, OCI1003

Figure 6 Projected Mean Concentration vs Time Profile for two Roxicodone 15-mg Doses Administered 4 Hours Apart in the Fasted State and in the Fed State

To further characterize the range of expected concentrations associated with these Roxicodone regimens, the Cmax value for each individual subject's projected PK profile was calculated. The distributions of projected Cmax values for the administration of 2 doses of Roxicodone with 4 hours between doses in the fasting and fed states are shown in Figure 7.



Source: Derived from study data OCI1002, OCI1003
Cmax units = ng/mL

Figure 7 Cmax Distributions For Projected Oxycodone PK Profiles Following Two Roxicodone Doses Administered 4 hours Apart in the Fasting and Fed States

Examination of Figure 7 shows that projected Cmax values range up to 95 ng/mL (fasting) and 97.7 ng/mL (fed) following Roxicodone administered as 15-mg doses q4h x 2. The green and red horizontal lines delineate the overall range of projected Cmax values for these Roxicodone regimens.

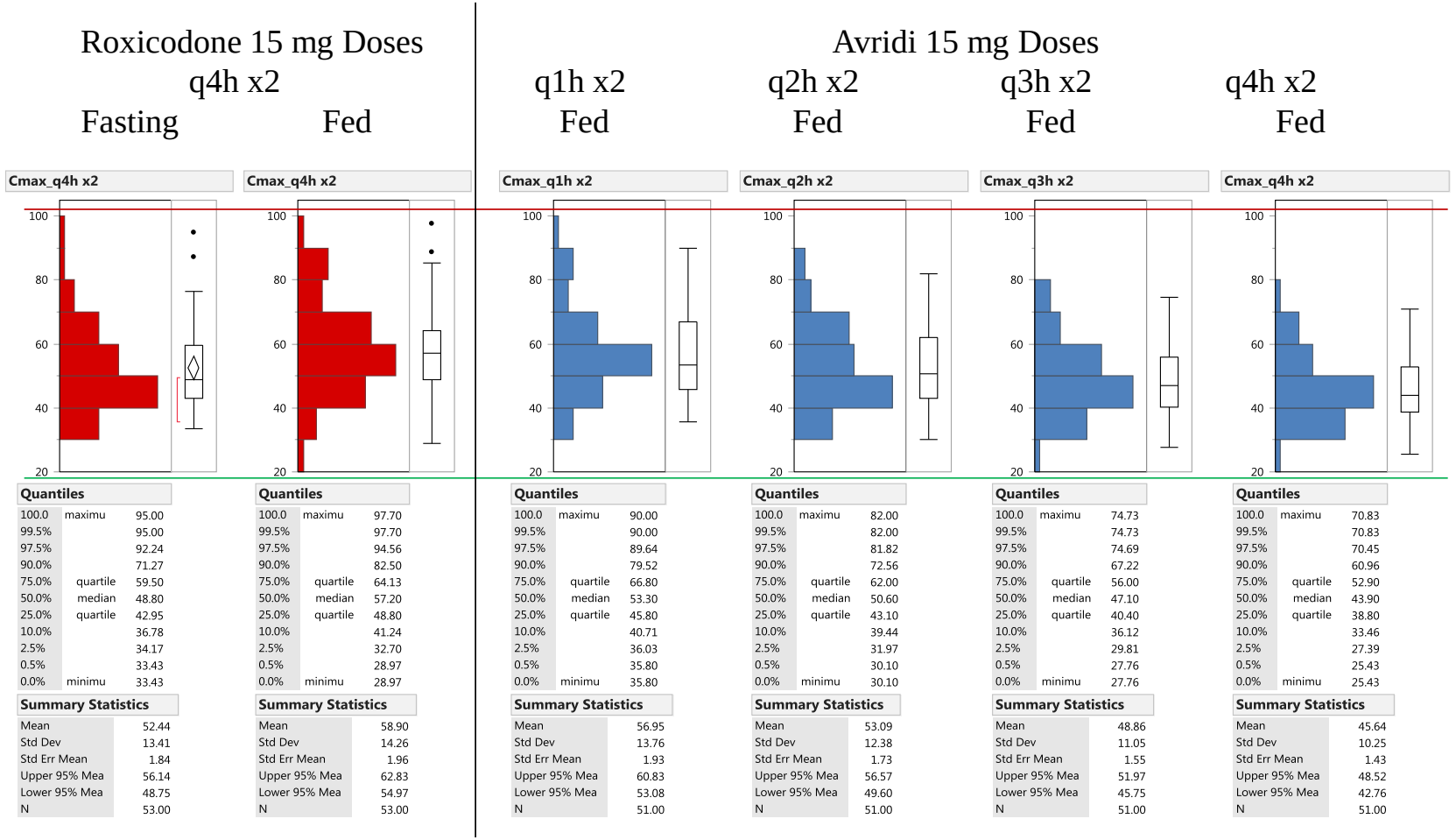
Projected Oxycodone Exposures Following Administration of Two Avridi 15-mg Doses Administered 1, 2, 3, or 4 Hours Apart Under Fasting and Fed conditions

To explore the oxycodone profiles that would result following administration of Avridi with food and the possible safety concern if a patient takes another dose of Avridi earlier than the next dosing interval, 2 sets of scenarios were characterized. For both scenarios, it was assumed that the second Avridi dose would be taken 1, 2, 3, or 4 hours after the initial Avridi dose.

In the first scenario, it was assumed that both the first and the second Avridi doses would be taken in the fed state. The first dose is taken with the meal and the second dose 1, 2, 3 or 4 hours later would also be taken in the fed state. In the second scenario, it was assumed that the first Avridi dose would be taken with food, and that the second Avridi dose would be taken in the fasted state. For this scenario, each subject's individual observed fed Avridi PK profile was used as the first Avridi dose. Because no crossover data are available to provide both fasting and fed Avridi profiles for individual subjects, a representative fasting Avridi PK profile had to be established to represent the second Avridi dose. Median and 90^{th} percentile concentration time profiles calculated from the 51 individual concentration values available at each time point were used for the representative fasting Avridi PK profile. The median provides a base case while the 90^{th} percentile provides a conservative fasting Avridi PK profile.

Scenario 1 - Avridi Fed + Fed Dosing: Modeled as Two Avridi 15-mg Fed Doses Administered 1, 2, 3, or 4 Hours Apart

The resulting Cmax distributions for Scenario 1, with 1, 2, 3, or 4 hours between the two Avridi fed doses are shown in the 4 histograms furthest to the right in Figure 8. To the left of these are the 2 histograms shown previously for the Roxicodone regimens. The figure shows that none of the projected Cmax values for any of the 51 subjects who received Avridi with food in study OCI1003 exceeded the upper bound of the range of Cmax values estimated for the reference Roxicodone regimens defined previously. This was true regardless of whether the modeled second Avridi fed dose was administered 1, 2, 3, or 4 hours after the first Avridi fed dose.

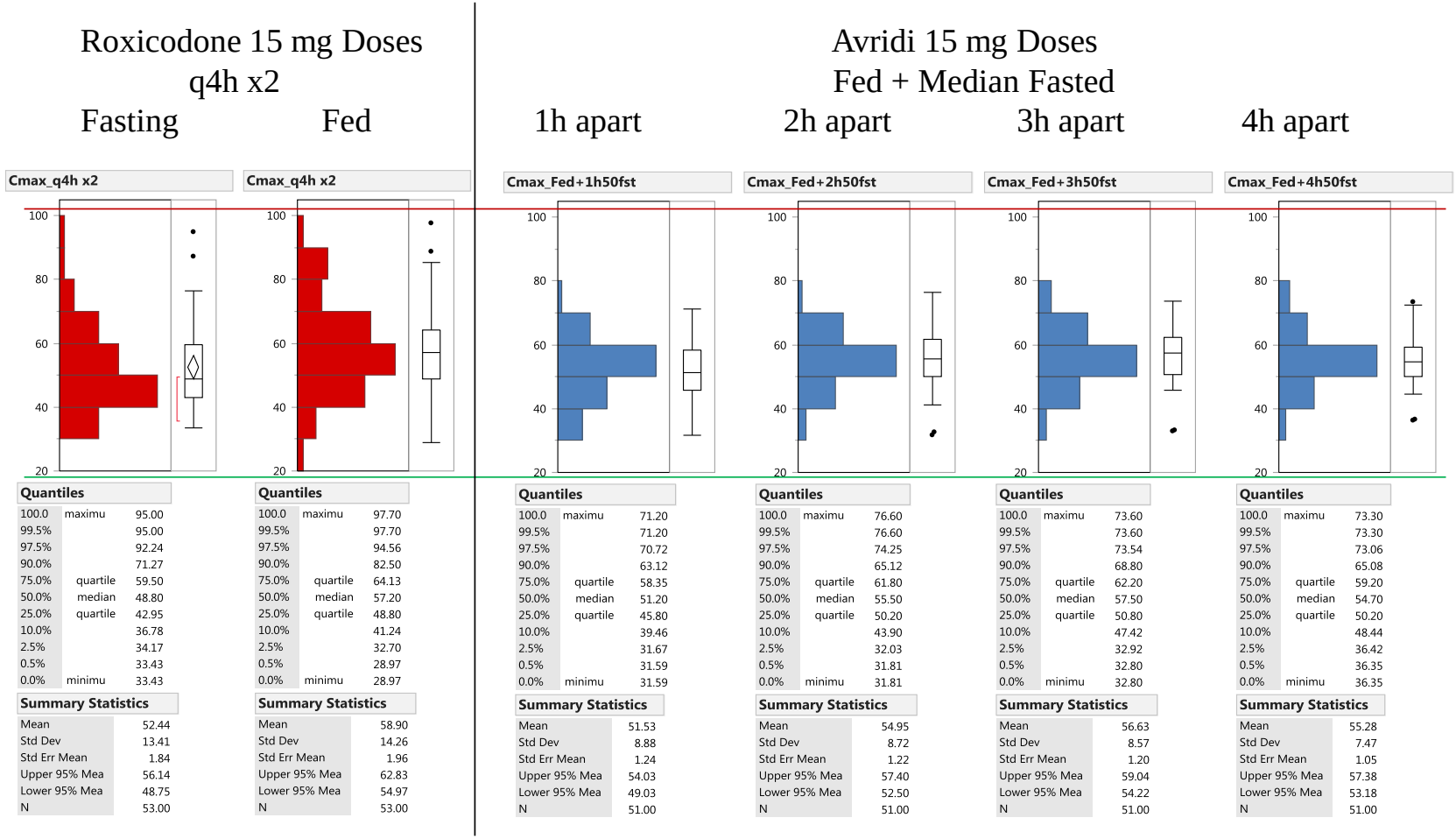


Source: Derived from study data OCI1002, OCI1003
Abbreviation: OCI=Avridi; Cmax units = ng/mL

Figure 8 PRN IR Oxycodone Use; Scenario 1 - Avridi Fed + Fed Dosing: Projected Cmax Distributions for Two Avridi Fed Doses Administered 1, 2, 3, or 4 Hours Apart

Scenario 2 - Avridi Fed + Fasted Dosing: Modeled as One Avridi 15-mg Fed Dose Followed by a Fasted Avridi Dose 1, 2, 3, or 4 Hours Apart

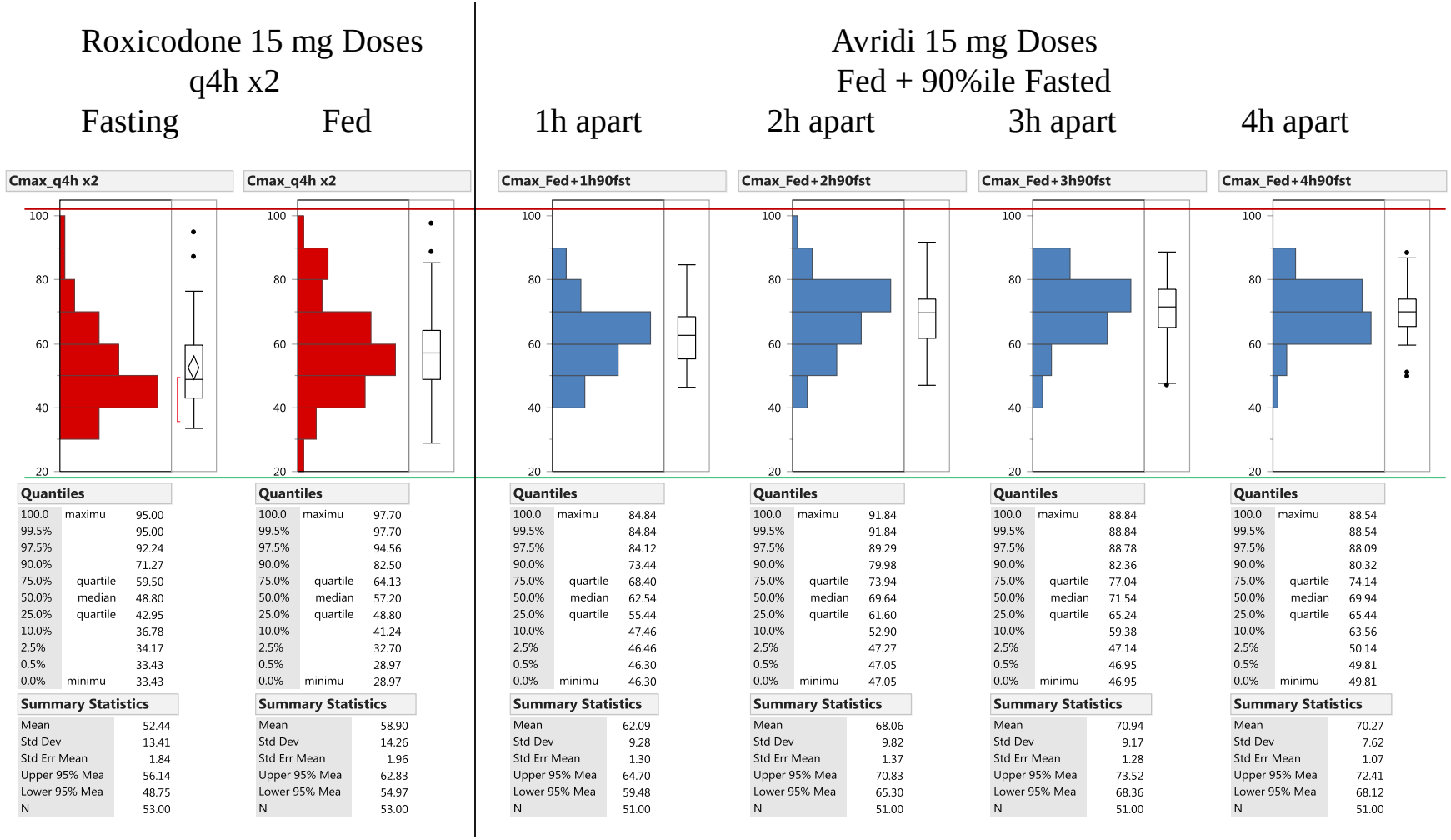
Figure 9 presents the resulting Cmax distributions for Scenario 2, with 1, 2, 3, or 4 hours between Avridi fed and median fasted doses as shown in the 4 histograms furthest to the right. These distributions represent the sets of Cmax values modeled using each individual subject's observed Avridi fed dose as the first dose, followed by the calculated median oxycodone concentration vs time profile for the second dose. To the left of these are the 2 histograms shown previously for the reference Roxicodone regimens. The figure shows that none of the projected Cmax values for any of the 51 subjects who received Avridi in the fed state in study OCI1003 exceeded the upper bound of the range of Cmax values projected for the reference Roxicodone regimens defined previously. This was true regardless of whether the modeled median second Avridi fasting dose was administered 1, 2, 3, or 4 hours after the first Avridi fed dose.



Source: Derived from study data OCI1002, OCI1003
Abbreviation: OCI=Avridi; Cmax units = ng/mL

Figure 9 PRN IR Oxycodone Use; Scenario 2 - Avridi Fed + Fasted Dosing: Projected Cmax Distributions for a Fed Avridi Dose Followed by a Median Fasted Avridi Dose Administered 1, 2, 3, or 4 Hours Later

To use a conservative case as a sensitivity analysis, Figure 10 presents the resulting Cmax distributions for Scenario 2, where the second dose is modeled using 90th percentile data at each time point. The figure shows scenarios with 1, 2, 3, or 4 hours between the two Avridi doses as shown in the 4 histograms furthest to the right. These distributions represent the sets of Cmax values modeled using each individual subject's observed Avridi fed dose oxycodone concentration vs time profile as the first dose, followed by the calculated 90th percentile oxycodone concentration vs time profile for the second dose. To the left of these are the 2 histograms shown previously for the reference Roxicodone regimens. In this conservative case, similar to the base case, none of the projected Cmax values for any of the 51 subjects who received Avridi in the fed state in study OCI1003 exceeded the upper bound of the range of Cmax values estimated for the reference Roxicodone regimens defined previously. This was true regardless of whether the modeled 90th percentile second Avridi fasting dose was administered 1, 2, 3, or 4 hours after the first Avridi fed dose.



Source: Derived from study data OCI1002, OCI1003
Cmax units = ng/mL

Figure 10 PRN IR Oxycodone Use; Scenario 2 - Avridi Fed+Fasted Dosing: Projected Cmax Distributions for a Fed Avridi Dose Followed by a 90th Percentile Fasted Avridi Dose Administered 1, 2, 3, or 4 Hours Later

4.4.3 PRN IR Oxycodone Use Scenarios Conclusions

PK modeling scenarios relevant for PRN dosing of both Roxicodone and Avridi were performed. PK modeling was used to project Cmax distributions for the Roxicodone reference regimens: two Roxicodone 15- mg doses administered 4 hours apart under fasting conditions and under fed conditions, respectively, and compared with 2 Avridi fed dosing scenarios in which 2 Avridi doses are taken from 1 to 4 hours apart.

The results demonstrate that regardless of whether the second Avridi dose is assumed to be either a second fed or fasted Avridi dose (Scenario 1 and Scenario 2) or a conservatively modeled 90th percentile fasted Avridi dose (sensitivity analysis, Scenario 2), and regardless of whether the modeled second Avridi dose is taken 1, 2, 3, or 4 hours after the initial fed Avridi dose, the resulting projected range of Cmax values does not exceed the upper bound of the reference Roxicodone Cmax distributions.

4.5 Around-the Clock IR Oxycodone Use Scenarios: Around-the-Clock IR Oxycodone Administration at 4- to 6- Hour Intervals for Patients With Acute Pain Greater than Several Days Duration or With Chronic Pain

4.5.1 Description of Pattern Utilization

As described in Section 6, IR single-entity oxycodone products are most often prescribed for short-term use, but there is evidence showing that a large number of patients continue IR single-entity oxycodone treatment for longer periods (> 90 days). The number of patients using IR single-entity oxycodone for long-term use is, in fact, comparable to or greater than the number of patients prescribed ER oxycodone for long-term use. Patients who are using a drug around-the-clock, not PRN, may be more able to adopt a dosing regimen that avoids dosing with food.

Patients receiving around-the-clock IR oxycodone are expected to reach steady-state oxycodone plasma concentrations within approximately 2 days, with trough and maximum oxycodone drug concentrations providing adequate analgesia.

4.5.2 PK Projections Related to Around-the-Clock IR Oxycodone Administration at 4- to 6-Hour Intervals (Management of Acute Pain Greater Than a Few Days Duration or Chronic Pain)

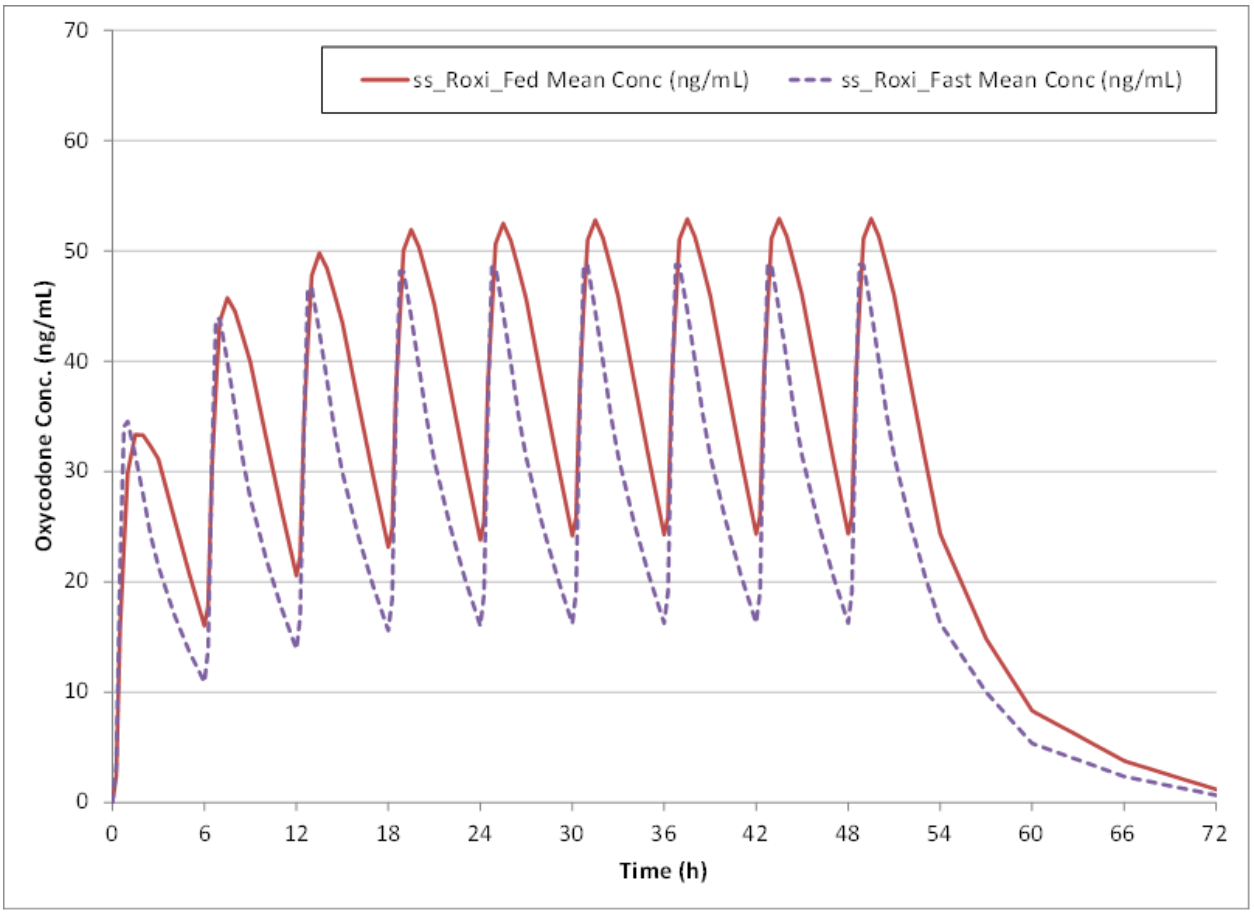
Roxicodone dosage and administration instructions (Roxicodone Package Insert 2009) state that IR oxycodone can be used for analgesia in patients with chronic pain:

> "Patients with chronic pain should have their dosage given on an around-the-clock basis to prevent the re-occurrence of pain rather than treating the pain after it has occurred. This dose can then be adjusted to an acceptable level of analgesia taking into account side effects experienced by the patient.
>
> For control of severe chronic pain, ROXICODONE should be administered on a regularly scheduled basis, every 4 to 6 hours, at the lowest dosage level that will achieve adequate analgesia."

Based on the therapeutic intent of an around-the-clock IR oxycodone regimen, trough concentrations at steady state (Cmin,ss) are intended to provide adequate analgesia. In addition, maximum concentrations at steady state (Cmax,ss) can be assumed to be generally safe and adequately well-tolerated in patients for whom the regimen achieves an appropriate balance between analgesia and AEs. Thus, PK modeling of around-the-clock Roxicodone PK profiles can be used to generate reference distributions for both Cmax,ss and Cmin,ss, representing ranges between peak and trough concentrations that can be assumed to be safe and efficacious.

Projected Oxycodone Exposures Following Roxicodone 15-mg doses Administered Every 6 Hours to Steady State Under Fasting and Fed Conditions

Using linear superposition, the mean concentration vs time profiles observed following administration of single 15-mg doses of Roxicodone in the fasted (OCI1002) and fed (OCI1003) states were used to project the corresponding mean profiles following multiple dose administration of Roxicodone 15-mg tablets every 6 hours (q6h) under both fasted and fed conditions. A q6h schedule was chosen because it is more feasible for an around-the-clock regimen than a q4h schedule. The resulting projected mean concentration vs time profiles are shown in Figure 11.



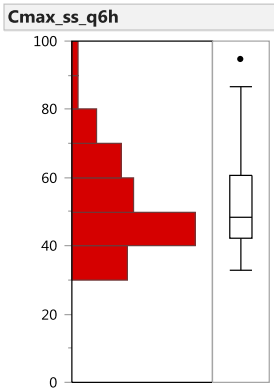
Roxi=Roxicodone
Source: Derived from study data OCI1002, OCI1003

Figure 11 Projected Mean Steady-State Concentration vs Time Profiles for Roxicodone 15- mg Doses Administered Every 6 Hours in the Fasted State and in the Fed State

The same mathematical method was used to generate corresponding steady-state PK profiles for each of the individual subjects who received Roxicodone under fasted (study OCI1002, n=53) and fed (study OCI1003, n=53) conditions. Cmax,ss and Cmin,ss values were determined from each of these individual subject steady-state projections. The distributions of these projected reference Cmax,ss and Cmin,ss concentrations for Roxicodone dosed 15 mg q6h to steady state are shown in Figure 12.

Roxicodone 15 mg, Fasting
q6h Projected Steady-State

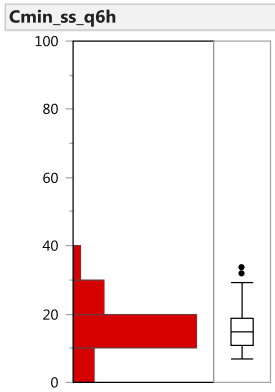
Cmax,ss



Quantiles		
100.0	maximu	94.73
99.5%		94.73
97.5%		91.90
90.0%		72.14
75.0%	quartile	60.68
50.0%	median	48.43
25.0%	quartile	42.39
10.0%		36.16
2.5%		33.40
0.5%		33.03
0.0%	minimu	33.03

Summary Statistics	
Mean	52.44
Std Dev	13.67
Std Err Mean	1.88
Upper 95% Mea	56.21
Lower 95% Mea	48.67
N	53.00

Cmin,ss

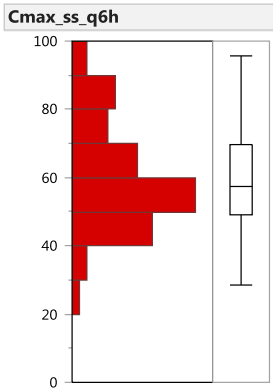


Quantiles		
100.0	maximu	33.66
99.5%		33.66
97.5%		33.01
90.0%		24.32
75.0%	quartile	18.76
50.0%	median	14.71
25.0%	quartile	10.86
10.0%		9.69
2.5%		7.16
0.5%		6.91
0.0%	minimu	6.91

Summary Statistics	
Mean	15.99
Std Dev	6.15
Std Err Mean	0.84
Upper 95% Mea	17.68
Lower 95% Mea	14.29
N	53.00

Roxicodone 15 mg, Fed
q6h Projected Steady-State

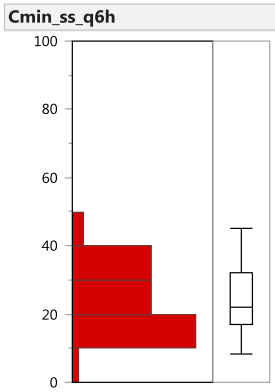
Cmax,ss



Quantiles		
100.0	maximu	95.63
99.5%		95.63
97.5%		93.88
90.0%		85.37
75.0%	quartile	69.53
50.0%	median	57.53
25.0%	quartile	49.27
10.0%		42.86
2.5%		32.29
0.5%		28.44
0.0%	minimu	28.44

Summary Statistics	
Mean	60.05
Std Dev	15.19
Std Err Mean	2.09
Upper 95% Mea	64.24
Lower 95% Mea	55.86
N	53.00

Cmin,ss



Quantiles		
100.0	maximu	45.14
99.5%		45.14
97.5%		44.38
90.0%		35.86
75.0%	quartile	32.18
50.0%	median	22.10
25.0%	quartile	17.06
10.0%		13.29
2.5%		9.22
0.5%		8.39
0.0%	minimu	8.39

Summary Statistics	
Mean	23.92
Std Dev	8.95
Std Err Mean	1.23
Upper 95% Mea	26.39
Lower 95% Mea	21.46
N	53.00

Source: Derived from study data OCI1002, OCI1003
Cmax units = ng/mL

Figure 12 Cmax,ss and Cmin,ss Distributions For Projected Steady-State PK Profiles Following Roxicodone 15-mg Doses Administered Every 6 Hours in the Fasted State and in the Fed State

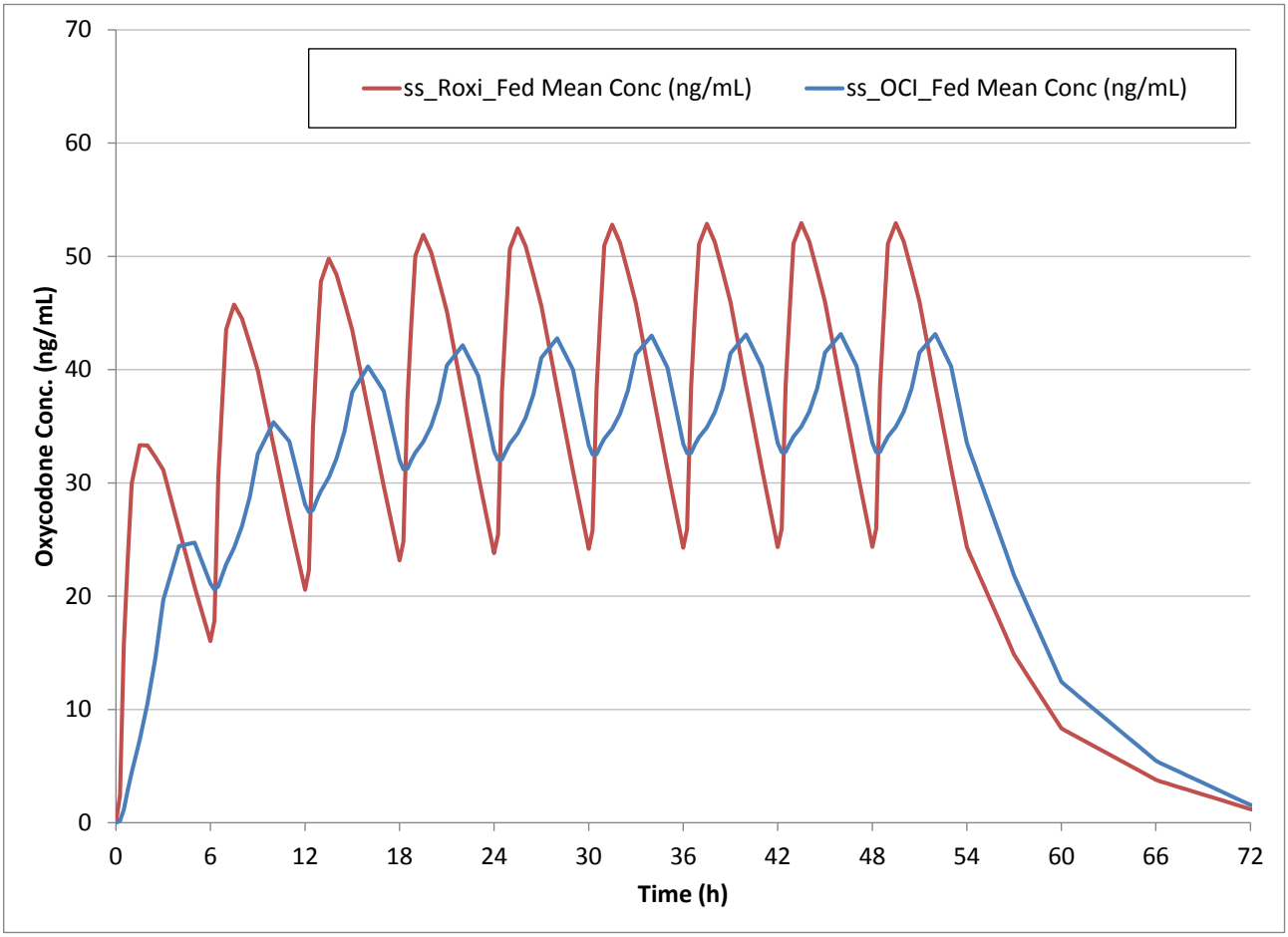
Consistent with the single-dose findings, projected Cmax,ss and Cmin,ss values for Roxicodone are higher under fed conditions than fasted conditions. Since Roxicodone can be administered without regard to meals, the distributions of maximum and minimum steady-state concentrations represent values expected to be safe, adequately tolerated, and efficacious in patients for whom an around-the-clock Roxicodone 15-mg dose is appropriate.

Projected Oxycodone Exposures Following Avridi 15-mg Doses Administered Every 6 Hours to Steady State Under Fasting and Fed Conditions

Patients prescribed Avridi tablets will be instructed to take the medication in the fasted state. However, it is possible that patients will not always comply with this aspect of proper Avridi dosing. PK projections were completed to evaluate the potential consequences of noncompliance with fasted Avridi dosing. In scenario 1, PK profiles were projected under the assumption that all doses of Avridi are taken in the fed state, ie, complete nonadherence with the fasted dosing instructions for Avridi. In scenario 2, PK profiles were projected to evaluate the consequences of administration of an Avridi dose with food in a patient already at steady state on a q6h Avridi regimen under fasted conditions. The potential consequences of these scenarios were evaluated through comparison with around-the-clock Roxicodone reference PK profiles.

Scenario 1: Modeled as Multiple Administrations of Avridi 15-mg Doses Every 6 Hours Under Fed Conditions

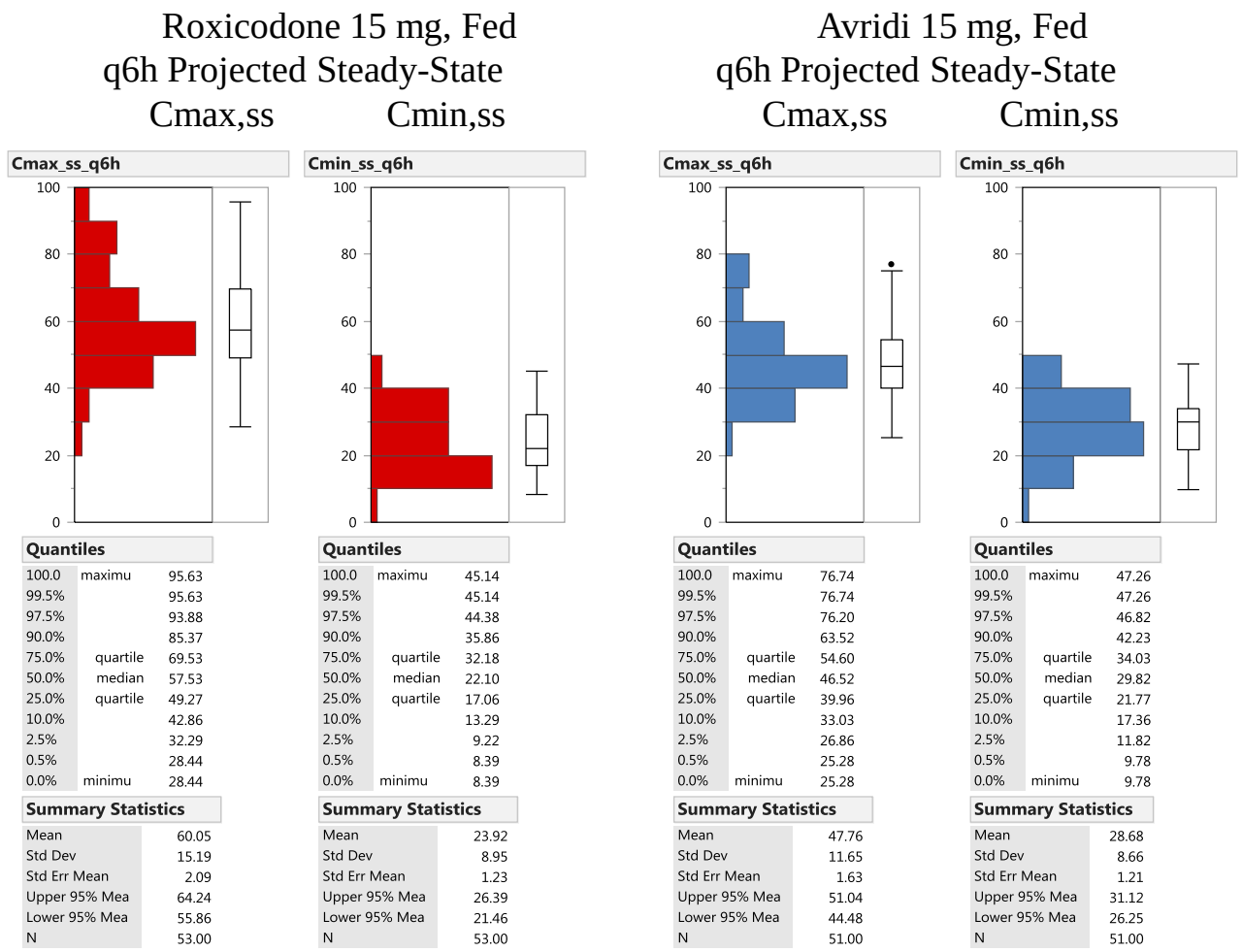
Using the same modeling methods described above, the mean concentration vs time profile observed following administration of single 15-mg doses of Avridi in the fed state (OCI1003, n=51) was used to project the corresponding mean profile following multiple administration of Avridi 15-mg tablets q6h under fed conditions. The resulting projected mean concentration vs time profile for Avridi and the corresponding reference profile for Roxicodone dosed under the same conditions are shown in Figure 13. The reduction in the rate of oxycodone absorption following Avridi administration in the fed state observed in the single-dose bioequivalence study (OCI1003) translates into a projected steady-state profile that features lower maximum concentrations and higher minimum concentrations as compared with projections for the more rapidly absorbed reference product, Roxicodone.



Source: Derived from study data OCI1003
Abbreviation: OCI=Avridi; Roxi=Roxicodone.

Figure 13 Projected Mean Steady-State Concentration vs Time Profiles for Roxicodone 15-mg Doses and Avridi 15-mg Doses Administered Every 6 Hours in the Fed State

The same mathematical method was used to generate corresponding steady-state PK profiles for each of the individual subjects who received single 15-mg doses of Roxicodone (n=53) and Avridi (n=51) in the fed state (study OCI1003). Cmax,ss and Cmin,ss values were determined from each of these individual subject steady-state projections. The distributions of the resulting projected Cmax,ss and Cmin,ss values for Avridi 15- mg doses administered q6h in the fed state to steady state are shown to the right of the corresponding reference distributions for Roxicodone in Figure 14.



Source: Derived from study data OCI1003
Cmax units = ng/mL

Figure 14 Cmax,ss and Cmin,ss Distributions For Projected Steady-State PK Profiles Following 15-mg Doses of Roxicodone and Avridi Administered Every 6 Hours in the Fed State

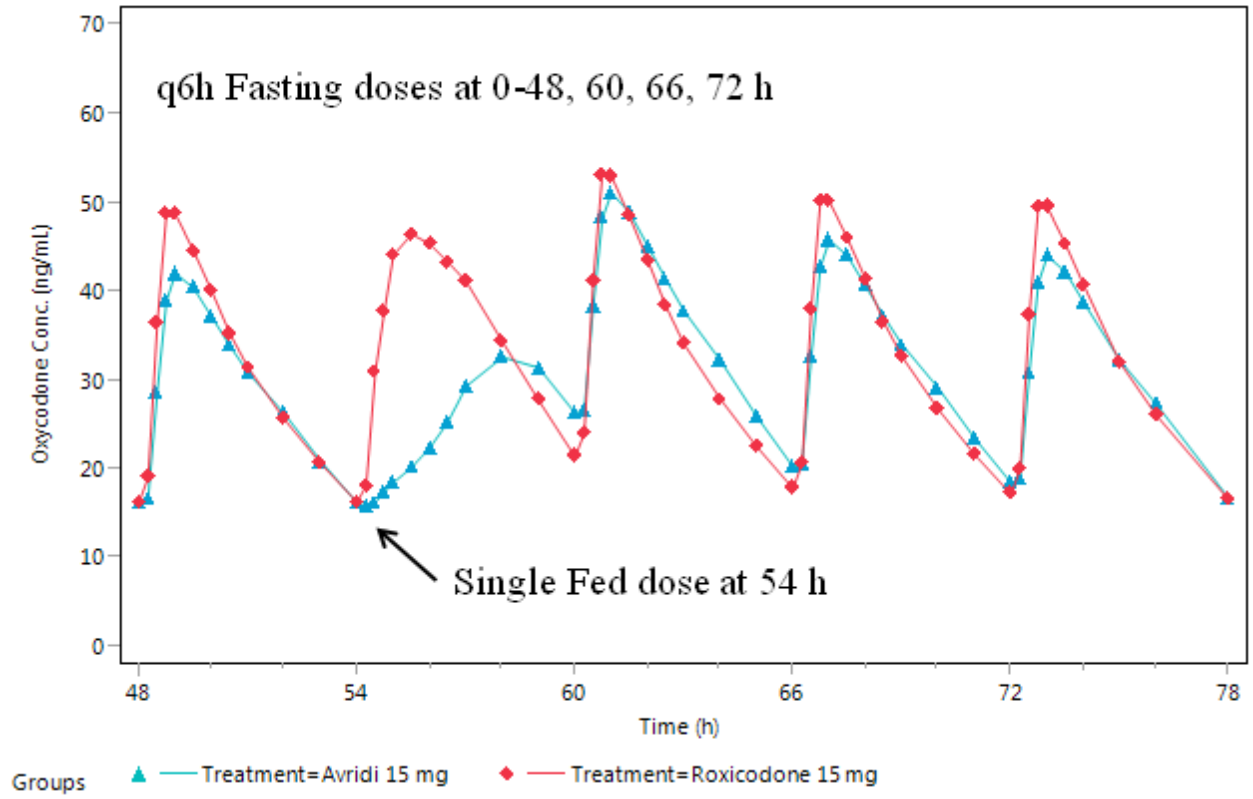
Consistent with the projected mean steady-state PK profiles for Roxicodone and Avridi shown in Figure 13, the distribution of the projected individual subject Cmax,ss values for Avridi under fed conditions is lower than the corresponding distribution for Roxicodone dosed in the same manner. Figure 14 also shows that the distribution of the projected individual subject Cmin,ss values for Avridi administered under fed conditions is higher than the corresponding distribution for Roxicodone dosed in the same manner. This finding of lower projected Cmax,ss values and higher projected Cmin,ss values suggests that even if Avridi were to be taken around-the-clock under fed conditions only, the minimum and maximum oxycodone concentrations are expected to lie within

the range that would result if Roxicodone was taken under the same conditions. Thus, this dosing scenario does not raise clinically significant safety or lack of efficacy concerns.

Scenario 2: Modeled as Multiple Administrations of Avridi 15-mg Doses Every 6 Hours Under Fasted Conditions Followed by an Avridi 15-mg Dose Under Fed Conditions

This scenario examines the consequences of taking a dose of Avridi in the fed state following consistent fasted dosing of Avridi to steady state. The mean PK profile and distributions of Cmax and Cmin following this dosing pattern are compared with those for Roxicodone, which can be administered without regard to meals. Because Roxicodone and Avridi doses were compared in separate fasted (OCI1002) and fed (OCI1003) BE studies, there are no within-subject fed vs fasted comparison data. Therefore, this scenario is modeled using the mean single-dose concentration vs time data for both Roxicodone and Avridi following fasted administration in study OCI1002. The fed dose administered at 54 hours is modeled using the observed single-dose concentration vs time data for each of the subjects in the fed state (study OCI1003). This preserves the character of the individual subject fed state PK profiles for each product as they are applied to the sequence of mean fasted doses that precede (0-48 hours) and follow (60-72 hours) the single fed dose at 54 hours.

For clarity, Figure 15 omits the initial fasted dosing of each product, beginning with the first fasted dose at time 0 and continuing with q6h dosing through 48 hours. The final fasted dose is shown at 48 hours, followed by a single dose administered under fed conditions at 54 hours and then further fasted doses at 60, 66, and 72 hours. Comparison of the projected mean PK profiles for this dosing scenario (Figure 15) shows that insertion of a single fed Avridi dose in a q6h sequence of fasted Avridi doses is associated with a temporary increase in minimum concentrations and a temporary decrease in maximum concentrations over the initial 54- to 60-hour interval, followed by a slight increase in maximum concentrations in the 60- to 66-hour interval. This latter effect arises because the modeled scenario includes delayed absorption of oxycodone from an Avridi dose following administration with food, as reflected by the upper bound of 9 hours for the range of Tmax values associated with single doses of Avridi administered in the fed state.



Source: Derived from study data OCI1002, OCI1003

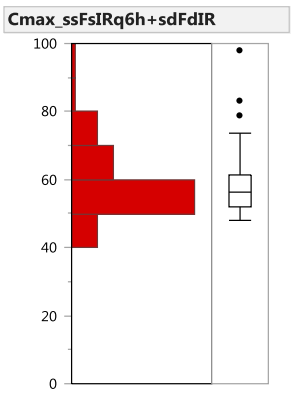
Figure 15 Projected Mean Steady-State Concentration vs Time Profiles for 15-mg Doses of Roxicodone and Avridi Administered in the Fasted State Every 6 Hours From 0 to 48 Hours, Followed by a Single Dose Administered in the Fed State at 54 Hours and then Fasted Dosing at 60, 66, and 72 Hours

The same mathematical method was used to generate corresponding composite PK profiles for each of the individual subjects who received single 15-mg doses of Roxicodone (n=53) and Avridi (n=51) in the fed state (study OCI1003) in combination with mean concentration vs time data for fasting administrations of Roxicodone and Avridi. Cmax,ss and Cmin,ss values were determined from each of these individual subject steady-state projections over the period following the single fed dose administered at 54 hours.

The distributions of the resulting projected Cmax,ss and Cmin,ss values for both Roxicodone and Avridi dosed according to this scenario are shown in the left and right panels of Figure 16, respectively. Consistent with the projected mean steady-state PK profiles for Roxicodone and Avridi (shown in Figure 15), the distribution of the projected individual subject Cmax,ss values for Avridi dosed according to this scenario is slightly lower than the corresponding distribution for Roxicodone dosed in the same manner. Figure 16 also shows that the distribution of the projected individual subject Cmin,ss values for Avridi dosed according to this scenario is similar to the corresponding distribution for Roxicodone dosed in the same manner.

Roxicodone 15 mg
q6h Fasting + One Fed Dose

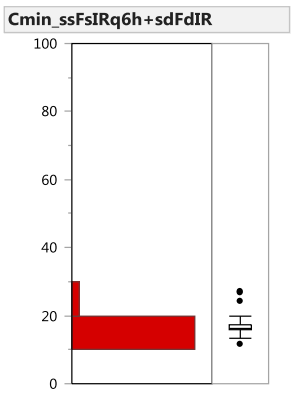
Cmax,ss



Quantiles		
100.0	maximu	97.72
99.5%		97.72
97.5%		92.57
90.0%		71.41
75.0%	quartile	61.29
50.0%	median	56.47
25.0%	quartile	52.15
10.0%		49.69
2.5%		48.12
0.5%		47.90
0.0%	minimu	47.90

Summary Statistics	
Mean	58.82
Std Dev	9.61
Std Err Mean	1.32
Upper 95% Mea	61.47
Lower 95% Mea	56.17
N	53.00

Cmin,ss

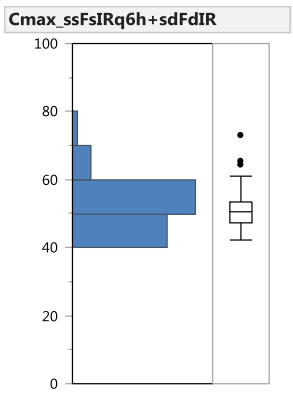


Quantiles		
100.0	maximu	27.06
99.5%		27.06
97.5%		26.95
90.0%		19.48
75.0%	quartile	17.43
50.0%	median	16.19
25.0%	quartile	15.74
10.0%		14.44
2.5%		12.13
0.5%		11.48
0.0%	minimu	11.48

Summary Statistics	
Mean	16.88
Std Dev	2.72
Std Err Mean	0.37
Upper 95% Mea	17.63
Lower 95% Mea	16.13
N	53.00

Avridi 15 mg
q6h Fasting + One Fed Dose

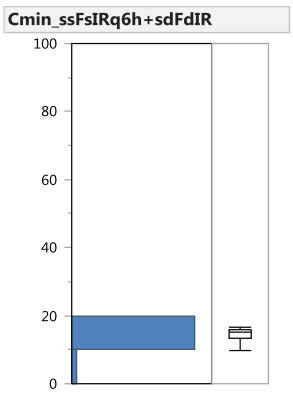
Cmax,ss



Quantiles		
100.0	maximu	72.76
99.5%		72.76
97.5%		70.50
90.0%		60.46
75.0%	quartile	53.52
50.0%	median	50.52
25.0%	quartile	47.29
10.0%		45.35
2.5%		42.62
0.5%		42.23
0.0%	minimu	42.23

Summary Statistics	
Mean	51.66
Std Dev	5.83
Std Err Mean	0.82
Upper 95% Mea	53.30
Lower 95% Mea	50.02
N	51.00

Cmin,ss



Quantiles		
100.0	maximu	16.50
99.5%		16.50
97.5%		16.43
90.0%		16.08
75.0%	quartile	15.77
50.0%	median	15.05
25.0%	quartile	13.20
10.0%		11.56
2.5%		9.82
0.5%		9.80
0.0%	minimu	9.80

Summary Statistics	
Mean	14.29
Std Dev	1.86
Std Err Mean	0.26
Upper 95% Mea	14.81
Lower 95% Mea	13.77
N	51.00

Source: Derived from study data OCI1002, OCI1003

Note: Cmax,ss and Cmin,ss are for the period beginning at 54 hours, just prior to the administration of the single fed dose in this scenario.

Figure 16 Cmax,ss and Cmin,ss Distributions for 15-mg Doses of Roxicodone and Avridi Administered in the Fasted State Every 6 Hours from 0 to 48 Hours, Followed by a Single Dose Administered in the Fed State at 54 Hours and then Fasted Dosing at 60, 66, and 72 Hours

This scenario examined the consequences of taking a dose of Avridi in the fed state following consistent fasted dosing of Avridi to steady state assuming maximum delay in Tmax. This finding of slightly lower projected Cmax,ss values and comparable projected Cmin,ss values suggests that administration of Avridi with food in a patient at steady state following prior q6h administration of Avridi under fasting conditions produces minimum and maximum oxycodone concentrations that are expected to remain within the range that would result if Roxicodone was taken under the same conditions. Thus, this dosing scenario does not raise significant safety or lack of efficacy concerns.

4.5.3 Around-the-Clock IR Oxycodone Use Scenarios Conclusions

PK modeling scenarios relevant to around-the-clock dosing of both Roxicodone and Avridi were performed. The results demonstrate that regardless of whether all of the Avridi doses are taken under fed conditions or if a dose of Avridi is taken with food following consistent fasted dosing of Avridi to steady state, the minimum and maximum oxycodone concentrations are within the range associated with Roxicodone under the same conditions.

4.6 PRN IR Oxycodone Use + Around-the-Clock ER Opioid Scenarios: IR Oxycodone Administration for Breakthrough Pain in Patients Taking an ER Around-the-Clock Opioid

4.6.1 Description of Pattern Utilization

As described in Section 6, data show that approximately 16% of patients newly prescribed IR single-entity oxycodone also had an ER opioid prescribed at some point during their treatment.. Among patients prescribed IR single-entity oxycodone with ER opioids at any time during follow-up, 60% were prescribed the 5-mg tablet strength of IR single-entity oxycodone at the time of their ER opioid prescription.

4.6.2 PK Projections Related to IR Oxycodone Administration for Breakthrough Pain in Patients Taking an Around-the-Clock ER Opioid

An additional IR use scenario is the PRN administration of IR oxycodone to treat breakthrough pain during around-the-clock administration of an ER oxycodone product. The specific use case modeled here is that of a patient taking OxyContin® 80 mg q12h in conjunction with an IR oxycodone 15-mg dose, as needed, for the treatment of breakthrough pain. Breakthrough pain may happen without regard to a meal; despite labeling and instructions, patients may dose with Avridi PRN in this setting despite the recent ingestion of a meal.

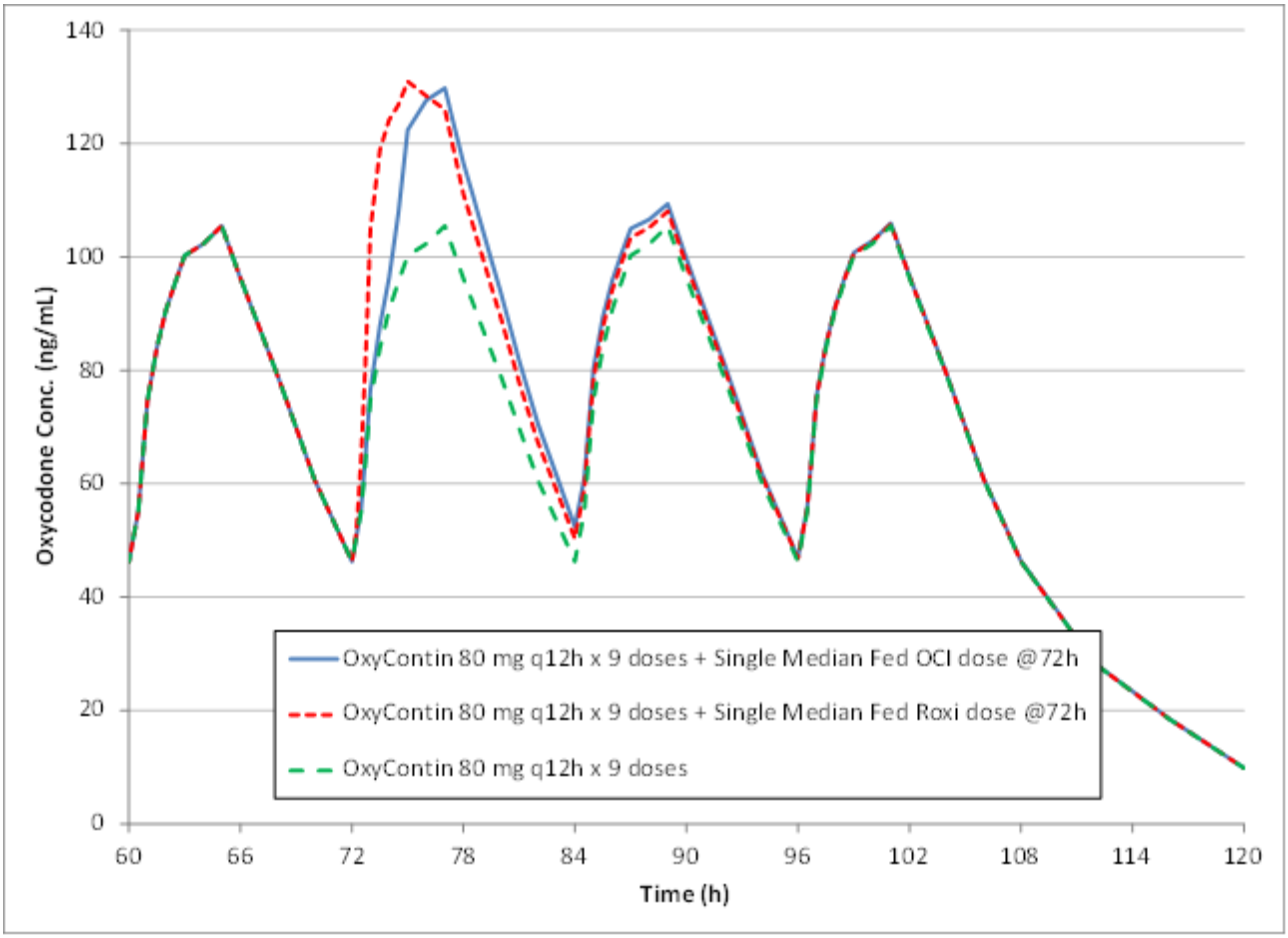
Projected Oxycodone Exposures Following Administration of a Single 15-mg Dose of Roxicodone or Avridi under Fed Conditions During Around-the-Clock (q12h) Administration of OxyContin 80-mg doses

Using linear superposition, the mean concentration vs time profiles observed following administration of single 80-mg doses of OxyContin tablets were used to generate the underlying oxycodone concentration vs time profile for around-the-clock ER oxycodone administration.

Figure 17 shows the around-the-clock mean ER oxycodone concentration at steady state. In addition, the corresponding concentration vs time profiles are shown when a single 15-mg dose of either Roxicodone or Avridi is administered at 72 hours under fed conditions in addition to the ER oxycodone.

The same methodology was used to project the results of this dosing scenario for each individual subject who received Roxicodone and Avridi in the fed state. The distributions of Cmax,ss and time to Cmax,ss (Tmax,ss) values are shown in Figure 18.

Consistent with their respective single-dose concentration vs time profiles in the fed state (see Figure 2), both Roxicodone and Avridi doses produce incremental increases in oxycodone concentration. The magnitude of the increases are comparable; however, the Roxicodone dose causes a more rapid rise in oxycodone concentration. The similarity of Cmax,ss values and the differences in Tmax,ss values are shown in the left and right panels of Figure 18, respectively.

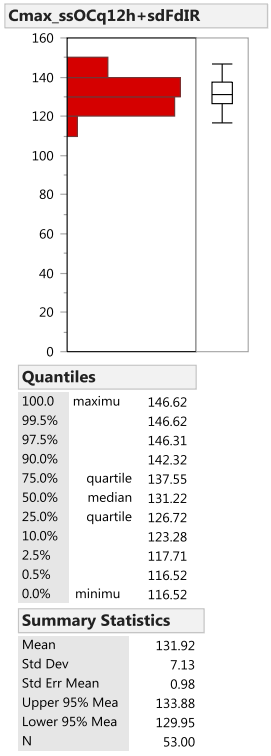


Source: Derived from study data OCI1002, OCI1003, OTR1008
Abbreviation: OCI=Avridi; Roxi=Roxicodone

Figure 17 Projected Mean Steady-State Concentration vs Time Profiles for OxyContin 80-mg Tablets Administered Every 12 Hours With a Single Roxicodone or Avridi 15-mg Dose Administered in the Fed State at 72 Hours

Steady-State OxyContin 80 mg q12h + Single Fed 15 mg IR dose at 72 h

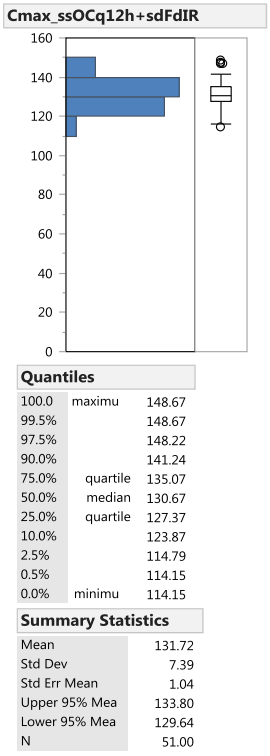
Roxicodone



Quantiles		
100.0	maximu	146.62
99.5%		146.62
97.5%		146.31
90.0%		142.32
75.0%	quartile	137.55
50.0%	median	131.22
25.0%	quartile	126.72
10.0%		123.28
2.5%		117.71
0.5%		116.52
0.0%	minimu	116.52

Summary Statistics	
Mean	131.92
Std Dev	7.13
Std Err Mean	0.98
Upper 95% Mea	133.88
Lower 95% Mea	129.95
N	53.00

Avridi

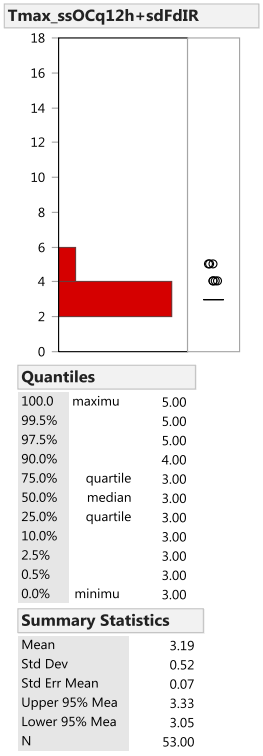


Quantiles		
100.0	maximu	148.67
99.5%		148.67
97.5%		148.22
90.0%		141.24
75.0%	quartile	135.07
50.0%	median	130.67
25.0%	quartile	127.37
10.0%		123.87
2.5%		114.79
0.5%		114.15
0.0%	minimu	114.15

Summary Statistics	
Mean	131.72
Std Dev	7.39
Std Err Mean	1.04
Upper 95% Mea	133.80
Lower 95% Mea	129.64
N	51.00

Steady-State OxyContin 80 mg q12h + Single Fed 15 mg IR dose at 72 h

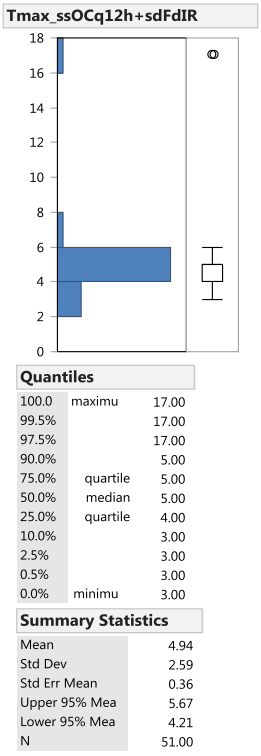
Roxicodone



Quantiles		
100.0	maximu	5.00
99.5%		5.00
97.5%		5.00
90.0%		4.00
75.0%	quartile	3.00
50.0%	median	3.00
25.0%	quartile	3.00
10.0%		3.00
2.5%		3.00
0.5%		3.00
0.0%	minimu	3.00

Summary Statistics	
Mean	3.19
Std Dev	0.52
Std Err Mean	0.07
Upper 95% Mea	3.33
Lower 95% Mea	3.05
N	53.00

Avridi



Quantiles		
100.0	maximu	17.00
99.5%		17.00
97.5%		17.00
90.0%		5.00
75.0%	quartile	5.00
50.0%	median	5.00
25.0%	quartile	4.00
10.0%		3.00
2.5%		3.00
0.5%		3.00
0.0%	minimu	3.00

Summary Statistics	
Mean	4.94
Std Dev	2.59
Std Err Mean	0.36
Upper 95% Mea	5.67
Lower 95% Mea	4.21
N	51.00

Source: Derived from study data OCI1002, OCI1003, OTR1008
Cmax units = ng/mL

Figure 18 Cmax,ss and Tmax,ss Distributions for Projected Mean Steady-State Concentration vs Time Profiles for OxyContin 80-mg Tablets Administered Every 12 Hours With a Single Roxicodone or Avridi 15-mg Dose Administered in the Fed State at 72 Hours

4.6.3 PRN IR Oxycodone Use + Around-the-Clock Opioid Scenario Conclusion

This scenario examined the consequences of taking a single 15-mg dose of Avridi in the fed state while the patient is at steady state following consistent around-the-clock q12h dosing of the ER oxycodone product, OxyContin tablets. Both Avridi and Roxicodone produced similar incremental increases in oxycodone concentration. The magnitude of the increases are comparable; however, the Roxicodone dose causes a more rapid rise in oxycodone concentration. These findings suggest that administration of Avridi in the fed state for breakthrough pain in patients taking an around-the-clock ER opioid produces minimum and maximum oxycodone concentrations that are expected to remain within the range that would result if Roxicodone was taken under the same conditions. Thus, this dosing scenario does not raise clinically significant safety or lack of efficacy concerns.

4.7 Conclusions Regarding Safety Assessment of Avridi Dosing Scenarios

Although dosing instructions for Avridi tablets will specify administration in the fasted state (ie, one hour before or two hours after eating), it is possible that patients will not be fully compliant with this instruction. The potential consequences of various Avridi dosing scenarios with food (PRN dosing, steady-state dosing around-the-clock, PRN dosing in conjunction with an around-the-clock ER opioid) have been assessed using PK modeling to project resulting oxycodone vs time profiles and corresponding distributions for individual subject PK parameters (eg, Cmax, Tmax). In each case, comparisons were made between the PK profiles and PK parameter distributions for Avridi dosing and those for the reference drug, Roxicodone, using the same mg dose and dosing conditions. While some of these comparisons show that administration of Avridi with food results in delayed Tmax that could result in delayed onset of analgesia, all of the scenarios indicate that the range of oxycodone concentrations associated with Avridi, including maximum oxycodone concentrations, remain within the range associated with routine use of Roxicodone according to its full prescribing information. These results suggest that in the event that Avridi is administered with food, this should not raise clinically significant safety concerns.

5 ABUSE DETERRENCE

5.1 Overview

Oxycodone is a Schedule II controlled substance with an abuse liability that is similar to that of morphine (Riley 2008; Roxicodone Package Insert 2009). Tampering, such as crushing, grinding, or dissolving of IR formulations is typically conducted so that the drug becomes available for faster absorption by parenteral administration (eg, IV injection) or mucosal application (eg, IN insufflation) in order to achieve rapid euphoric effects not intended with oral administration of the intact drug product. For example, abusers crush IR oxycodone tablets (eg, Roxicodone), before snorting them or dissolving them in water for injection to provide a faster onset of action (see Section 6 for discussion of abusers by route).

Avridi tablets are formulated with abuse-deterrent properties to reduce IV and IN abuse potential by including:

1. A combination of gelling agents that deter IV abuse by producing a viscous gel when a tablet (crushed or whole) is dissolved in small volumes of aqueous media;
2. Sodium lauryl sulfate, an aversive agent that deters IN abuse by producing temporary aversive effects with IN administration of the crushed tablet.

The Avridi tablet is not hardened nor formulated to be resistant to crushing or other attempts to reduce particle size.

A series of studies have evaluated the abuse-deterrent properties of Avridi, consistent with evaluations described in the final guidance issued by FDA on the development of abuse-deterrent opioid formulations (FDA Guidance to Industry: *Abuse-Deterrent Opioids – Evaluation and Labeling*, April 2015). These assessments include laboratory-based *in vitro* manipulation and extraction studies (Category 1) and a clinical abuse potential study (Category 3). These premarket data indicate that Avridi is formulated with physicochemical barriers to IV abuse and is expected to result in a meaningful reduction in the abuse of oxycodone via the IN route.

5.2 Laboratory Manipulation and Extraction Studies (Category 1)

5.2.1 Overall Summary

Laboratory-based *in vitro* manipulation studies were conducted to evaluate the ease with which the abuse-deterrent properties of Avridi could be defeated or compromised. The comprehensive studies were designed to simulate common “real world” manipulations as well as more sophisticated methods of separation and extraction. The results determined both the strengths and weaknesses of the abuse-deterrent properties of the formulation. As noted, Avridi is an IR formulation and rapid oxycodone release and recovery is expected in many testing scenarios. Therefore, the primary goals of the studies were to:

1. Separate or inactivate the aversive agent (sodium lauryl sulfate) such that oxycodone is available for IN abuse without aversive effects;
2. Characterize the feasibility of preparing Avridi for IV injection.

Where relevant, side-by-side comparisons were made to the nonabuse-deterrent reference IR oxycodone drug, Roxicodone. An overview of the findings are presented below.

- Avridi is not formulated to resist crushing; therefore, as expected, Avridi tablets are easily crushed using common household tools. This is consistent with the aversion and gelling technology of Avridi to deter abuse, rather than a physical barrier like hardness.
- In pretreatment experiments of intact tablets, decomposition of both oxycodone HCl and sodium lauryl sulfate is observed under certain experimental conditions. In some cases, sodium lauryl sulfate degradation occurs at a faster rate than oxycodone; however, it would be difficult for an individual to determine if any conditions are optimal to degrade sodium lauryl sulfate while avoiding substantial loss of oxycodone .
- As expected from an IR formulation, extraction of oxycodone and sodium lauryl sulfate is generally rapid and efficient with a variety of household solvents. Importantly, sodium lauryl sulfate is generally extracted in equivalent amounts to oxycodone under these conditions. In certain specialized uncommon solvent systems, some differences in solubility between oxycodone and sodium lauryl sulfate are noted; isolating oxycodone from solutions for the purpose of abuse via the IN route is likely to be difficult and tedious, and the success rate is unknown.
- In contrast with Roxicodone, Avridi is difficult to prepare for IV injection. The gelling properties of Avridi excipients in combination with the large tablet size render small volumes (2-5 mL) of solvent too viscous for injection. Larger volumes of solvent are necessary to counter the gelling and the amount of powder; however, syringeability remains limited even when using large gauge needles (18G) at larger volumes. Select pretreatment conditions may somewhat increase the amount of oxycodone aspirated; however, even under these conditions, the amount of oxycodone aspirated remains much lower than that observed with Roxicodone.
- Neither Avridi nor Roxicodone are amenable for abuse via smoking.
- Attempted precipitation of free base oxycodone from Avridi is generally unsuccessful. With knowledge of chemistry, access to reagents, and willingness to expend significant time, cost, and effort, some immiscible organic solvents might be utilized to extract oxycodone base from solution; however, depending upon the nature of the solvent, sodium lauryl sulfate and gelling excipients may be present in the residue.
- As compared with Roxicodone, Avridi requires substantially more time, cost, effort, and expertise on the part of the abuser to successfully prepare the formulation (ie, separate oxycodone from sodium lauryl sulfate) for IN administration without aversive consequences.
- As compared with Roxicodone, the gelling and aversive components of Avridi tablets are expected to deter the IV and IN routes of abuse.

5.2.2 Background Information and Results

5.2.2.1 Overview

The studies were designed to simulate common “real world” manipulations as well as more sophisticated methods of tampering and extraction by employing an iterative and adaptive approach. The experimental protocols were comprehensive in assessing the effects of a variety of physical and

chemical manipulations including particle size reduction, solvent extraction, tablet pretreatments, and free base isolation techniques. Preparations for administration by alternate routes such as IN, IV injection, and smoking/free basing were considered. Since the abuse-deterrent properties of Avridi are not intended to resist crushing or other means of particle size reduction, the *in vitro* studies were focused on inactivation or extraction/separation of the aversive agent (sodium lauryl sulfate) and the characterization of the gelling agents with regard to abuse by IV injection. An independent expert in drug abuse and abuser tampering methods was consulted to ensure a link between "real-life" approaches to potential abuse of IR oxycodone and the experimental protocols developed for these studies. Additionally, full consideration was given to the information provided in FDA's draft guidance (at the time) on abuse-deterrent opioids for Category 1 studies (FDA Guidance to Industry: *Abuse-Deterrent Opioids – Evaluation and Labeling*, January 2013).

This comprehensive set of experiments provides detailed scientific data on the strengths and weaknesses of the Avridi formulation when subjected to currently known and potential new tampering attempts across a broad range of conditions. It is intended that this Category 1 assessment will be meaningful and directionally predictive of the other three categories outlined in the FDA guidance, including; PK testing (Category 2), abuse potential studies (Category 3), and epidemiologic studies (Category 4). Cumulatively, the outcome of premarketing studies Category 1through 3 should provide an understanding of the overall abuse potential of the product as will be determined in planned postmarketing epidemiologic studies.

Results for 7 comprehensive *in vitro* abuse-deterrence studies are described herein. A description of the studies is found in Table 5.

Table 5 Description of Avridi In Vitro Abuse-Deterrence Studies

Study	*Relevant Route of Abuse*	*Purpose*
Physical Manipulation (Crushing)	IN, IV	Assess commonly employed household tools used to crush tablets and determine the particle size distribution. Standardize test articles and ensure resulting tablet powders are reproducible and uniform.
Tablet Pretreatments	IN	Determine the amount of recoverable oxycodone HCl and sodium lauryl sulfate after various pretreatments to characterize potential selective degradation of sodium lauryl sulfate in attempt to isolate oxycodone HCl for IN administration.
Syringeability (Preparation for injection)	IV	Determine the ability to aspirate tablet solutions through a needle into a syringe; determine the amount of oxycodone HCl present in the aspirate; experimental variables include extraction duration, agitation, temperature, needle gauge, solution volume, solvent, and tablet pretreatment.
Simulated Smoking (Vaporization)	Smoking	Characterize heat dependent vaporization; determine recovery of oxycodone HCl from vapors and crushed tablet residue after simulated smoking procedures.
Household Solvent Extraction	IN	Determine extraction efficiency of oxycodone HCl and sodium lauryl sulfate in a variety of household solvents under ambient and elevated temperatures to characterize potential for selective isolation of oxycodone HCl and possible degradation of sodium lauryl sulfate. Solvent characteristics include household liquids of varying pH and ionic strength.
Advanced Solvent Extraction	IN	Determine extractability and solubility of oxycodone HCl and sodium lauryl sulfate using a variety of uncommon "advanced solvents" to understand potential for separation of oxycodone and sodium lauryl sulfate.
Oxycodone Free Base Isolation	Free Basing/Smoking	Convert oxycodone HCl to solid free base, attempt isolation, determine recovery and purity.

5.2.2.2 Design Principles

In keeping with Purdue's continued approach to conducting objective, rigorous, and relevant *in vitro* abuse-deterrent studies and following the FDA guidance for abuse-deterrent opioids, (FDA Guidance to Industry: *Abuse-Deterrent Opioids – Evaluation and Labeling*, April 2015), the principles outlined below were implemented in developing and executing the *in vitro* testing plan for Avridi.

Expert Consultation

Studies were designed in consultation with Edward Cone, PhD (Adjunct Professor of Psychiatry, Department of Psychiatry and Behavioral Sciences, Johns Hopkins; Former Chief of the Chemistry and Drug Metabolism Section, NIDA), who is considered an expert in opioid product tampering. Dr. Cone helped in providing a testing regimen that replicated likely "real world" attempts at defeating this product as well as applying a systematic and iterative approach to ensure that the product was tested comprehensively.

Independent 3rd Party Laboratories

After extensive development, many studies were carried out under protocol by Contract Research Organizations (CROs).

Comprehensive Study Conditions Including Failure Limits

A wide range of solvent types, temperatures, times, etc. were employed to fully characterize the behavior of the formulation including failure limits wherever possible.

Sufficient Number of Replicates

Using results (n=5) from crushed tablet extraction method verification testing by 4 laboratories (3 CROs and Purdue), the repeatability variance component was calculated. This approach incorporated variability introduced by different analysts and laboratories as well as by the analytical procedures, including repeatability (replicate analysis), tablet grinding, and partitioning into dosage units. The overall standard deviation of this dataset was 2.8 for oxycodone HCl analysis and 5.4 for sodium lauryl sulfate analysis. From this, CIs were calculated for the mean to predict how precise the expected results would be based on sample size. Using 4 samples to calculate the average estimates, the true mean was within approximately ±4.3% and ±8.7% for oxycodone HCl and sodium lauryl sulfate analyses, respectively. This is below 10% and, therefore, determined to be acceptable. Most studies were performed using 4 replicates. In certain scenarios, 2 or 3 replicates were used due to difficulty in performing the procedure.

Suitable Comparators and Controls

Roxicodone is a currently marketed IR oxycodone comparator to Avridi that does not have abuse-deterrent properties. Where appropriate, the highest available dosage strength (30 mg) of Roxicodone was evaluated in the testing scenarios. In addition, sodium lauryl sulfate, as well as the free base and hydrochloride salt forms of oxycodone were used as controls when necessary to understand the performance of a specific method.

Tablet Strengths and Test Article Information

All Avridi dosage strengths have the same total tablet weight (approximately 400 mg) and the same qualitative composition. All strengths are also quantitatively the same with the exception of the amounts of oxycodone HCl and filler, microcrystalline cellulose. Thus, the amounts of gelling agents and aversive agent are fixed across the dosage strengths. The 30-mg tablet strength contains the highest amount of API and the lowest amount of filler. The 5-mg strength contains the lowest amount of API and the highest amount of filler. The 30-mg and 5-mg tablet strengths bracket all other intermediate strengths; therefore, the *in vitro* abuse deterrence studies employed a bracketing approach using the highest and lowest strengths. The Avridi formulation has no inherent resistance to crushing; therefore, tests were performed using intact tablets and uniformly crushed tablets. Although most experimentation was performed on both tablet strengths, results for the more abuser-relevant dose (30 mg) are most often presented in this document.

.

5.2.2.3 Results of *In Vitro* Abuse-deterrent Studies

A summary of the objectives and results of each of the 7 comprehensive *in vitro* abuse-deterrence studies is presented below.

5.2.2.4 Physical Manipulation (Crushing) Overview

5.2.2.4.1 Goals and Design

Avridi tablets were developed using gelling agents and a nasal aversive agent as potential deterrents to abuse; the tablets were not formulated to be resistant to crushing or other attempts to reduce particle size. Crushing is a common first step to prepare a formulation for alternate routes of administration. Ease of crushing for this aversive-containing formulation is important to facilitate concurrent exposure to sodium lauryl sulfate when administered by the IN route. Tablet crushing was standardized to provide reproducible methods for creating uniform tablet powders.

Crushing results using each household tool were similar.

Intact Avridi (5 and 30 mg) and Roxicodone are shown in Figure 19. Average tablet weights and dimensions for Avridi and Roxicodone are shown below the figure. Avridi tablets are considerably larger than Roxicodone tablets.

Figure 19 Intact Avridi and Roxicodone Tablets

Average Weight and Dimensions of Avridi Tablets and Roxicodone Tablets

Tablet	*Weight (mg)*	*Length (mm)*	*Width (mm)*	*Thickness (mm)*
Avridi 5 mg	400	16	7	5
Avridi 30 mg	397	16	7	5
Roxicodone 30 mg	101	N/A	6 (diameter)	3

5.2.2.5 Tablet Pretreatment

5.2.2.5.1 Goals and Design

The goal of tablet pretreatment studies was to assess the impact of two different methods of tablet pretreatment on recoverable amounts of oxycodone HCl and sodium lauryl sulfate. The study determined the feasibility of degrading sodium lauryl sulfate while maintaining high recovery of oxycodone HCl for the purposes of IN abuse of without aversive effects.

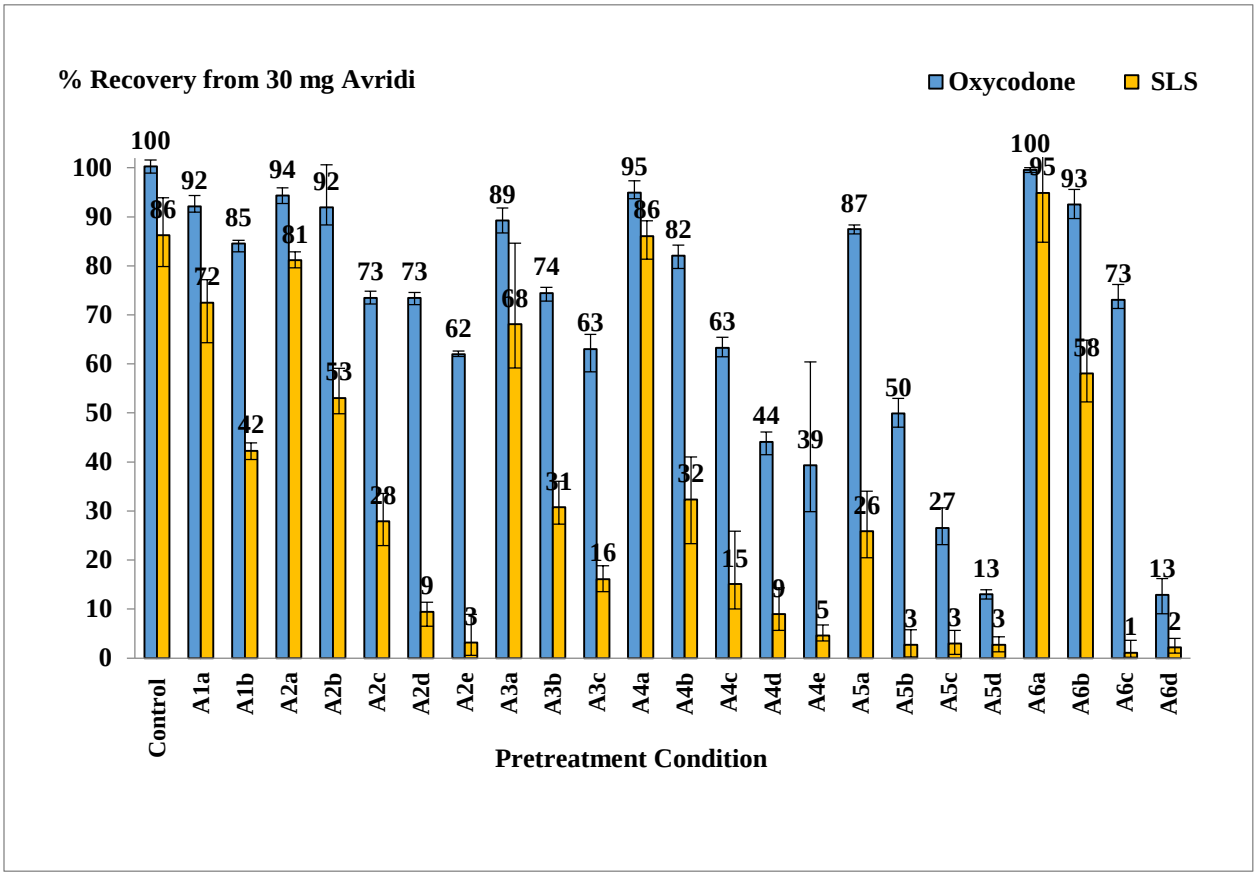
As these studies were designed to determine effects on selective degradation of sodium lauryl sulfate, analysis of the comparator Roxicodone formulation, which does not contain sodium lauryl sulfate, was unnecessary.

5.2.2.5.2 Results

Pretreatment Method A

Results for pretreated tablets are compared with recovery of oxycodone HCl and sodium lauryl sulfate obtained for untreated Avridi tablets (control). Representative results for tablet pretreatment studies for Avridi 30-mg tablets are presented in Figure 20. Pretreatment conditions are presented on the x-axis in each graph. Percent recovery for oxycodone HCl (blue) and sodium lauryl sulfate (yellow) are represented by bars.

Differences were observed for the recovery profile of oxycodone HCl and sodium lauryl sulfate. As expected, recovery of both oxycodone HCl and sodium lauryl sulfate decreased under select experimental conditions. Faster rates of degradation of sodium lauryl sulfate compared with oxycodone HCl were observed for some pretreatment conditions; however, as shown, the majority of pretreatment conditions resulted in substantial recovery of sodium lauryl sulfate or degradation of oxycodone HCl.

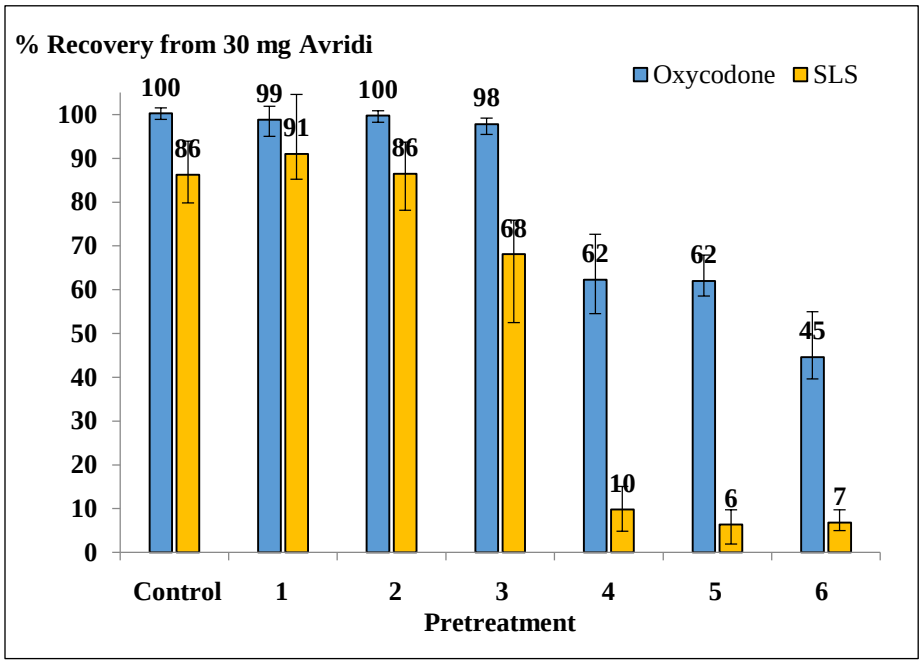


Note: Average percent label claim presented; error bars represent the range of results. SLS=sodium lauryl sulfate.

Figure 20 Average Results for Avridi 30-mg Pretreated Tablets (Method A) – Recovery of Oxycodone HCl and Sodium Lauryl Sulfate

Method B

Results for pretreated Avridi tablets were compared to recovery of oxycodone and sodium lauryl sulfate obtained for untreated Avridi tablets (control). Oxycodone HCl and sodium lauryl sulfate degradation profiles for Avridi 30-mg tablets after pretreatment method B are presented in Figure 21. Significant reduction in recovery of both oxycodone HCl and sodium lauryl sulfate occurred for some pretreatment conditions. The degree of degradation was higher for sodium lauryl sulfate than oxycodone HCl.



Note: Average percent label claim presented; error bars represent the range of results. SLS=sodium lauryl sulfate.

Figure 21 Average Results for Avridi 30-mg Pretreated Tablets (Method B) – Recovery of Oxycodone HCl and Sodium Lauryl Sulfate

5.2.2.5.3 Conclusion

Pretreatment resulted in similar changes to recovery of oxycodone API and sodium lauryl sulfate; however, select experimental conditions caused sodium lauryl sulfate to degrade at a faster rate than oxycodone API. Regardless, it would be difficult for an individual to determine which pretreatment method is optimal to degrade sodium lauryl sulfate while avoiding substantial loss of oxycodone. Attempts to isolate oxycodone HCl from sodium lauryl sulfate for the purposes of IN abuse would require significant time, cost, and effort on the part of an abuser.

5.2.2.6 Syringeability

5.2.2.6.1 Goals and Design

Avridi tablets contain excipients that gel when hydrated, a property that is expected to decrease abuse by IV injection. The goal of this experiment was to assess the limits of the Avridi formulation with regard to susceptibility to preparation for abuse via injection. The amount of oxycodone HCl available to the abuser as well as the total volume of solution aspirated through a needle and into a syringe were determined. Readily injectable volumes of solvent, 2 mL, as well as larger volumes, 5 mL and 10 mL, were studied to determine both the "real world" performance of Avridi and Roxicodone as well as determine the limitations. Use of 2 mL volume of solvent for preparation with Avridi was not studied because of the inability of smaller volumes of solvent to wet the large amount (400 mg) of tablet powder. Conversely, Roxicodone tablets are smaller, weighing approximately 100 mg, and are readily prepared for injection with 2 mL of solvent; therefore, this volume was studied only for Roxicodone.

Intact and crushed Avridi tablets were studied to determine the effects of particle size on extraction of oxycodone HCl and on the gelling properties of Avridi. A wide range of needle gauges were used to evaluate realistic scenarios, such as use of common 27 G insulin needles as well as more extreme conditions using larger less common 18G needles. An additional variety of extraction parameters were studied as well.

An associated goal to those outlined above was to determine whether pretreating tablets would alter extraction efficiency of intact and crushed tablets.

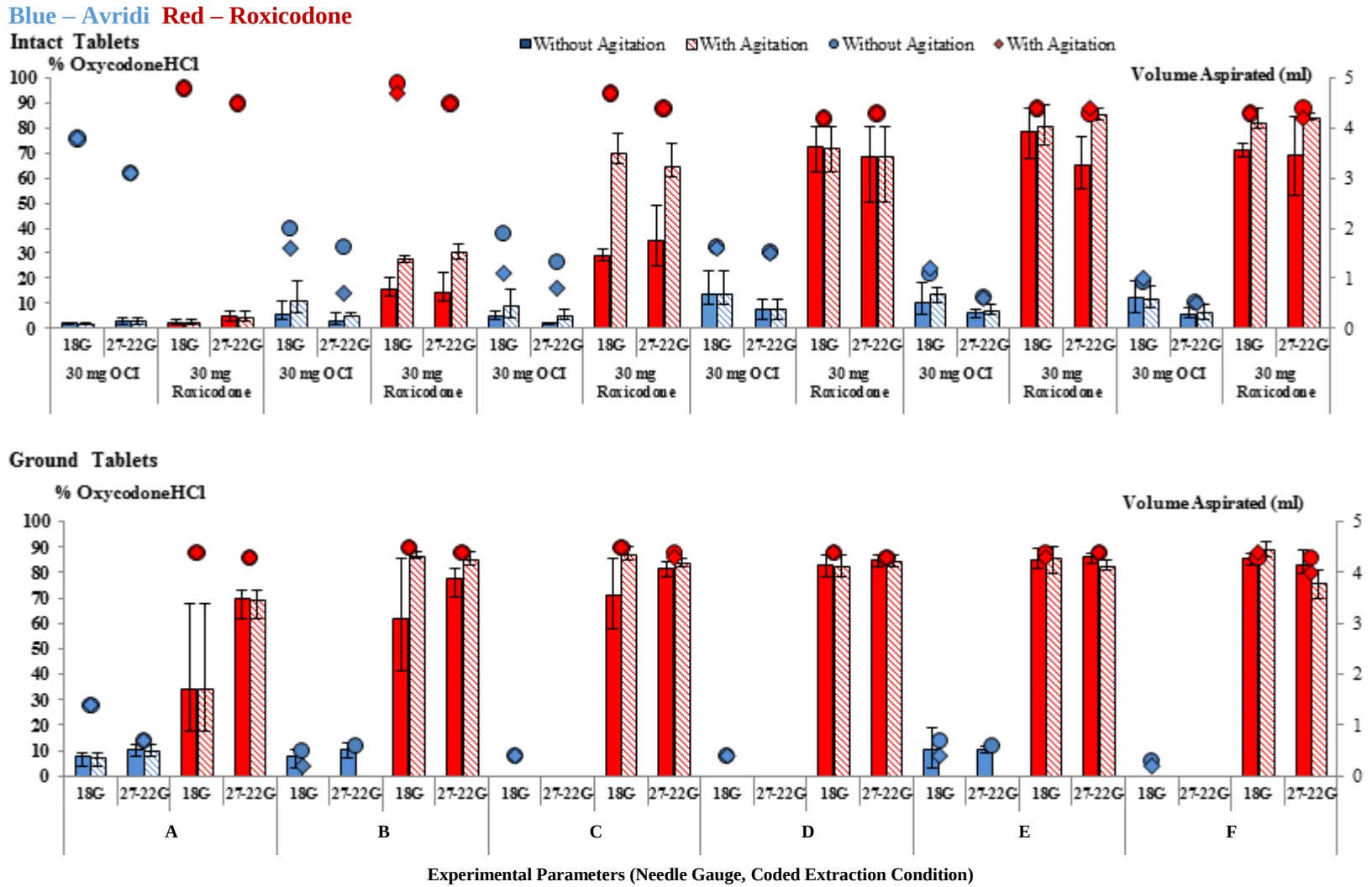
Roxicodone was tested as a comparator.

5.2.2.6.2 Results

Comparison of Avridi and Roxicodone in Solvent A

Ground Roxicodone tablets were readily prepared for IV injection in 2 mL of solvent A. Much of the 2 mL preparatory volume (1.3 to 1.8 mL) was successfully aspirated into the syringe, with recoveries of oxycodone HCl as high as 78%. Avridi could not be prepared for injection using 2 mL of solvent A due to the large amount (400 mg) of powder obtained from 1 dosage unit. The tablet material absorbed all of the liquid present.

For the 5 mL preparatory volume of solvent A, both Avridi and Roxicodone tablets were studied and results are shown in Figure 22. The top figure presents data for intact tablets; the bottom figure presents data for crushed tablets. The x-axis contains extraction and testing conditions (including needle gauge and extraction condition). Data bars are presented by color to identify amount of oxycodone HCl aspirated per product; data points present volume aspirated using the same color scheme. Error bars represent the range of results. As shown, for extraction of ground and intact Avridi 30-mg tablets in 5 mL of solvent A, no testing condition (including particle size, needle gauge, extraction condition) resulted in meaningful aspiration of oxycodone HCl. Using the largest bore needle (18G), 14% (or 5 mg) was the average most oxycodone HCl aspirated from an Avridi 30-mg tablet. Most ground tablet conditions studied resulted in unsuccessful aspiration. In contrast, results for Roxicodone tablets were as high as 86% for intact tablets and 89% for crushed samples. With few exceptions, agitating the sample did not significantly affect extraction efficiency.



Note: Average percent label claim (vertical bars) and volume aspirated (data points) presented; error bars represent the range of results.

Figure 22 Average Syringeability Results for Avridi 30-mg Tablet Compared With Roxicodone – 5 mL Solvent A Preparatory Volume

Figure 23 summarizes the results obtained for the various studies performed for Avridi tablets.

At the top of each data column, the preparatory volume of solvent and needle gauge are identified. On the left, the test article condition and extraction conditions are presented. Data boxes shaded dark green with hash marks indicate the conditions in which aspiration is unsuccessful (ie, the sample is too viscous to aspirate > 10% of the preparatory volume of solvent). To facilitate data interpretation and to understand when experimental variables caused change in syringeability, color coding is used. The colors represent the total amount of oxycodone HCl aspirated and the concentration of the aspirate in mg/mL. Dark green shading presents the conditions in which ≤ 5 mg of oxycodone HCl was successfully aspirated, regardless of concentration. When ≥ 6 mg of oxycodone HCl was aspirated, color coding is determined by concentration. The amount of oxycodone HCl available in 1 mL is the realistic amount available for injection when using the common insulin syringe (27G or 28G needle attached to 1 mL syringe barrel). Aspirate concentrations are presented incrementally; ≤ 2.5 mg/mL (light green), 2.6-5.0 mg/mL (yellow), 5.0-10.0 mg/mL (orange), and > 10.0 mg/mL (red).

As previously noted, for extraction of Avridi 30-mg tablets in 5 mL of solvent A, no testing condition (including particle size, needle gauge, time, or temperature) resulted in meaningful aspiration of oxycodone HCl. Using the largest bore needle (18G), 14% (or 5 mg) was the most oxycodone HCl aspirated. Most conditions studied resulted in unsuccessful aspiration. Larger volumes of solvent A resulted in greater aspiration of oxycodone HCl; however, the total amount of oxycodone HCl recovered from the 10 mL preparatory volumes was 3-37% for 18G needles and 5-24% for 22-27G needles. The concentration of aspirate for these conditions was low, ≤ 2.5 mg/mL.

Extraction with solvent B and solvent C resulted in some increase in the ability to aspirate Avridi tablet solutions (eg, 32% oxycodone HCl recovered in the 18G/5 mL study in Solvent B, Extraction Condition A, compared with unsuccessful aspiration for the same conditions using Solvent A). The highest amounts aspirated for Solvent B and Solvent C using 22-27G needles were 28% and 34%; respectively. In contrast, results for Roxicodone tablets were as high as 89% using Solvent A.

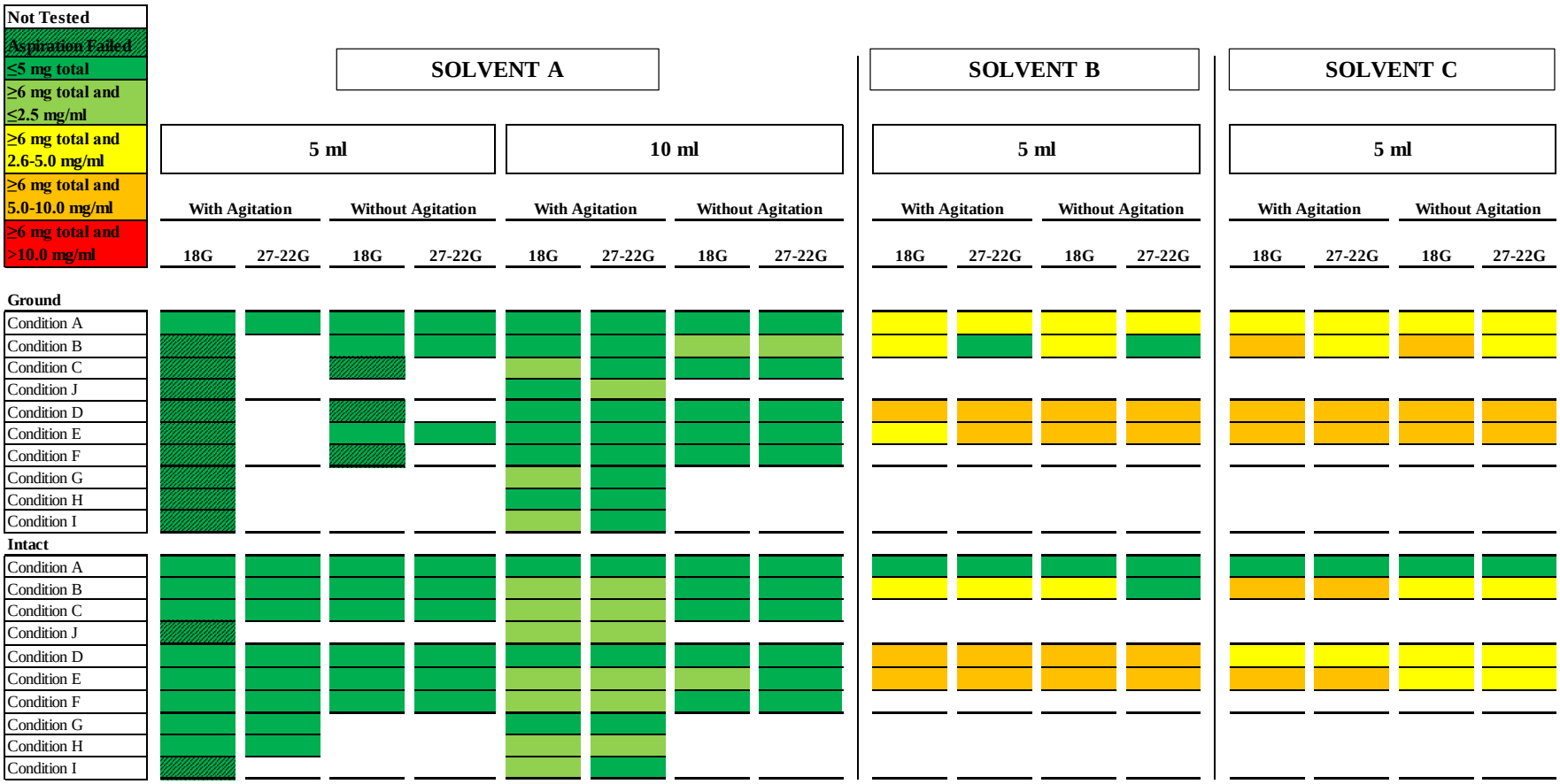


Figure 23 Color-Coded Syringeability Results for Avridi 30-mg Tablet in Solvent A, Solvent B, and Solvent C

Pretreated Avridi Tablets in Solvent A

Figure 24 shows the effect of pretreatment on the amount of oxycodone HCl recovered after preparation for injection with 5 mL of solvent A. The figure contains the absolute percent difference between untreated (control) and pretreatment B results. The x-axis in each graph contains the needle gauge, tablet condition, and extraction condition. Results for pretreatment B represent the worst case with regard to increase in oxycodone HCl aspirated. Pretreatment C results are similar to those for pretreatment B. Pretreatment A resulted in slightly less oxycodone HCl aspirated overall and pretreatment D resulted in the least amount of oxycodone HCl aspirated.

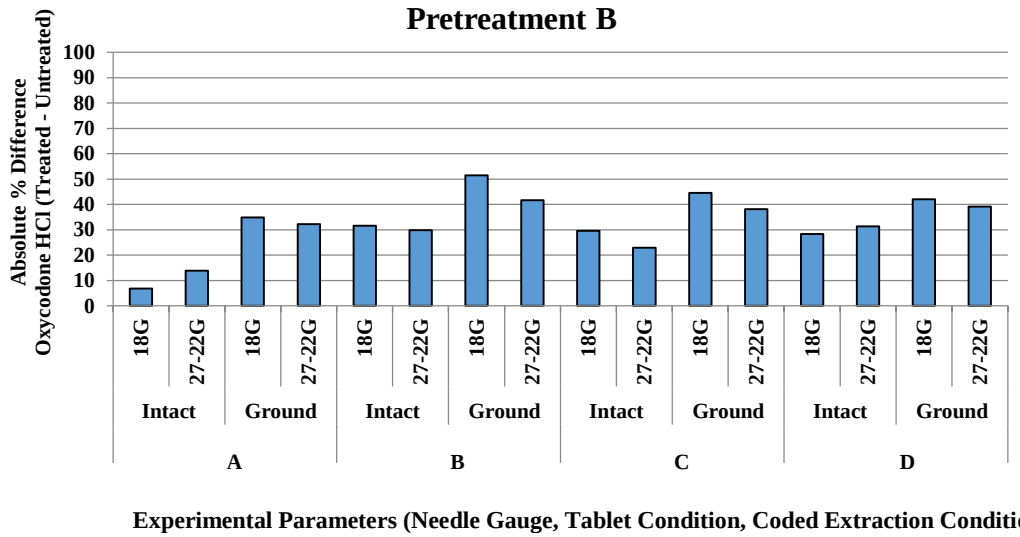


Figure 24 Average Difference in Syringeability Results for Avridi 30-mg Tablets in Solvent A (Pretreated - Untreated)

5.2.2.6.3 Conclusion

The success of syringeability practices for preparing a tablet for abuse by IV injection is a combination of two factors; the release of API from tablets during the period of extraction and the viscosity of liquid for aspiration. The presence of gelling agents in Avridi tablets and the large tablet size either produce a solution too viscous to aspirate or the solvent is completely absorbed by the tablet mass when small volumes were used for preparation. Under most experimental conditions, Avridi was difficult, and sometimes nearly impossible, to aspirate and prepare for injection.

Although larger volumes of solvent countered the viscosity of the solution, the resultant aspirate contained < 5 mg oxycodone HCl or was low in concentration (≤ 2.5 mg/mL). Certain solvents and select pretreatment conditions resulted in somewhat more successful syringeability for both large gauge (18 G) and smaller gauge (27-22 G) needles although even with optimal pretreatment, recovery of oxycodone HCl (amount that can be injected) was generally ≤ 50% of

the available dose and was low in concentration. Determination of the pretreatment conditions must also be considered; it is difficult to determine which pretreatment conditions will not result in substantial loss of oxycodone HCl. Those used in these experiments were carefully selected.

In contrast to the difficulty in preparing Avridi for injection, Roxicodone was readily prepared for injection, with more than 89% availability of oxycodone HCl in a small volume of solution.

5.2.2.7 Simulated Smoking (Vaporization)

5.2.2.7.1 Goals and Design

The experiment was designed to simulate abuse via smoking and inhalation by determining the heat-dependent vaporization and recoverable oxycodone from ground Avridi tablets. Inhalation was simulated with a gel Sep-Pak® (solid phase extraction cartridge) apparatus. This apparatus uses standard bonded silica column technology and solid phase extraction to trap the vapors generated after heating and vaporizing Avridi tablets. Upon completion of the experiment, the Sep-Pak® cartridge was removed and extracted with solvent to recover the total amount of trapped oxycodone HCl. For mass balance purposes, the residue left behind after pyrolysis was also extracted with solvent and assayed. Oxycodone HCl content that was not vaporized or left as a residue was presumably lost from thermal degradation.

Comparator data were generated from manipulated Roxicodone tablets. Oxycodone free base was analyzed as a control to ensure the integrity of the experiments.

5.2.2.7.2 Results

Table 6 presents the results for the vaporization of Avridi, Roxicodone, and the oxycodone base. Total recovered oxycodone vapor from Avridi 30- mg tablets was ≤ 4%, even when the oxycodone HCl content in the tablet residue decreased to ≤ 10%. Total recovery of both vapors and residue decreased due to decomposition of oxycodone HCl. A similar response was observed for the comparator, Roxicodone, where vaporization of oxycodone HCl was ≤ 8%.

The free base form was vaporized with optimal conditions (CA), resulting in approximately 79% vaporization with 4% remaining in the sample residue.

Table 6 Simulated Smoking Oxycodone Recovery Results for Avridi 30 mg, Roxicodone 30 mg, and Control (Vapors)

	% Oxycodone Recovered from Vapors		
Experimental Condition	***Avridi 30 mg***	***Roxicodone 30 mg***	***Oxycodone Base (Control)***
AA	2	3	11
AB	3	2	28
BA	3	5	41
BB	3	4	78
CA	4	8	79
CB	2	7	72

5.2.2.7.3 Conclusions

These experiments were developed to determine the extent to which it might be possible to abuse Avridi tablets by vaporization and inhalation under optimized conditions. The experiments were carried out to achieve a maximum amount of vaporized API without leaving residual API in the analysis tube. These results demonstrated that smoking attempts with Avridi would be highly inefficient. Overall, the amounts of vaporized oxycodone HCl from both Avridi and Roxicodone, even after experimental optimization, were low (≤ 8%).

Due to the incorporation of the HCl salt form of oxycodone, neither Avridi nor Roxicodone were found to be amenable to abuse via smoking.

5.2.2.8 Household Solvent Extraction

5.2.2.8.1 Goals and Design

Directly ingestible solutions as well as other household solvents representing a range of pH, polarity, and ionic concentrations were used to extract oxycodone HCl and sodium lauryl sulfate from Avridi tablets. Given that Avridi is an IR formulation, it is expected that oxycodone HCl will be released quickly; however, the studies were conducted for two purposes:

(1) to characterize the complete time course for extraction of oxycodone HCl and sodium lauryl sulfate from Avridi tablets, and

(2) to determine if preferential extraction of oxycodone HCl or separation of sodium lauryl sulfate could be achieved such that oxycodone HCl is available for IN abuse without aversive effects.

The effects of temperature, agitation, and the influence of particle size on the extraction rate were also studied. Roxicodone was studied as the comparator.

Extractions were performed using small volumes (30 mL, approximately equivalent to one ounce) to recreate conditions that mimic the “real world” circumstances of potential abuse. Agitation speed was optimized. Extensive development work was performed to determine the sampling times for both ground and intact tablets, and solvents and conditions were selected based on the results from these studies. Because Avridi is an IR formulation, the time course studied was shorter than would be needed for an ER formulation. The goal was to generate kinetic data where > 80% release or a plateau (no further oxycodone release) was achieved.

A summary of the scope of these studies is found in Table 7. A subset of these experiments was performed without agitation.

Table 7 Solvents and Extraction Time Points for Household Solvent Extraction (With Agitation) for Avridi 30-mg Tablets

	Extraction Time Points	
Solvent	***Intact Test Article***	***Ground Test Article***
A	2, 20, 60 min	30 sec, 2, 20 min, 2 hr
B	2, 20, 60 min	30 sec, 2, 20 min
C	2, 20, 60 min	30 sec, 2, 20 min, 2 hr
D	2, 20, 60 min (2 hr at 95°C only)	30 sec, 2, 20 min, 2 hr
E	2, 20, 60 min	30 sec, 2, 20 min
F	2, 20, 60 min	30 sec, 2, 20 min
G	2, 20, 60 min	30 sec, 2, 20 min
H	2, 20, 60 min	30 sec, 2, 20 min
I	2, 20, 60 min	30 sec, 2, 20 min
J	2, 20, 60 min	30 sec, 2, 20 min

5.2.2.8.2 Results

Extraction in Solvent A With and Without Agitation

Figure 25 and Figure 26 present results for extraction of ground and intact Avridi and Roxicodone tablets in Solvent A, respectively. In these figures, average results for oxycodone HCl release from Avridi and Roxicodone tablets are found on the left; average results for sodium lauryl sulfate release from Avridi tablets are found on the right.

As Avridi is designed to immediately release oxycodone HCl, the expectation is that oxycodone HCl would show significant release within a short extraction time in many solvents. With agitation, the extraction of oxycodone HCl from ground Avridi 30-mg tablets reached a plateau of > 80% release by the initial time point of 30 seconds. The comparator, ground Roxicodone tablets, showed similar release (> 80%) of oxycodone HCl at 30 seconds.

Regarding intact tablet performance for both Avridi and Roxicodone, extraction rate was typically correlated with solvent-dependent tablet disintegration. As shown in Figure 25, Avridi 30-mg tablet extraction in Solvent A was slower than for ground tablets; 69% was released at 20 minutes (at room temperature) and 78% was released at 20 minutes at high temperature. The disintegration time for Roxicodone intact tablets was 20 minutes at room temperature; therefore, oxycodone HCl release was low (22%) until 20 minutes. However, once disintegration occurred, oxycodone HCl release was $\geq$ 97%.

For ground tablets, both temperature and agitation does not seem to have an appreciable effect on extraction rate. In general, agitation and temperature increased the rate of release from intact tablets. No preferential extraction of oxycodone HCl was observed as sodium lauryl sulfate release mirrors oxycodone HCl release in all solvent A extraction conditions.

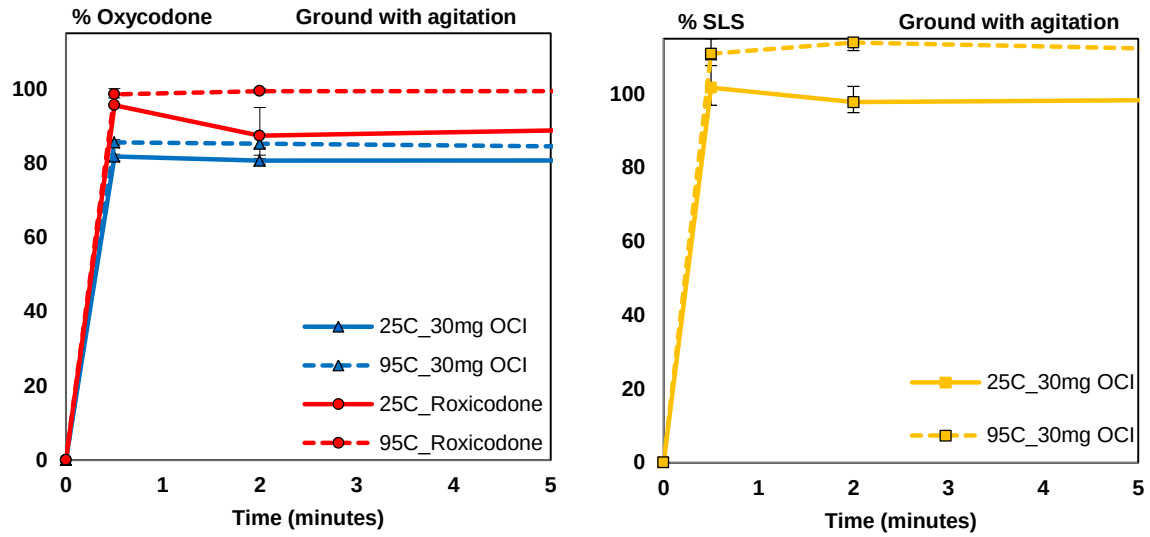


Figure 25 Solvent A Ground Tablet Extraction of Avridi 30 mg and Roxicodone 30 mg (With Agitation, 25°C and 95°C) – Expanded Scale

Note: Average percent label claim presented; error bars represent the range of results.

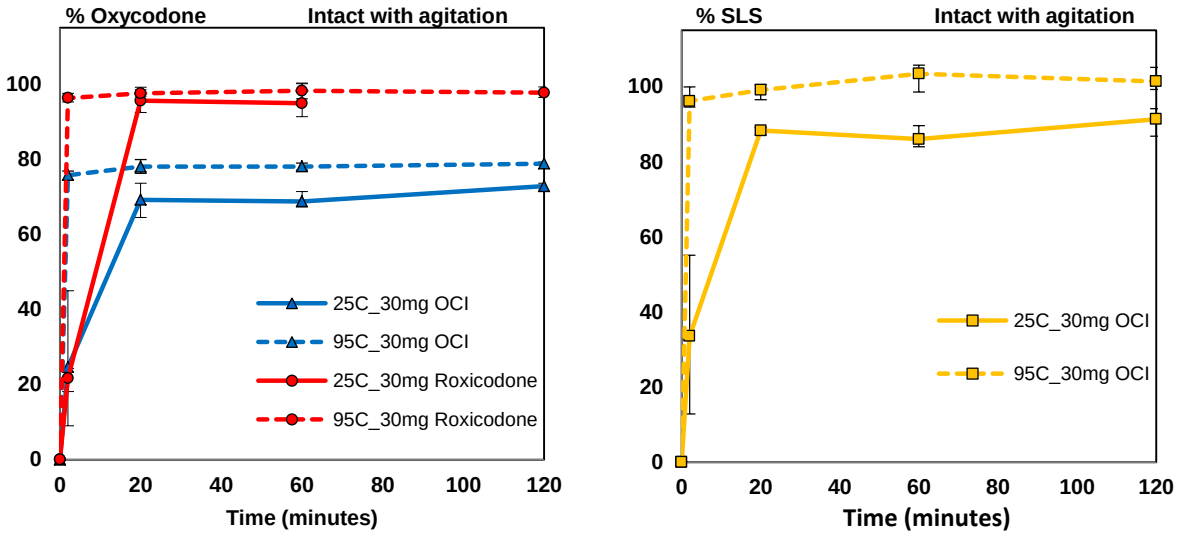


Figure 26 Solvent A Intact Tablet Extraction of Avridi 30 mg and Roxicodone 30 mg (With Agitation, 25°C and 95°C) – Full Scale

Note: Average percent label claim presented; error bars represent the range of results.

Extraction in a Variety of Other Solvents with Agitation

The results presented for solvent A are largely representative of all household solvents evaluated in this study. As expected of an IR formulation, extraction of oxycodone HCl and sodium lauryl

sulfate was generally rapid for both ground and intact Avridi tablets in all additional solvents studied with the following exceptions:

1) Low oxycodone HCl and sodium lauryl sulfate release was observed from intact Avridi tablets in Solvent B due to lack of disintegration of the tablets throughout the course of the experiment.
2) Low oxycodone HCl release was observed from Avridi and Roxicodone tablets in Solvents I and J. Sodium lauryl sulfate was released in higher amounts. These results were further investigated in the free base isolation study.

5.2.2.8.3 Conclusion

Extraction of oxycodone HCl and sodium lauryl sulfate from Avridi tablets was typically rapid and efficient with a variety of household solvents. Importantly, sodium lauryl sulfate was generally extracted in equivalent amounts under most conditions; thus, these solvents and conditions did not separate oxycodone HCl from sodium lauryl sulfate.

5.2.2.9 Advanced Direct Extraction from Tablets

5.2.2.9.1 Goals and Design

This goal of this study was to determine if preferential extraction of oxycodone HCl or separation of sodium lauryl sulfate could be achieved such that oxycodone HCl is available for IN abuse without aversive effects. A distinction between this experiment and that described in Section 5.2.2.8 is the removal of the extraction rate component. The purpose of this experiment was to determine the extractability of oxycodone HCl and sodium lauryl sulfate from ground tablets using a variety of less common "advanced solvents." Ten advanced solvents ranging in polarity and ionic strength were studied.

Avridi 30-mg tablets were studied in these experiments. Roxicodone was not included as a comparator because the tablets do not contain sodium lauryl sulfate; however, a 1:1 mixture of oxycodone HCl and sodium lauryl sulfate was also prepared in each solvent and evaluated as controls.

5.2.2.9.2 Results

Recovery of oxycodone is ≥ 60% in all solvents studied. Sodium lauryl sulfate was found to be mostly insoluble in a subset of specialized solvents. Some differences in recovery were observed using the control mixture of oxycodone and sodium lauryl sulfate; formulation excipients may cause variable recovery.

Results for Avridi 30-mg tablets and oxycodone HCl/sodium lauryl sulfate mixtures are summarized in Table 8.

Table 8 Average Recovery of Oxycodone HCl and Sodium Lauryl Sulfate From Advanced Solvent Extraction of Avridi 30-mg Tablets and Controls

	% Oxycodone HCl		*% SLS*	
	Avridi 30 mg tablet	***Oxycodone HCl + SLS***	***Avridi 30 mg tablet***	***Oxycodone HCl + SLS***
Solvent A	82	91	93	99
Solvent B	93	94	94	94
Solvent C	77	92	64	28
Solvent D	60	36	N/A*	N/A*
Solvent E	86	98	96	68
Solvent F	88	77	89	38
Solvent G	94	101	N/A*	N/A*
Solvent H	95	101	N/A*	N/A*
Solvent I	91	103	N/A*	N/A*
Solvent J	96	104	N/A*	N/A*

*Not tested because sodium lauryl sulfate is mostly insoluble in these solvents and therefore not in solution.
SLS=sodium lauryl sulfate.

5.2.2.9.3 Conclusion

Due to solubility differences, the potential for preferential separation of oxycodone HCl was observed with a few specific solvent systems; however, it is doubtful that these attempts would be routinely successful in a household setting. Before IN administration is attempted, an abuser must identify the solvent, the separation phases, and develop a method for complete separation of the formulation components. This requires significant motivation, time, effort, knowledge, and access to specific chemicals in some instances.

5.2.2.10 Oxycodone Free Base Isolation – Precipitation

5.2.2.10.1 Goals and Design

Although most drug users who attempt to smoke opioids do so directly with the existing formulation, some users may attempt to isolate the free base form for smoking. The goal of this study was to assess whether oxycodone free base could be produced and isolated from Avridi tablets. This study was conducted by dissolving ground Avridi tablets in a specific solution and altering the solution to precipitate free base. This was followed by attempts to isolate the precipitated free base. The study determined the time and effort expended as well as maximum amount and purity of oxycodone free base and sodium lauryl sulfate recovered. The experiment was performed with Avridi 30-mg tablets. No comparator was included in this study.

5.2.2.10.2 Results

Method development utilized oxycodone HCl raw material in solution instead of the Avridi tablet to optimize the process. Experimental variables were determined and optimized, including the relationship between oxycodone HCl and free base concentrations (time and temperature), salting effect, and separation of solids from liquids. These optimized conditions resulted in 85% conversion of oxycodone HCl raw material to free base. This method was used as a guide to determine the experimental parameters for the Avridi ground tablet procedure. After conversion, the resulting sample was a cloudy suspension; obvious precipitation was difficult to observe. Attempts were made to filter this solution through a coffee filter; however, this filtration step was

extremely slow. As an alternative to filtration, the solution was centrifuged at 5000 rpm for 10 minutes to aid in separation of the solid and liquid phases.

Results from this experiment showed that both oxycodone base and sodium lauryl sulfate were present in the recovered solid (Table 9). After significant time and effort (over 3 hrs) was expended in performing this experiment, the average oxycodone free base recovered was 17 mg in an average of 344 mg total solids. The oxycodone base purity of the solids recovered was only 5%.

Table 9 Recovery and Purity of Oxycodone Free Base and Sodium Lauryl Sulfate From Avridi 30-mg Tablets (Precipitation)

Sample	*Total Recovered Solid (mg)*	*Oxycodone Base In Solid*	*Base Purity in Solid*	*SLS In Solid*	*Recovered SLS Purity*
1	336 mg	16.7 mg (62%)	5%	6.7 mg (22%)	2%
2	352 mg	17.2 mg (64%)	5%	6.8 mg (23%)	2%

Note: the percent base recovered is label claim converted from HCl salt to free base (30 mg of oxycodone HCl is equivalent to 27 mg oxycodone free base). SLS=sodium lauryl sulfate.

5.2.2.10.3 Conclusion

In contrast to starting with pure oxycodone HCl raw material of which 85% is converted to oxycodone base, isolation of free base oxycodone from Avridi is generally unsuccessful. The presence of formulation excipients make it difficult to completely precipitate oxycodone free base from Avridi tablet solutions. The precipitate consisted of small amounts of oxycodone base (5%), and the procedure primarily resulted in precipitation of inert materials (excipients). Free basing oxycodone from Avridi tablet is tedious, time consuming, and inefficient. It should be noted that these results were generated using optimized parameters after extensive internal development. This application of scientific knowledge, laboratory equipment, and chemical reagents to obtain the maximum amount of oxycodone base from Avridi tablets is not reflective of what might be successful in the "real world" of everyday abusers.

5.2.2.11 Oxycodone Free Base Isolation – Liquid/Liquid Extraction

5.2.2.11.1 Goals and Design

In the previous study, the feasibility of precipitation of oxycodone free base from solution was studied. In order to further explore methods for free basing Avridi tablets, this study evaluated whether liquid/liquid extraction with a water immiscible organic solvent could isolate oxycodone free base. Although not commonly available to everyday abusers, a range of organic solvents was studied to represent a worst case with regard to potential conversion to and isolation of the free base.

The study determined the time and effort expended as well as maximum amount of oxycodone free base and sodium lauryl sulfate recovered. The experiment was performed with Avridi 30-mg tablets. No comparator was included in this study.

5.2.2.11.2 Results

This study is a continuation of the previous free base isolation studies wherein the procedures for initial conversion to and precipitation of oxycodone free base from ground Avridi tablets were optimized.

As noted in Table 10, in all solvents studied, average recovery of oxycodone base was 23-26 mg or 85%-96%. The purity of the free base recovered could not be determined as the solid material could not be removed from the separatory funnel and was therefore extracted *in situ*. The weight of the total solids recovered from the organic layer was not obtained. The total time required to generate free base oxycodone using this procedure was approximately 3.75 hours. As a result of one experimental step, sodium lauryl sulfate was destroyed and therefore not recovered from these experiments.

Table 10 Recovery of Oxycodone Base (Liquid/Liquid Extractions)

Solvent	***Sample***	***Base Recovered***
Solvent A	1	23.9 mg (89%)
	2	24.3 mg (90%)
Solvent B	1	25.7 mg (95%)
	2	25.2 mg (93%)
Solvent C	1	22.7 mg (84%)
	2	22.5 mg (83%)

Note: the percent base recovered is label claim converted from hydrochloride salt to free base (30 mg of oxycodone HCl is equivalent to 27 mg oxycodone free base).

5.2.2.11.3 Conclusion

The results indicate that with knowledge of chemistry, access to reagents, and willingness to expend significant time and effort; some immiscible organic solvents might be utilized to extract oxycodone base from solution; however, depending upon the nature of the solvent, excipients would be present in the residue. As noted for the previous study, these results were generated using optimized parameters after extensive internal development. This application of scientific knowledge, specialized laboratory equipment, and chemical reagents to obtain maximum amount of oxycodone base from Avridi tablets is not reflective of what might be performed in the "real world" of everyday abusers.

5.2.3 Overall Conclusions

The comprehensive *in vitro* abuse-deterrent assessment of Avridi tablets has shown that the formulation will present barriers to physicochemical manipulations that are expected to serve to deter abuse by the IV and IN routes. As compared with the reference drug, Roxicodone, Avridi requires substantially more time and effort, and in many cases specialized equipment and expertise on the part of the abuser, to potentially prepare the formulation for nonoral routes of abuse without aversive consequences.

As expected of an IR formulation, the release rate of oxycodone HCl was rapid in most solvents under most conditions. Importantly, sodium lauryl sulfate was also quickly extracted and present in combination with oxycodone. Of the 20 solvents studied, the possibility of separating sodium

lauryl sulfate from oxycodone as a function of solubility difference was observed for 5 specialized solutions. None of these are common household solutions and subsequent steps to isolate oxycodone are likely to be difficult, tedious, and have an unknown success rate.

Pretreatment studies showed that only a few experimental conditions studied produced appreciable preferential degradation of sodium lauryl sulfate over oxycodone, although in most cases some sodium lauryl sulfate remained and substantial amounts of oxycodone HCl were lost. Furthermore, the gelling properties of Avridi made preparation for abuse by IV injection difficult and in some instances, nearly impossible, whereas Roxicodone tablets could be readily prepared by extracting nearly all oxycodone API into a small volume of solvent. Other studies demonstrated that Avridi was not amenable to smoking, and free base isolation was an inefficient and difficult method of preparation for abuse.

Although Avridi tablets might be successfully prepared for purposes of abuse using complicated techniques by highly motivated abusers, doing so would require considerable knowledge and planning as well as significant expenditures of time and effort compared with Roxicodone, which can be easily prepared for IN abuse (simple crushing) and IV abuse (crushed and dissolved in 2 mL water).

5.3 Clinical Abuse Potential Studies (Category 3)

5.3.1 Overall Summary

A clinical study was conducted to evaluate the abuse potential of Avridi following physical manipulation and administration via the IN route (Category 3). The study design is consistent with the FDA Guidance to Industry: *Abuse-Deterrent Opioids – Evaluation and Labeling,* April 2015) as follows:

- This study was designed as a randomized, double-blind, placebo- and positive-controlled crossover study and was conducted in nondependent recreational opioid users who had experience with the IN route of abuse. These subjects provided the most sensitive population for an IN abuse potential study because they represent the population most at risk for abusing opioids in this manner. In addition, these subjects are better able to tolerate the IN route of administration. As an added precaution, a naloxone challenge test which provided a clinical assessment of withdrawal signs and symptoms was performed on all subjects during the screening phase to ensure that subjects were not opioid-dependent.

- Roxicodone was selected as the positive control for comparison of IN abuse potential relative to Avridi and for comparison with placebo to validate the study and clinical endpoints. Placebo powder was used as a placebo control to establish the frequency and magnitude of changes in clinical endpoints that may have occurred in the absence of active treatment as well as to minimize subject and investigator bias.

- The IN crushed Avridi treatment was included to represent the manipulation that would cause the highest release of the product and the highest plasma oxycodone concentrations. Avridi administered as an intact tablet orally was also included to explore the abuse potential of orally administered Avridi compared with placebo tablet.

- To maintain blinding across routes of administration, a double-dummy procedure was used such that subjects received an intact tablet for oral administration and a crushed tablet (or powder) for IN administration at each treatment period. Recognizing that Avridi contains an aversive agent with near immediate effects and that there are differences in appearance between Avridi and Roxicodone tablets, treatments were blinded to the greatest extent possible to reduce potential bias during data collection and evaluation of clinical endpoints.

An overview of the study findings are presented below.

- The physicochemical and aversive properties of Avridi significantly reduced oxycodone abuse potential when administered IN; this was demonstrated by statistically significant reductions in the magnitude of "drug liking" and lower scores on "overall drug liking" and "willingness to take again" compared with Roxicodone, despite similar oxycodone PK. An analysis of percent reduction in drug liking VAS peak effects of IN crushed Avridi compared with IN crushed Roxicodone supported the analysis of peak scores on "drug liking."

- The physicochemical and aversive properties of Avridi produced greater negative effects and subject-rated irritation effects compared with Roxicodone.

- Nasal discomfort was the most common treatment-emergent AE (TEAE); the incidence was highest after IN crushed Avridi (62.9%),compared with IN crushed Roxicodone (28.6%). Nasal congestion, throat irritation, rhinorrhea, cough, dyspnoea, lacrimation increased, and ocular hyperaemia were also common and occurred at a considerably higher incidence with IN crushed Avridi than with any other treatment. These nasal/oropharyngeal AEs were considered highly unpleasant and led to substantial decrease in drug liking. None of these TEAEs was considered serious, and none led to injury of the nasal mucosa. These AEs are consistent with the intended abuse-deterrent properties of the formulation.

- Additionally, the inability of nearly half of the subjects to successfully insufflate the entire dose of crushed Avridi was likely related to its local aversive effects, and supports that Avridi's excipients would confer significant and meaningful abuse-deterrent effects.

5.3.2 Study OCI1005 IN Abuse Potential

Study Objectives:

Primary:

- To evaluate the abuse potential and pharmacodynamic (PD) effects of IN administration of crushed Avridi compared with crushed Roxicodone and placebo.

Secondary:

- To evaluate the safety and tolerability of IN administration of crushed Avridi
- To determine the PK profile of IN crushed Avridi compared with IN crushed Roxicodone
- To explore the abuse potential, PD, and PK effects of orally administered intact Avridi.

Methods:

This was a single-center, double-blind, double-dummy, randomized, placebo-controlled and active-controlled study in healthy nondependent recreational drug users with IN opioid experience. The study consisted of 4 phases: screening, qualification, treatment, and follow-up.

In the qualification phase, subjects were administered single doses of IN crushed Roxicodone 30 mg and IN placebo powder in a randomized fashion (washout period of 24 hours). The qualification phase identified subjects who could reproducibly distinguish IN crushed Roxicodone 30 mg from placebo powder and thus be suitable for entry into the treatment phase of the study.

During the treatment phase, subjects received each of the following 4 treatments according to the randomization schedule:

- Avridi 30 mg, crushed, IN
- Roxicodone 30 mg, crushed, IN (positive control)
- Avridi 30 mg intact, oral
- placebo powder, IN (placebo control)

There was a 72-hour washout period between study drug administrations.

The primary PD measures were bipolar visual analog scale (VAS) for "at this moment drug liking", "overall drug liking", and "take drug again". Secondary measures included: "high" VAS, "bad effects" VAS, subjective drug value, and subject-rated assessment of irritation. Pupillometry was included as an objective physiological PD measure of opioid effects. It is a sensitive measure of central opioid activity and appears to be resistant to tolerance development with repeated administration. Open-ended feedback on the overall drug experience was also solicited from subjects at the end of each treatment period. PD measures were collected at multiple time points up to 24 hours postdose.

PD endpoints for the treatment phase were analyzed using a mixed-effects model for a crossover study. From each model, means, 95% CIs and *P*-values for treatments and treatment differences were computed.

Blood samples for determining oxycodone plasma concentrations were obtained for each subject after study drug administration during each of the treatment periods. Standard PK metrics were calculated for oxycodone and summarized using descriptive statistics.

Safety was assessed by AEs; vital signs; clinical laboratory assessments; 12-lead electrocardiograms (ECGs); and physical examination findings.

Results:

Thirty-six qualified subjects (30M/6F) with ages ranging from 23 to 52 years (mean: 34.6 years) were randomized into the treatment phase and 35 subjects (97.2%) completed the study. One subject (2.8%) discontinued due to subject's choice.

All 35 subjects who received IN crushed Roxicodone insufflated 100% of the dose. Of the 35 subjects who received the IN crushed Avridi treatment, 19 (54.3%) insufflated 100% of the dose. The remaining 16 subjects (45.7%) were unable to insufflate the full dose; among these subjects,

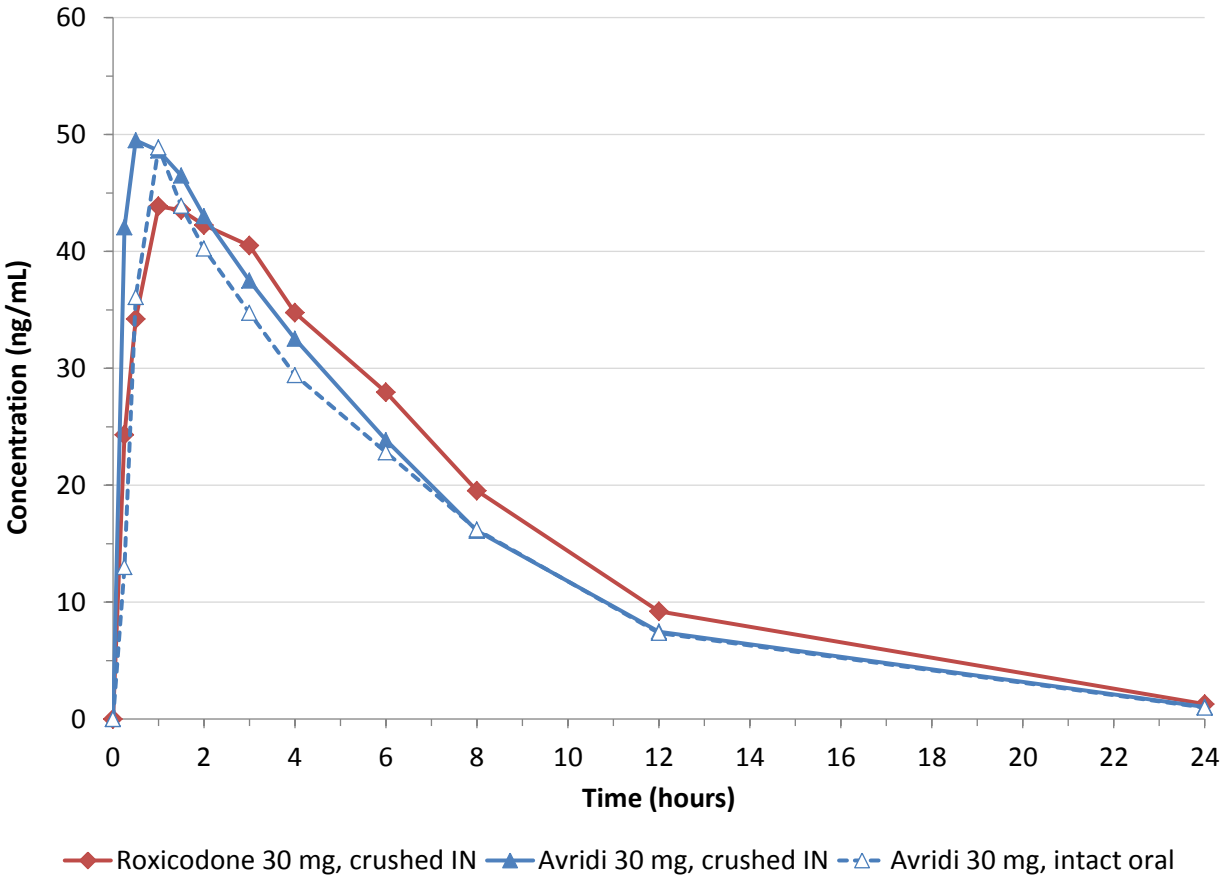
the percentage of dose insufflated ranged from 11% to 98%, with a mean of 85.8%. This inability to successfully insufflate the entire dose was likely related to the local aversive effects of Avridi tablets.

Pharmacokinetics

The mean oxycodone plasma concentrations over time are shown in Figure 27, and PK metrics are presented in Table 11.

Although some subjects had difficulty insufflating crushed Avridi, exposure to oxycodone was comparable following administration of IN crushed Roxicodone, IN crushed Avridi, and oral intact Avridi. Oxycodone peak plasma concentrations were achieved more rapidly after IN crushed Avridi and resulted in slightly higher early exposure (Cmax and AUC0-3h) compared with all other treatments, while AUCinf was similar.

Median Tmax for IN crushed Roxicodone, IN crushed Avridi, and oral intact Avridi were 1.6, 0.6 and 1.1 hours postdose, respectively.



Source: CSR Figure 14.2.1.1
IN=intranasal

Figure 27 Mean Oxycodone Plasma Concentrations Over Time (Study OCI1005)

Table 11 Pharmacokinetic Metrics for Oxycodone (Study OCI1005)

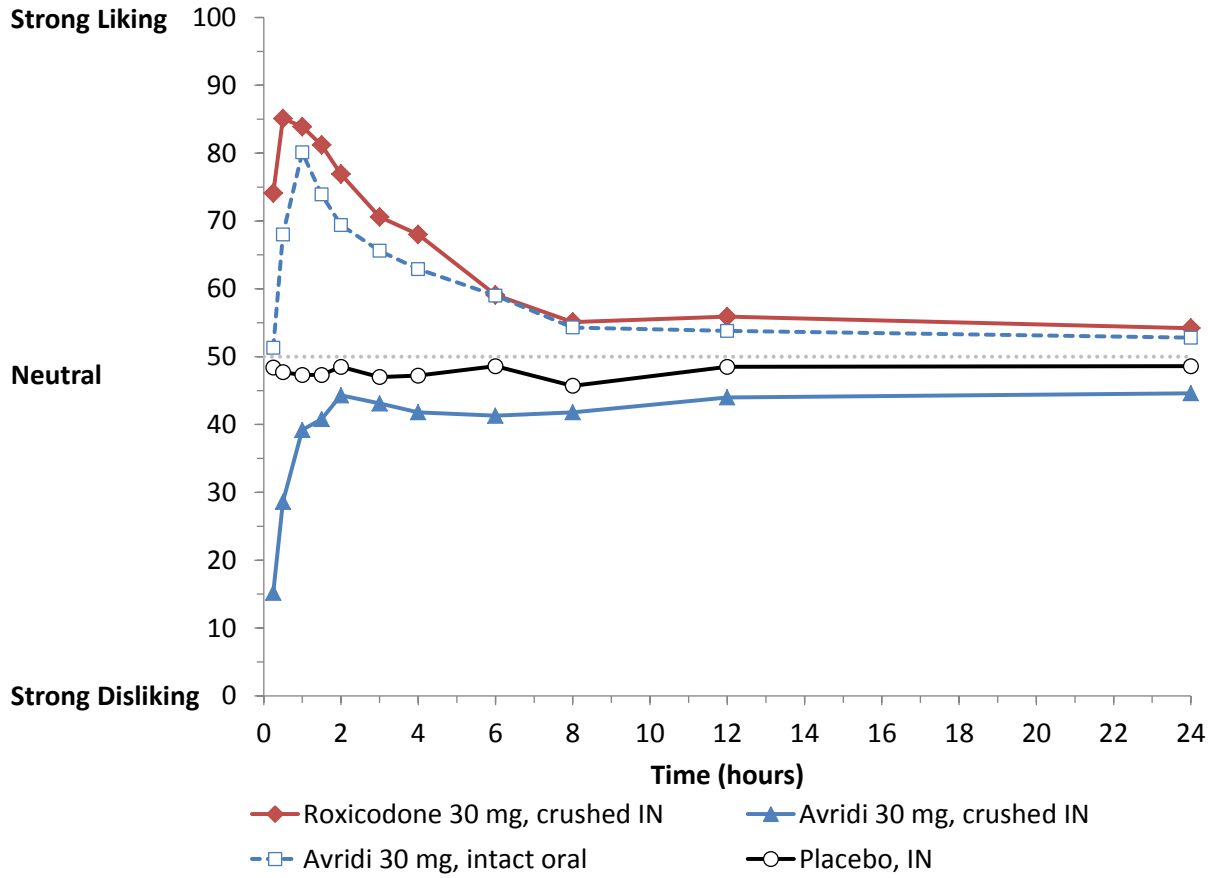
	Cmax (ng/mL)	AUC0-3h (h*ng/mL)	AUCinf (h*ng/mL)	Tmax (h)	t½ (h)
Roxicodone 30 mg, crushed IN (N=35)					
Mean (SD)	50.21 (12.71)	112.6 (28.16)	394.5 (93.19)	–	–
Median	49.10	113.8	412.7	1.65	4.18
Range	18.9–73.9	44–160	208–653	0.30–6.17	3.16–4.95
Avridi 30 mg, crushed IN (N=35)					
Mean (SD)	55.47 (18.15)	127.9 (43.97)	369.1 (127.6)	–	–
Median	57.50	128.7	377.2	0.62	4.03
Range	10.7–87.8	23.8–211	59.3–582	0.28–3.17	2.94–4.83
Avridi 30 mg, intact oral (N=35)					
Mean (SD)	55.03 (15.51)	109.2 (34.67)	340.5 (75.17)	–	–
Median	53.70	113.9	341.0	1.15	3.95
Range	21.6–96.3	18.9–187	167–533	0.30–6.17	2.99–4.75

Source: Table 14.2.1.2
AUC0-3h=area under the plasma concentration vs time curve from time zero to 3 hours postdose; AUCinf=area under the plasma concentration vs time curve extrapolated to infinity; Cmax=maximum plasma concentration; IN=intranasal; SD=standard deviation; t½=terminal elimination half-life; Tmax=time to maximum plasma concentration.

Pharmacodynamics

Study Validity: Statistically significant maximum effect (Emax) differences between IN crushed Roxicodone and placebo for the primary measures of "at this moment drug liking" (90.2 vs 49.9, respectively; P <0.001) and feeling "high" (85.9 vs 8.6, respectively; P <0.001) were observed, confirming the sensitivity of the measures and study validity.

Figure 28 shows that despite similar oxycodone PK, significantly lower "at this moment drug liking" scores were reported for IN crushed Avridi compared with IN crushed Roxicodone and oral intact Avridi.

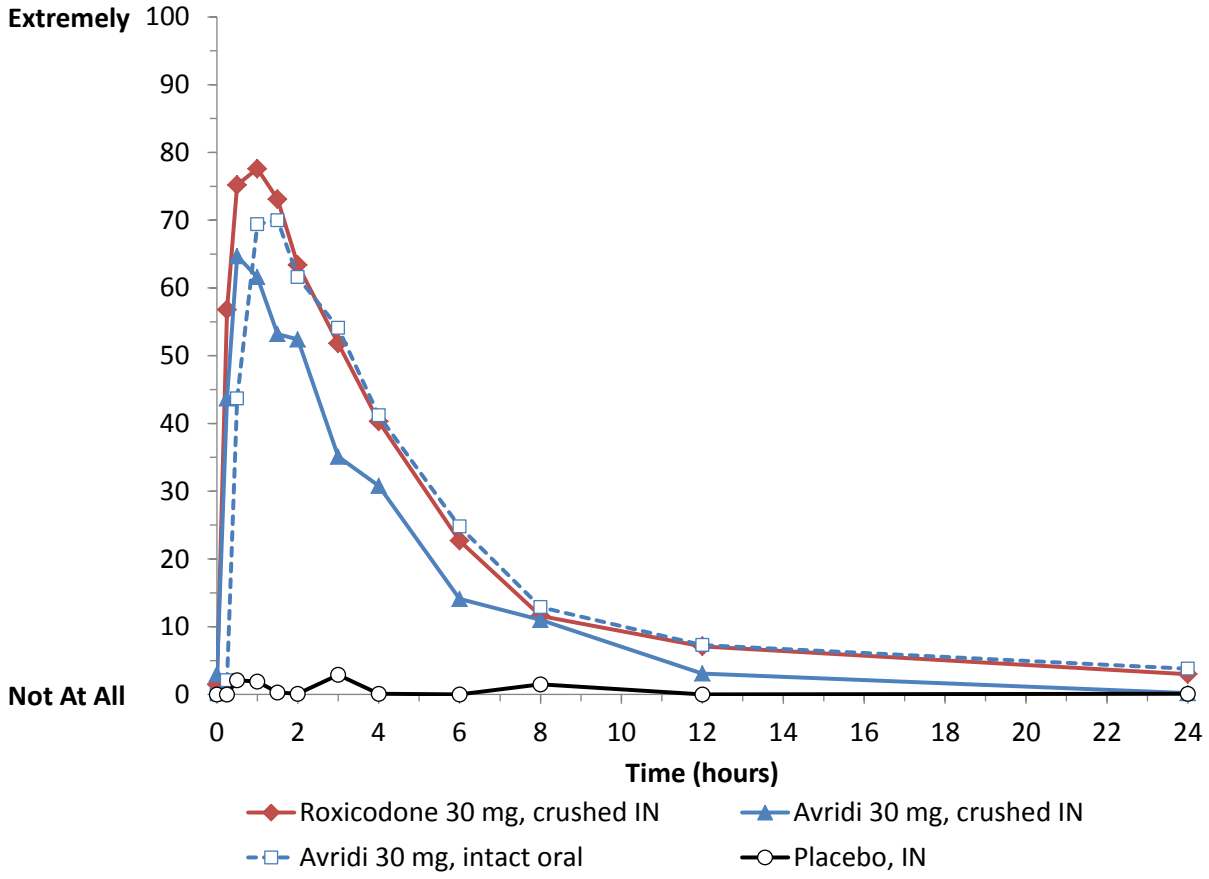


Source: CSR Figure 14.2.3.1.1.1
IN=intranasal
"At this moment Drug Liking" VAS item: "At this moment, my liking for this drug is," where values ranged from 0 (Strong disliking) to 100 (Strong liking), and 50 (Neither like nor dislike) was the neutral point.

Figure 28 Mean Scores Over Time for "At This Moment Drug Liking" VAS (Study OCI1005)

IN administration of crushed Avridi resulted in significantly lower scores compared with IN administration of crushed Roxicodone (*P* <.001)and oral intact Avridi (*P* <.001) on the primary endpoint of Emax for "at this moment drug liking" VAS. IN crushed Avridi also had a significantly lower minimum effect (Emin), a secondary endpoint, for "at this moment drug liking" VAS, which was within the disliking range (ie, < 50) compared with the other treatments. IN administration of crushed Avridi resulted in a minimum effect (Emin) within the disliking range (ie, <50), significantly lower (*P* <.001)compared with both IN administration of crushed Roxicodone) and oral intact Avridi. Mean Emin values were at or near the neutral mark (50) for all treatments except IN crushed Avridi, for which Emin values were near 0 (ie, strong disliking). Time to Emin for IN crushed Avridi occurred very early in the time course, which is consistent with the onset of its local irritant effect (see Figure 28).

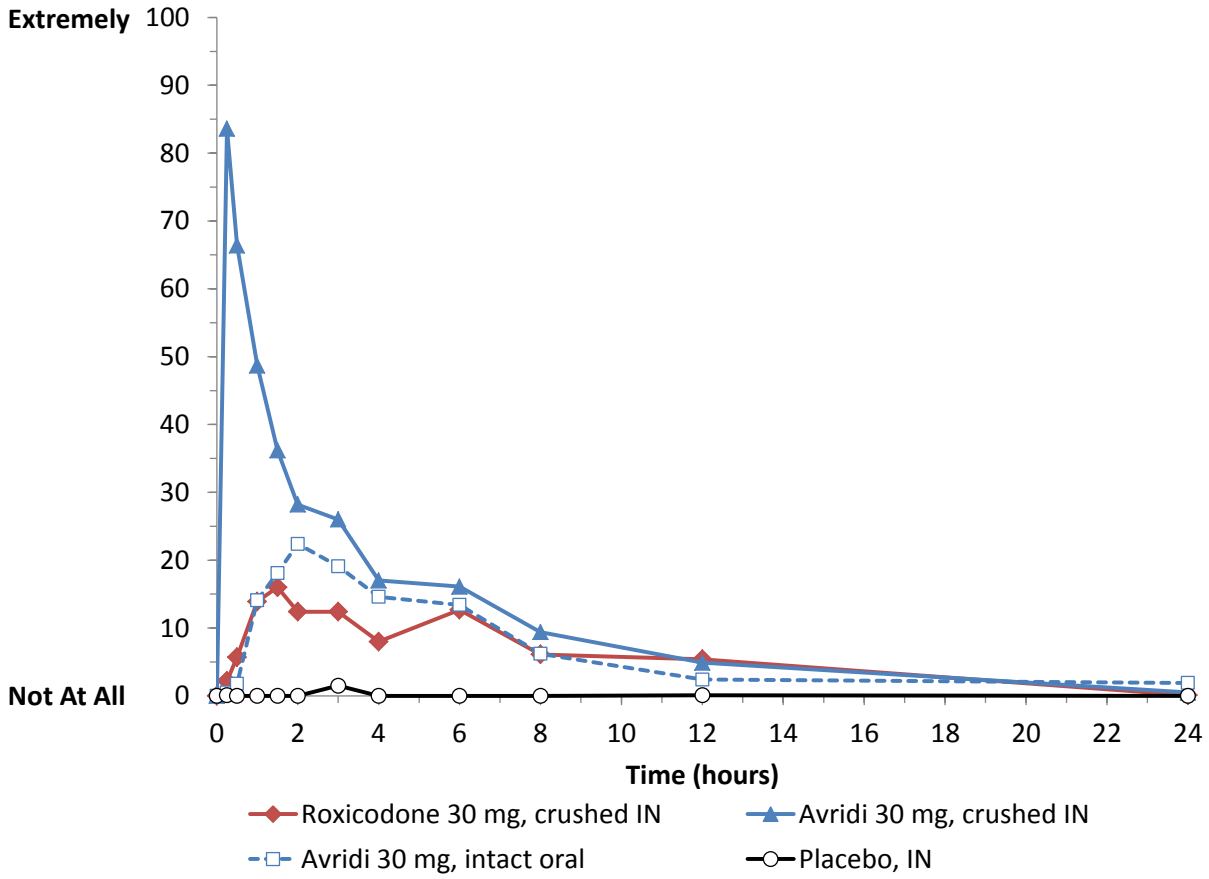
Figure 29 shows the mean "high" VAS scores over time. The mean Emax values for IN crushed Roxicodone, IN crushed Avridi, oral intact Avridi, and placebo were 85.9, 76.5, 79.4, and 8.6, respectively. IN administration of crushed Avridi showed significantly lower "high" VAS scores compared with IN administration of crushed Roxicodone (*P*=.003).



Source: CSR Figure 14.2.4.2.1.1
IN=intranasal
High VAS item: "I am feeling high," where values ranged from 0 (Not at all) to 100 (Extremely).

Figure 29 Mean Scores Over Time for "High" VAS (Study OCI1005)

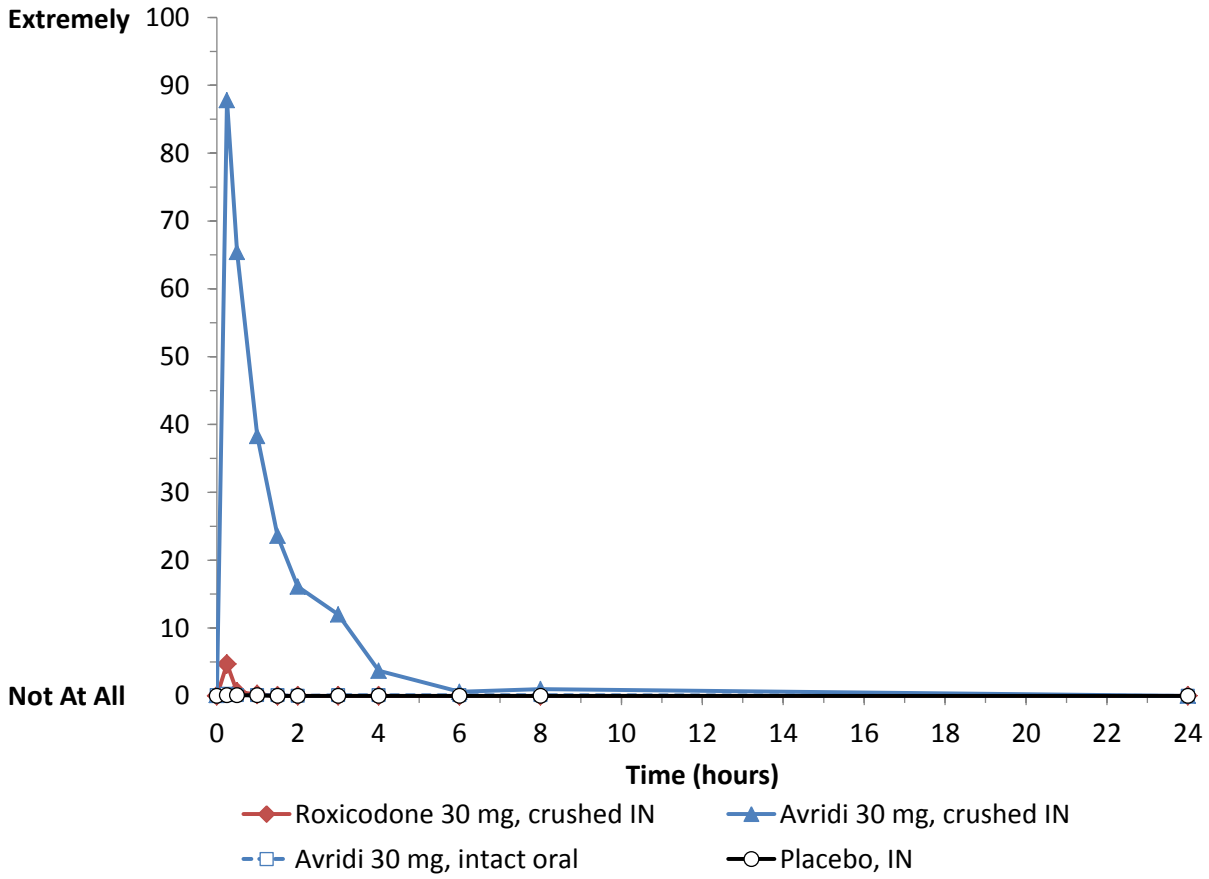
Figure 30 shows the mean "bad effects" VAS scores over time. The mean Emax values for IN crushed Roxicodone , IN crushed Avridi, oral intact Avridi, and placebo were 28.4, 88.3, 35.6, and 1.7, respectively. IN administration of crushed Avridi was associated with significant increases in Emax on the "bad effects" VAS compared with IN administration of crushed Roxicodone (*P*<.001), IN administration of placebo powder (*P*<.001), and oral administration of intact Avridi (*P*<.001).



Source: CSR Figure 14.2.5.1.1.1
IN=intranasal
Bad Effects VAS item: "I can feel bad drug effects," where values ranged from 0 (Not at all) to 100 (Extremely).

Figure 30 Mean Scores Over Time for "Bad Effects" VAS (Study OCI1005)

Figure 31 shows the mean subject-rated assessment of IN irritation burning scores over time. The mean Emax values for IN crushed Roxicodone, IN crushed Avridi, oral intact Avridi, and placebo were 4.7, 88.6, 0.5, and 0.2, respectively.



Source: CSR Figure 14.2.5.3.1.1
IN=intranasal
Burning VAS item: "Please rate the severity of the symptom," where values ranged from 0 (Not at all) to 100 (Extremely).

Figure 31 Mean Scores Over Time for Subject-Rated Assessment of IN Irritation - Burning (Study OCI1005)

Table 12 shows that subject-rated assessment of irritation effects were low for IN crushed Roxicodone and placebo, with mean VAS scores less than 11 (0 = not at all to 100 = extremely) throughout the time course of assessment. In contrast, IN crushed Avridi showed much higher scores on all subject-rated assessment of irritation measures early in the time course. IN crushed Avridi was associated with significant increases in Emax for subjective-rated assessment of irritation VAS, including burning, nasal congestion, facial pain/pressure, need to blow nose / runny nose, and throat irritation compared with IN crushed Roxicodone, IN placebo powder, and oral intact Avridi.

Table 12 Subject-Rated Assessment of Irritation (Study OCI1005)

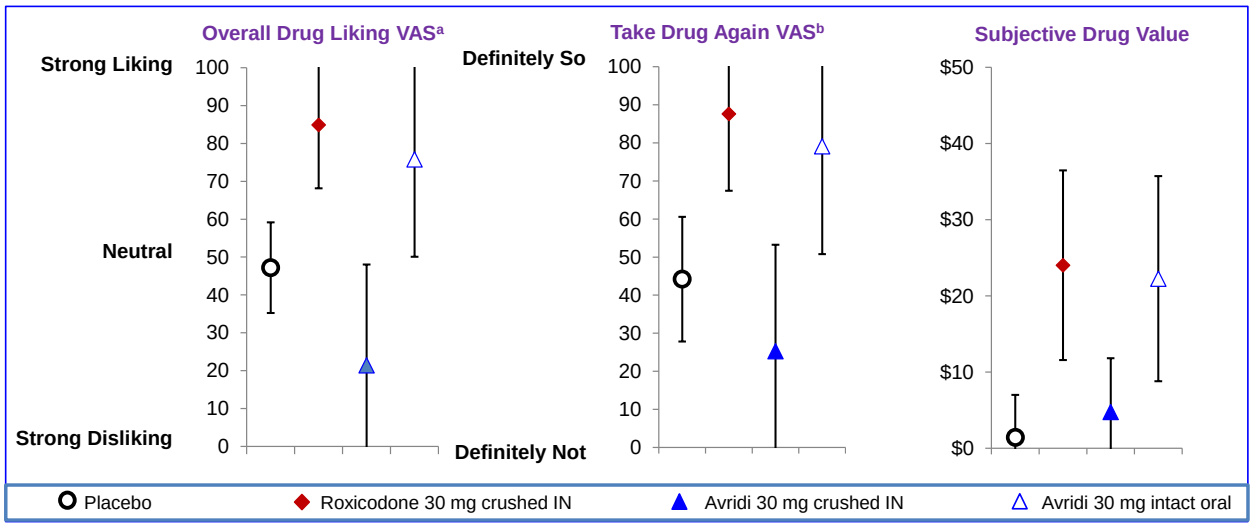
VAS Subscale*	Statistic	Placebo powder, IN	Roxicodone 30 mg, crushed IN	Avridi 30 mg, crushed IN	*P*-value Avridi 30 mg, crushed IN vs Roxicodone 30 mg crushed IN
Burning	Mean (SE)	0.2 (0.1)	4.7 (1.9)	88.6 (2.6)	
	Median	0	0	93	<.001
Throat irritation	Mean (SE)	2.3 (1.7)	6.2 (2.6)	82.1 (4.8)	
	Median	0	0	96	<.001
Facial pain/pressure	Mean (SE)	0.4 (0.3)	1.0 (0.5)	62.1 (6.3)	
	Median	0	0	69	<.001
Nasal congestion	Mean (SE)	1.6 (0.6)	6.2 (2.6)	72.6 (5.4)	
	Median	0	1	84.5	<.001
Need to blow nose	Mean (SE)	4.4 (1.6)	5.7 (2.1)	91.3 (2.0)	
	Median	0	0	100	<.001
Runny nose/Nasal discharge	Mean (SE)	5.1 (1.5)	10.8 (2.9)	91.0 (2.0)	
	Median	0	1.5	97.5	<.001

*Unipolar VAS scales: 0 = "Not at all" to 100 = "Extremely"

Source: CSR Tables 14.2.5.3.2.1, 14.2.5.4.2.1, 14.2.5.5.2.1, 14.2.5.6.2.1, 14.2.5.7.2.1 and 14.2.5.8.2.1

Based on open-ended feedback, subjects indicated they would take IN crushed Roxicodone and oral intact Avridi because of the pleasant "high," but would not take placebo again because of the lack of effect. Most subjects would not consider taking IN crushed Avridi again because of the burning sensation associated with its administration (eg, "I would never snort this again. I felt like I was going to die"; "Snorting that drug is complete insanity"; "I wouldn't take this drug ever again cause it had my whole head on fire and hurting and it was the worse pain ever"), although a few subjects reported that the local aversive effects might not deter them (4 of 35 subjects) or heavy users from snorting it to get high (1 of 35 subjects).

Figure 32 shows the mean "overall drug liking" VAS," take drug again" VAS, and subjective drug value scores at 24 hours postdose.



[a]Bipolar scale [b]Unipolar scale
Source: Derived from CSR Tables 14.2.3.2.1.2, 14.2.3.3.1.2, 14.2.3.4.1.2

Figure 32 Hour 24 Mean (SD) Emax Scores for "Overall Drug Liking" VAS, "Take Drug Again" VAS, and Subjective Drug Value (Study OCI1005)

The mean "overall drug liking" VAS scores at 24 hours postdose for IN crushed Roxicodone, IN crushed Avridi, oral intact Avridi, and placebo were 84.9, 21.4, 75.8, and 47.2, respectively, indicating that IN crushed Avridi was in the disliking range.

The mean "take drug again" VAS scores at 24 hours postdose for IN crushed Roxicodone, IN crushed Avridi, oral intact Avridi, and placebo were 87.6, 23.5, 79.1, and 44.2, respectively. IN crushed Avridi was associated with a very low willingness to take the drug again.

IN crushed Avridi was significantly lower in "overall drug liking" and "take drug again" compared to IN crushed Roxicodone ($P<.001$), placebo ($P<.001$), and oral intact Avridi ($P<.001$), indicating that IN crushed Avridi was significantly disliked and subjects were not willing to take it again, even compared to placebo.

The mean (median) subjective drug value (SDV) scores at 24 hours postdose for IN crushed Roxicodone, IN crushed Avridi, oral intact Avridi, and placebo were 24.00 (20.80), 4.80 (0.25), 22.30 (20.00) and 1.40 (0.25) dollars, respectively. IN crushed Roxicodone and oral intact Avridi had similarly high mean and median SDV scores, and IN crushed Avridi and placebo had the lowest SDV scores, with median values of $0.25 (ie, the lowest value possible).

Figure 33 presents a comparison of "drug liking" for IN crushed Avridi compared with IN crushed Roxicodone in subjects who received both treatments. The Y-axis represents the percent of subjects attaining a percent reduction in "drug liking" for IN crushed Avridi vs IN crushed Roxicodone greater than or equal to the value on the X-axis.

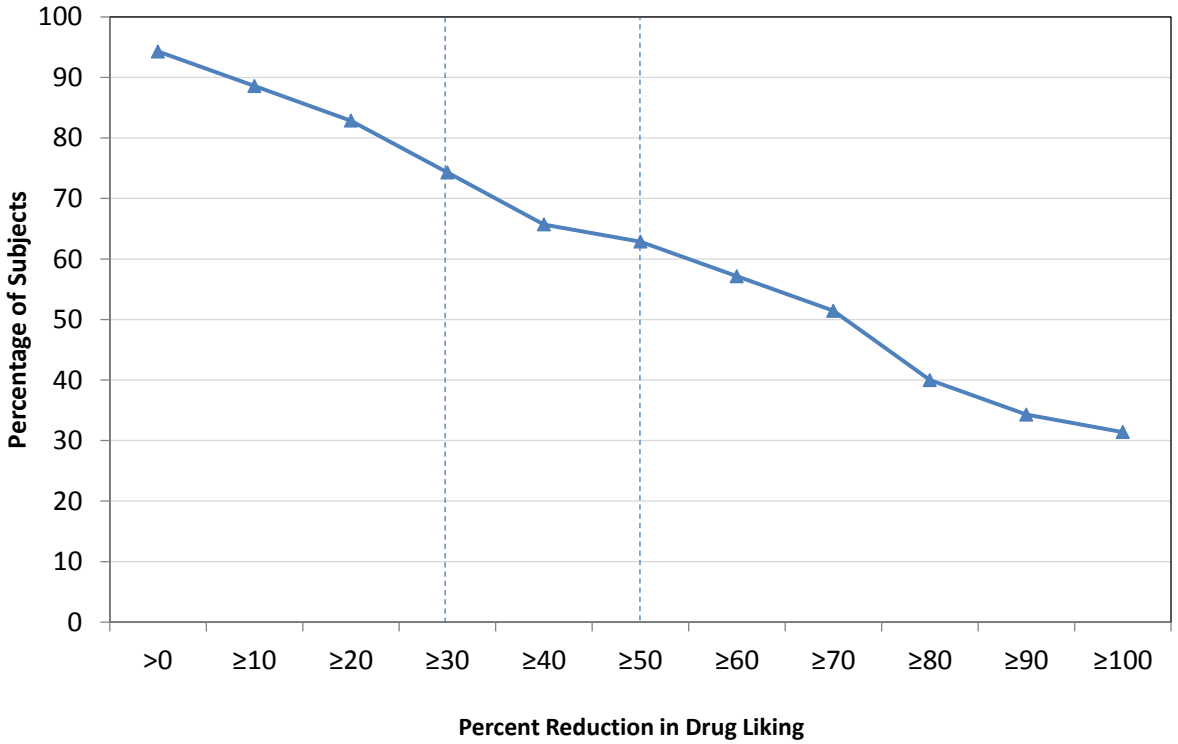


Figure 33 Percent Reduction in "Drug Liking" VAS Emax of IN Crushed Avridi Compared With IN Crushed Roxicodone (OCI1005)

Approximately 94% (n = 33) of subjects had some reduction in "drug liking" associated with IN administration of crushed Avridi relative to IN administration of crushed Roxicodone. Seventy-four percent (n = 26) of subjects receiving IN crushed Avridi had a reduction of at least 30% in "drug liking" and approximately 63% (n = 22) had a reduction of at least 50% in "drug liking", relative to IN crushed Roxicodone. Furthermore, 34% (n = 12) of subjects receiving IN crushed Avridi had a reduction of at least 90% in drug liking relative to IN administration of crushed Roxicodone.

Safety Evaluation

Overall, the highest incidence of TEAEs was observed after administration of IN crushed Avridi, (91.4%), followed by oral intact Avridi (61.1%), IN crushed Roxicodone (60.0%), and placebo (28.6%). Most TEAEs were mild in intensity and likely related to the study drug. Four subjects experienced a total of 5 severe AEs (4 episodes of dyspnea and 1 episode of throat irritation), all of which occurred following administration of IN crushed Avridi.

Nasal discomfort was the most common TEAE; the incidence was highest after IN crushed Avridi (62.9%), followed by oral intact Avridi, (30.6%), IN crushed Roxicodone (28.6%), and IN placebo powder (5.7%). Nasal congestion, throat irritation, rhinorrhea, cough, dyspnoea, lacrimation increased, and ocular hyperaemia were also common and occurred at a considerably higher incidence with IN crushed Avridi than with any other treatment.

Eructation, nausea, vomiting, feeling hot, dizziness, headache, somnolence, tremor, IN paraesthesia, oropharyngeal pain, rhinalgia, upper-airway cough syndrome, pruritus generalised, and pruritus were also reported by ≥ 5% of subjects for at least 1 treatment.

Table 13 summarizes the incidence of TEAEs reported in the study by preferred term.

Table 13 TEAEs Reported by ≥ 5% of Subjects (for Any Treatment) by Treatment at Onset and by System Organ Class and Preferred Term (Safety Population; Study OCI1005)

MedDRA System Organ Class / Preferred Term	Number of Subjects (%)			
	Placebo (N=35)	Roxicodone 30 mg, crushed IN (N=35)	Avridi 30 mg, crushed IN (N=35)	Avridi 30 mg, intact oral (N=36)
Any System Organ Class				
Any event	10 (28.6)	21 (60.0)	32 (91.4)	22 (61.1)
Eye disorders				
Lacrimation increased	1 (2.9)	2 (5.7)	28 (80.0)	0
Ocular hyperaemia	0	0	7 (20.0)	0
Gastrointestinal disorders				
Eructation	0	0	2 (5.7)	0
Nausea	0	5 (14.3)	4 (11.4)	7 (19.4)
Vomiting	0	2 (5.7)	3 (8.6)	3 (8.3)
General disorders and administration site conditions				
Feeling hot	0	1 (2.9)	3 (8.6)	3 (8.3)
Nervous system disorders				
Dizziness	0	3 (8.6)	2 (5.7)	2 (5.6)
Headache	2 (5.7)	3 (8.6)	8 (22.9)	1 (2.8)
Somnolence	0	3 (8.6)	5 (14.3)	9 (25.0)
Tremor	0	0	2 (5.7)	0
Respiratory, thoracic and mediastinal disorders				
Cough	0	1 (2.9)	7 (20.0)	0
Dyspnoea	0	0	7 (20.0)	0
IN paraesthesia	0	2 (5.7)	0	1 (2.8)
Nasal congestion	6 (17.1)	2 (5.7)	15 (42.9)	3 (8.3)
Nasal discomfort	2 (5.7)	10 (28.6)	22 (62.9)	11 (30.6)
Oropharyngeal pain	0	0	4 (11.4)	0
Rhinalgia	0	1 (2.9)	3 (8.6)	0
Rhinorrhoea	0	1 (2.9)	12 (34.3)	1 (2.8)
Throat irritation	1 (2.9)	1 (2.9)	15 (42.9)	0
Upper-airway cough syndrome	0	2 (5.7)	0	1 (2.8)
Skin and subcutaneous tissue disorders				
Pruritus	0	1 (2.9)	1 (2.9)	2 (5.6)
Pruritus generalised	0	8 (22.9)	3 (8.6)	8 (22.2)

Source: OCI1005 CSR Table 14.3.1.2
IN=intranasal; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event (AE that starts or worsens after treatment with study drug)
Percentage was calculated based on the number of subjects per treatment as the denominator. For each row category, a subject with 2 or more adverse events in that category was counted only once.

Conclusions

Avridi, when crushed and administered by the IN route in recreational opioid users, demonstrated significantly lower ratings of drug liking, overall liking, and willingness to take the drug again, as well as significantly greater local aversive effects compared with IN crushed Roxicodone, despite similar oxycodone PK. Oral administration of intact Avridi produced positive reinforcing effects, as expected for an IR single-entity oxycodone formulation.

Consistent with the subjective reports of IN effects, nasal TEAEs including nasal discomfort, nasal congestion, and rhinorrhea, and TEAEs of lacrimation and throat irritation were more common after IN administration of crushed Avridi compared with IN crushed Roxicodone. These nasal/oropharyngeal AEs were considered highly unpleasant and led to substantial decrease in drug liking. None of these TEAEs was considered serious, and none led to injury of the nasal mucosa

As demonstrated by the primary measures of abuse potential, the local aversive effects following IN administration of crushed Avridi are likely to result in a significant reduction in IN abuse compared with opioid products without abuse-deterrent properties.

5.4 Abuse Deterrence: *In vitro* Studies and Clinical Abuse Potential Conclusions

A comprehensive series of studies have evaluated the abuse-deterrent properties of Avridi tablets, consistent with the FDA guidance on abuse-deterrent opioids (FDA Guidance to Industry: *Abuse-Deterrent Opioids – Evaluation and Labeling*, April 2015). It is expected that abuse of oxycodone from manipulated Avridi tablets will be deterred by the gelling properties of the excipients and the local aversive effects of sodium lauryl sulfate.

In vitro manipulation and extraction studies demonstrated that considerable effort, knowledge of chemistry, and time would be required to isolate oxycodone from the excipients, with limited success. The gelling properties of Avridi tablets resulted in very low syringeability, supporting that the excipients would deter IV abuse.

The IN irritating effects of sodium lauryl sulfate make administration by the IN route highly aversive, with effects persisting for several hours. Results of the clinical abuse potential study suggest that the negative effects of IN crushed Avridi, and resultant reductions in drug liking, overall drug liking, and willingness to take the drug again relative to IN crushed Roxicodone are expected to result in meaningful reductions in misuse and abuse by the IN route in the community.

Although Avridi tablets have abuse-deterrent properties, abuse of Avridi by the IV, IN, and oral routes is still possible. Planned postmarketing epidemiologic studies, when available, may provide further information on the impact of Avridi on reducing abuse in the community.

6 NEED FOR AN IR SINGLE-ENTITY OXYCODONE WITH ABUSE-DETERRENT PROPERTIES

In order to understand the potential public health impact of Avridi tablets, it is necessary to review data on the utilization of IR single-entity oxycodone, as well as data on patterns of abuse and its consequences. This section will address the following key points related to current patterns of use and abuse of IR single-entity oxycodone:

1. **Frequency of Use of IR Single-Entity Oxycodone**

   IR single-entity oxycodone is the most commonly prescribed Schedule II single-entity opioid (ie, opioid without acetaminophen), with most patients prescribed short durations of therapy.

2. **Frequency of Use of IR Single-Entity Oxycodone for Longer Durations at Higher Doses**

   A large number of patients are prescribed long-term, high-dose IR single-entity oxycodone, although the number represents a small proportion of overall IR single-entity oxycodone patients.

3. **Mortality and Abuse Rates Associated with IR Single-Entity Oxycodone**

   IR single-entity oxycodone is highly abused and is associated with high rates of opioid overdose/poisoning and death.

4. **Snorting and Injecting IR Single-Entity Oxycodone**

   IR single-entity oxycodone is commonly abused through nonoral routes of administration (injecting and snorting).

5. **Potential Diversion of Opioids from Patients to Nonpatients for Purposes of Abuse**

   There is potential for diversion of opioids, such as IR single-entity oxycodone, from patients to nonpatients for purposes of nonmedical use/abuse, and IR single-entity oxycodone is associated with high rates of doctor-shopping, an indicator of diversion.

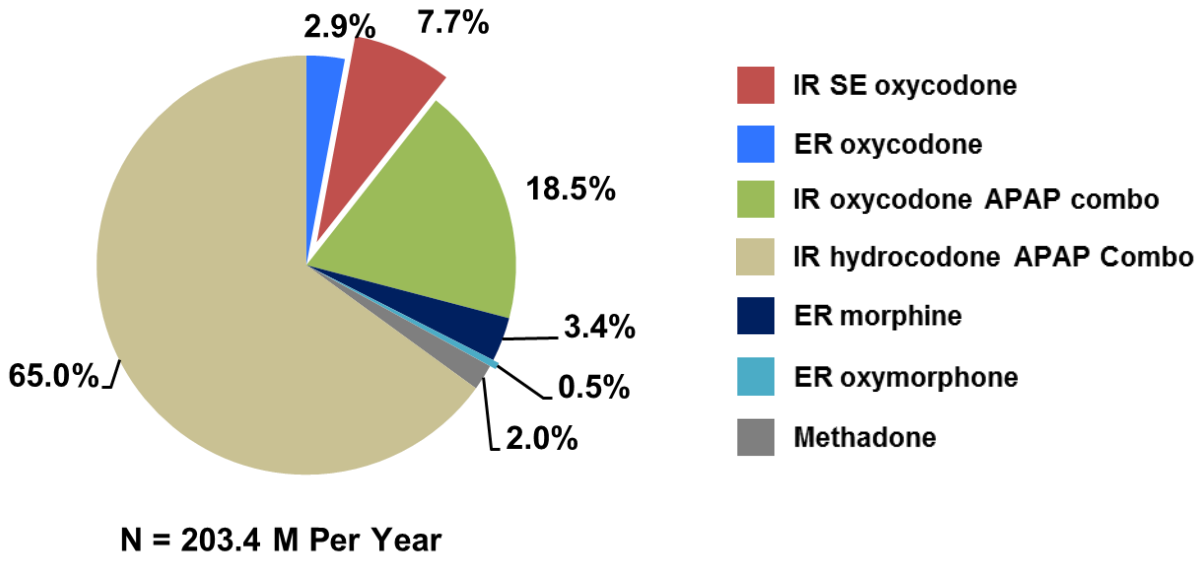
In addition to providing an understanding of the potential public health impact of the abuse-deterrent properties of Avridi tablets, data for current IR single-entity oxycodone formulations help to inform the anticipated size and characteristics of the population more likely to experience food effects associated with Avridi, enhancing Purdue's ability to mitigate any risks associated with these effects via labeling, prescriber and pharmacist education, enhanced pharmacovigilance, and other risk evaluation and management strategies described in Section 7.

6.1 Frequency of Use of IR Single-Entity Oxycodone

Oxycodone is marketed in the US for use as an analgesic as single-entity (IR and ER) and IR combination products (ie, oxycodone in combination with acetaminophen, aspirin, or ibuprofen). The oxycodone products are available in tablet strengths of 5 mg to 30 mg for IR single-entity

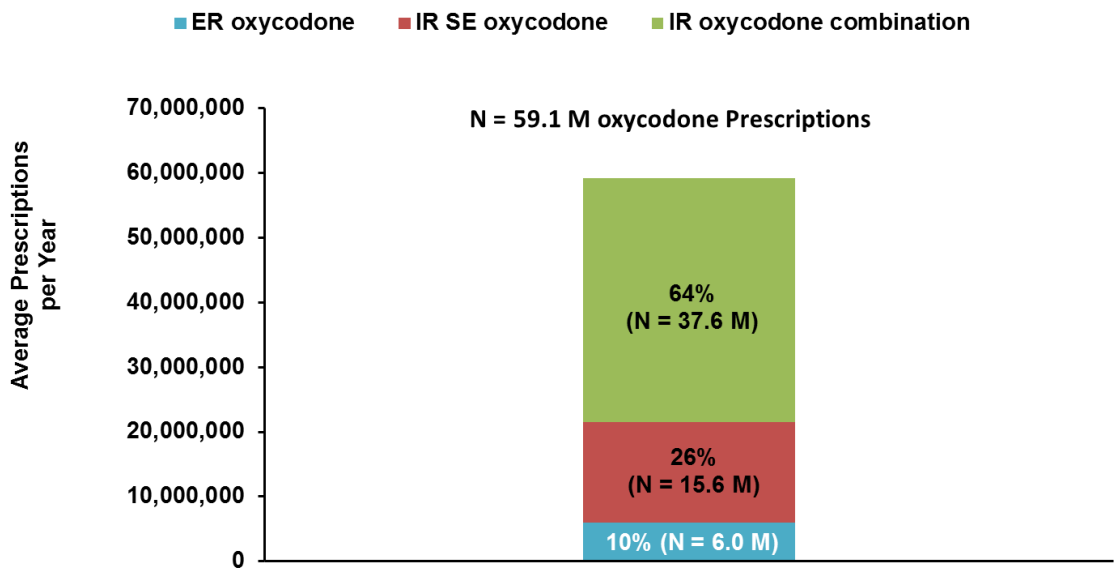
oxycodone products, 2.5 mg to10 mg for IR oxycodone combination products with nonopioid ingredients, and 10 mg to 80 mg for ER oxycodone. Thus, while IR single-entity oxycodone is available at lower tablet strengths, with less oxycodone per unit dose, there are also overlapping tablet strengths, with both single-entity IR and ER oxycodone available in 10-, 20-, and 30-mg tablet strengths. Both ER and IR opioid formulations may be used alone or concurrently (ie, ER opioids prescribed on an around-the-clock basis with IR opioids used PRN for the treatment of breakthrough pain).

From 2011-2013, IR single-entity oxycodone made up approximately 7.7% of all Schedule II opioid prescriptions dispensed in the US, while ER oxycodone made up 2.9% (Figure 34). IR single-entity oxycodone comprised approximately 26% of prescriptions for oxycodone, with an average of 15.6 million prescriptions dispensed per year, while ER oxycodone comprised approximately 10% of prescriptions for oxycodone, with an average of 6 million prescriptions dispensed per year (Figure 35). Overall, utilization of IR single-entity oxycodone is greater than utilization of ER oxycodone, indicating greater availability of IR oxycodone in the community and a consequently high level of access for abuse.



Source: IMS Health
SI=single entity

Figure 34 Opioid Prescriptions in the United States (2011-2013)



Source: IMS Health
SE=single=entity

Figure 35 Percent and Number of Oxycodone Prescriptions per Year (2011-2013) of IR Single-Entity Oxycodone and other Oxycodone Products

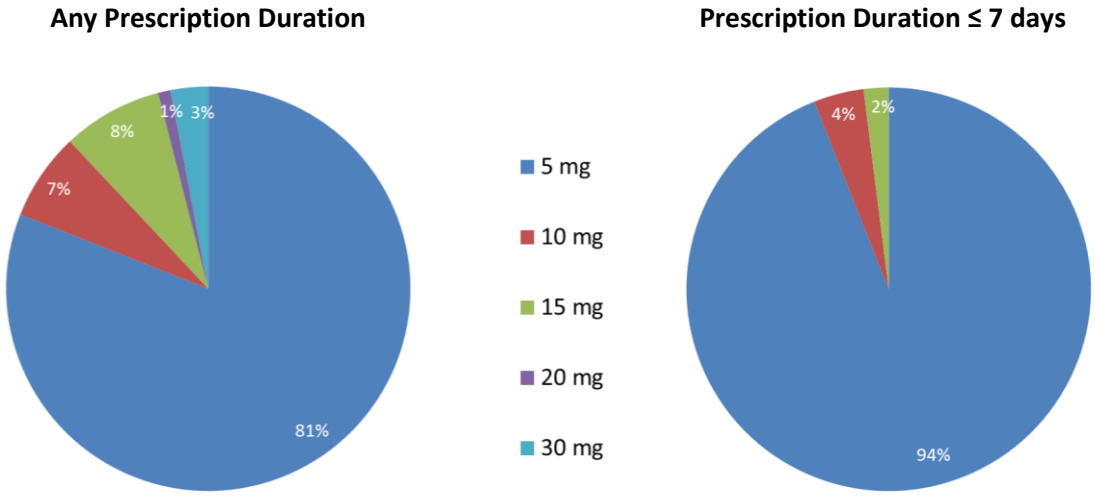
Most prescriptions for IR single-entity oxycodone are short in duration. The median duration of treatment for patients who had at least 6 months enrollment prior to the initial prescription of IR single-entity oxycodone, a population chosen to ensure new users (ie, no prescriptions in the previous 6 months), was 7 days; 86% of commercially insured and 75% of Medicaid insured patients had treatment duration of 30 days or less (Figure 36).

A. Commercial Insurance **B. Medicaid**

Source: Truven MarketScan Commercial Healthcare Claims Database (Medicaid: 2008-2013; Commercial: 2008-3Q2014)

Figure 36 Prescription Duration for IR Single-Entity Oxycodone Based on Data from the Truven MarketScan Commercial (A) and Medicaid (B) Insurance Databases

At the initial prescription, 81% of all patients newly dispensed IR single-entity oxycodone received prescriptions for the 5-mg tablet strength, as did 94% of those prescribed IR single-entity oxycodone for ≤ 7 days duration (Figure 37). It is important to note that although this analysis included new users of IR single-entity oxycodone (ie, no prescriptions for IR single-entity oxycodone in the 6 months preceding the initial prescription), 53% had prior opioid exposure while 47% were opioid naïve when they were initially prescribed IR single-entity oxycodone. The proportion of patients initially prescribed 5-mg tablets was slightly greater among patients who were opioid naïve (91%) compared with those who had prior opioid exposure (73%).



Source: Truven MarketScan Commercial Healthcare Claims Database (2008-3Q2014)

Figure 37 Tablet Strengths Prescribed at Initial IR Single-Entity Oxycodone Prescription, Overall, and Among Patients Prescribed for a Duration of ≤ 7 Days

Insurance claims databases can be used to identify new opioid users (as described above) as well as patients prescribed both IR single-entity oxycodone and ER opioids. Among this cohort of patients newly prescribed IR single-entity oxycodone, 15.8% had an ER opioid prescribed at some point during their treatment, and 6.6% had an ER opioid prescribed both before and after their initial IR single-entity oxycodone prescription. Among patients prescribed IR single-entity oxycodone with ER opioids at any time during follow-up, 60% were prescribed the 5-mg tablet strength of IR single-entity oxycodone at the time of their ER opioid prescription.

Unfortunately, it is not possible to differentiate PRN vs around-the-clock use in insurance claims databases as they do not capture PRN status.

6.2 Frequency of Use of IR Single-Entity Oxycodone for Longer Durations at Higher Doses

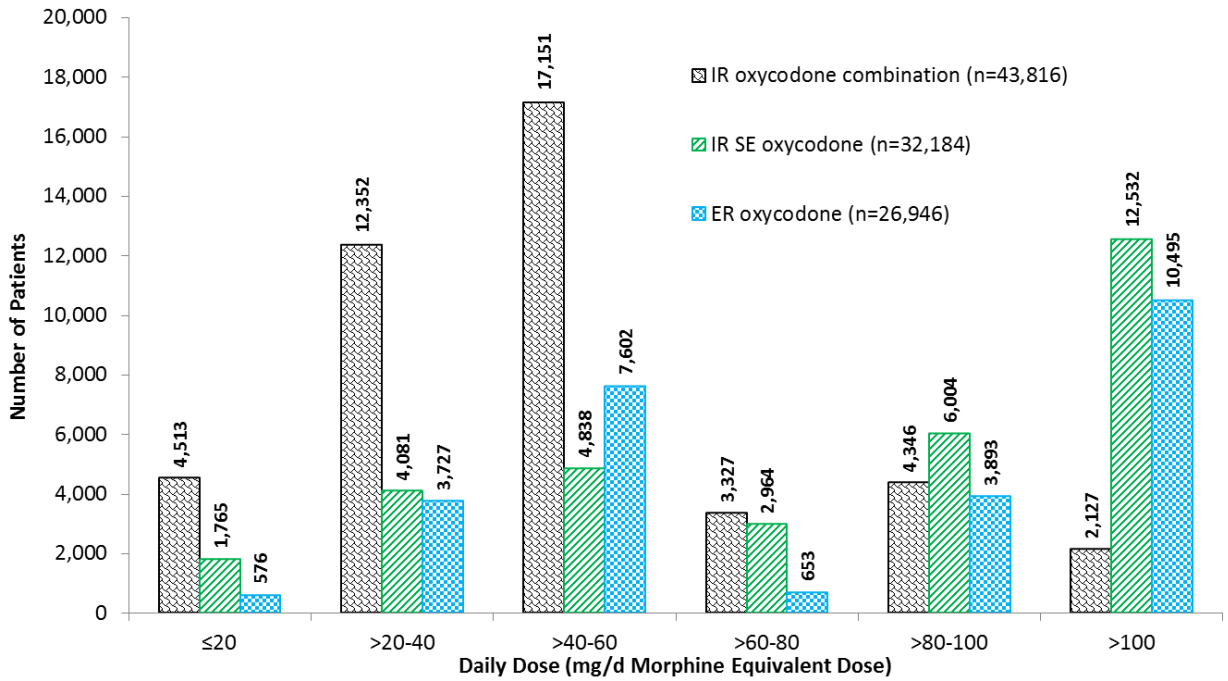
Although IR single-entity oxycodone products are often prescribed for short-term use, some evidence (cited below) suggests that a large number of patients continue IR single-entity

oxycodone treatment for longer periods (> 90 days) at higher doses. In some cases, patients using IR oxycodone will receive similar daily doses as those of patients receiving ER opioids for chronic pain.

In an FDA analysis of opioid prescription patterns, Source Healthcare Analytics' ProMetis Lx® examined the duration of therapy for oxycodone products, among other opioids, to determine the average cumulative length of therapy for patients using these products between 2010 and 2011. Although most patients used these products for less than 31 days, a proportion of patients (20%) used these products for 93 days or longer. Twenty percent (20%) corresponds to over 225,000 patients based on the total sample of IR single-entity oxycodone patients (FDA 2012a; FDA 2012b).

Additionally, in an analysis of opioid prescription patterns using the Truven MarketScan commercial insurance database, 8.5% of patients newly initiating IR single-entity oxycodone treatment continued for longer than 90 days, consistent with long-term therapy duration, and the absolute number of patients on therapy for > 90 days was comparable for IR single-entity oxycodone (n=22,970) and ER oxycodone (22,375) (DeVeaugh-Geiss 2015). When any episode of continuous use was included (including episodes occurring after an initial period of opioid use that did not meet *a priori* criteria for long-term use), the number of patients receiving long-term IR single-entity oxycodone was greater than the number on long-term ER oxycodone (n=32,184 and n=26,946, respectively). In addition, among patients on long-term treatment, the number of IR single-entity oxycodone patients on doses above 66 mg oxycodone per day (100 mg morphine equivalent dose per day) at month 4 exceeded the number on ER oxycodone above 66 mg oxycodone per day (n=12,532 and n=10,495, respectively; Figure 38).

While these analyses required 12 months of insurance enrollment following the initial prescription, a similar analysis was performed to explore the dose at month 4 among patients with no criteria for minimum insurance enrollment following their initial prescription. In this cohort, not only was there a greater proportion of patients prescribed IR single-entity oxycodone at doses exceeding a 100 mg/day morphine equivalent dose (vs ER oxycodone), the median dose among that subgroup of patients was greater for IR single-entity oxycodone (135 mg/day) than for ER oxycodone (120 mg/day) (Table 14).



Source: Truven MarketScan Commercial Healthcare Claims Database (2008-2013)

Figure 38 Dose at Month 4 Among Patients Treated Long-Term (> 90 days) by Category

Table 14 Demographics and Dose at Index Prescription Among Patients Treated with Long-Term ER Oxycodone (OxyContin) and IR Single-Entity Oxycodone at Doses Greater than 100 mg Morphine Equivalent Dose

	ER oxycodone (OxyContin) (n = 19,852)		IR SE oxycodone (n = 24,531)	
Characteristic	n	%	N	%
Gender				
Male	10,733	54.1	13,337	54.4
Female	9,119	45.9	11,194	45.6
Age category				
18-24	572	2.9	1,152	4.7
25-34	2,362	11.9	3,995	16.3
35-44	4,395	22.1	6,076	24.8
45-54	7,030	35.4	8,051	32.8
55-64	5,493	27.7	5,257	21.4
Dose (mg/day in morphine equivalents)				
Median	120		135	
Mean, SD	186.46 (1804.26)		192.10 (793.06)	

Source: Truven MarketScan Commercial Healthcare Claims Database (2008-1Q2014)
SE=single-entity

6.3 Mortality and Abuse Rates Associated with IR Single-Entity Oxycodone

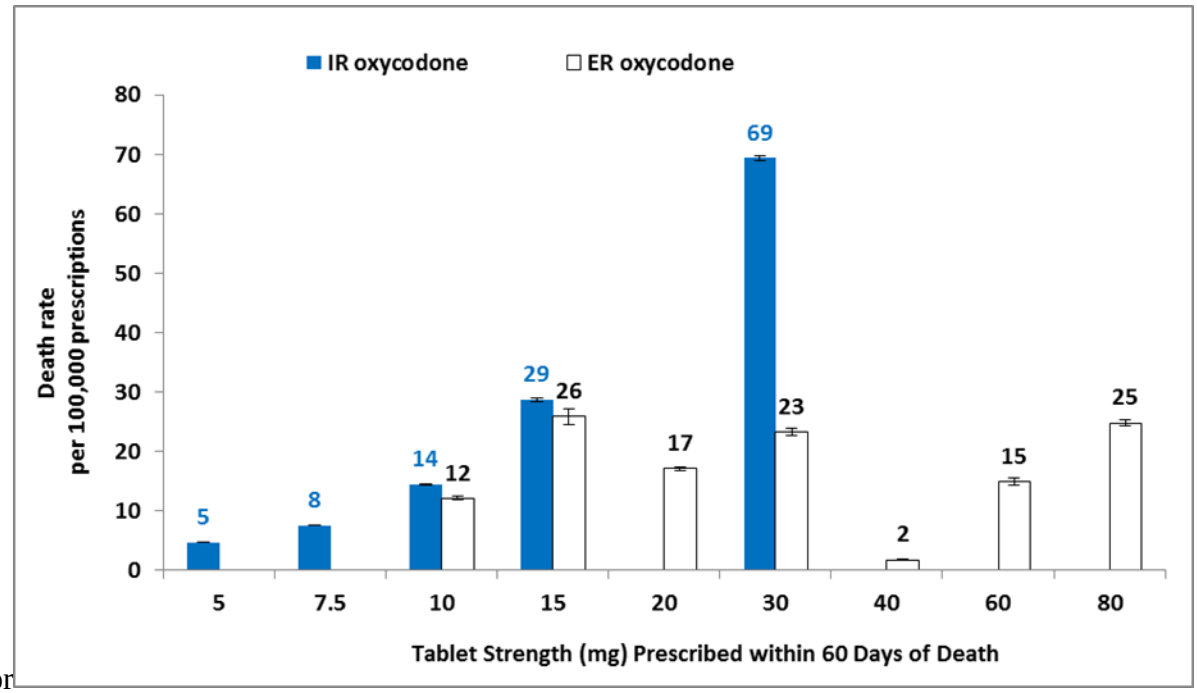
6.3.1 Mortality Rates among Individuals Dispensed IR Single-Entity Oxycodone

Overdoses due to opioid use and abuse can result in death; however, there are few datasets available to assess unintentional overdose fatalities associated with prescription opioids that also provide information on specific opioid formulations associated with the death. One way to assess this outcome is combining state prescription drug monitoring programs with state medical examiner databases (Hall 2008; Hirsch 2014). A limitation of this approach is that states must be evaluated separately.

A retrospective population-based study of medication histories of overdose decedents using data from state vital statistics, state medical examiner records, and state prescription drug monitoring program data was conducted using 2010 data from North Carolina (Hirsch 2014). The paper by Hirsch et al did not differentiate between IR single-entity oxycodone and IR oxycodone combination products; however, doses of 15 mg, 20 mg, and 30 mg are only available for IR single-entity oxycodone and therefore deaths and prescriptions for 30-mg tablets of IR oxycodone are for IR single-entity oxycodone. Doses of oxycodone above 30 mg are only available for ER oxycodone. The study used 2010 data, which is the year that reformulated OxyContin with abuse-deterrent properties was introduced in August, so 2010 data would capture a combination of original and reformulated OxyContin use.

The mortality rate adjusted for the number of prescriptions dispensed was high for IR oxycodone, particularly for the 30-mg tablet strength. For oxycodone products, the highest risk of death per prescription was associated with IR single-entity 30-mg oxycodone doses, with 69 deaths per 100,000 prescriptions dispensed (vs 23 per 100,000 prescriptions for OxyContin 30-mg tablets). For prescriptions written within 60 days of death, the risk of opioid death was more than double for IR single-entity oxycodone 30 mg vs OxyContin 80 mg (69 versus 25 per 100,000 prescriptions).

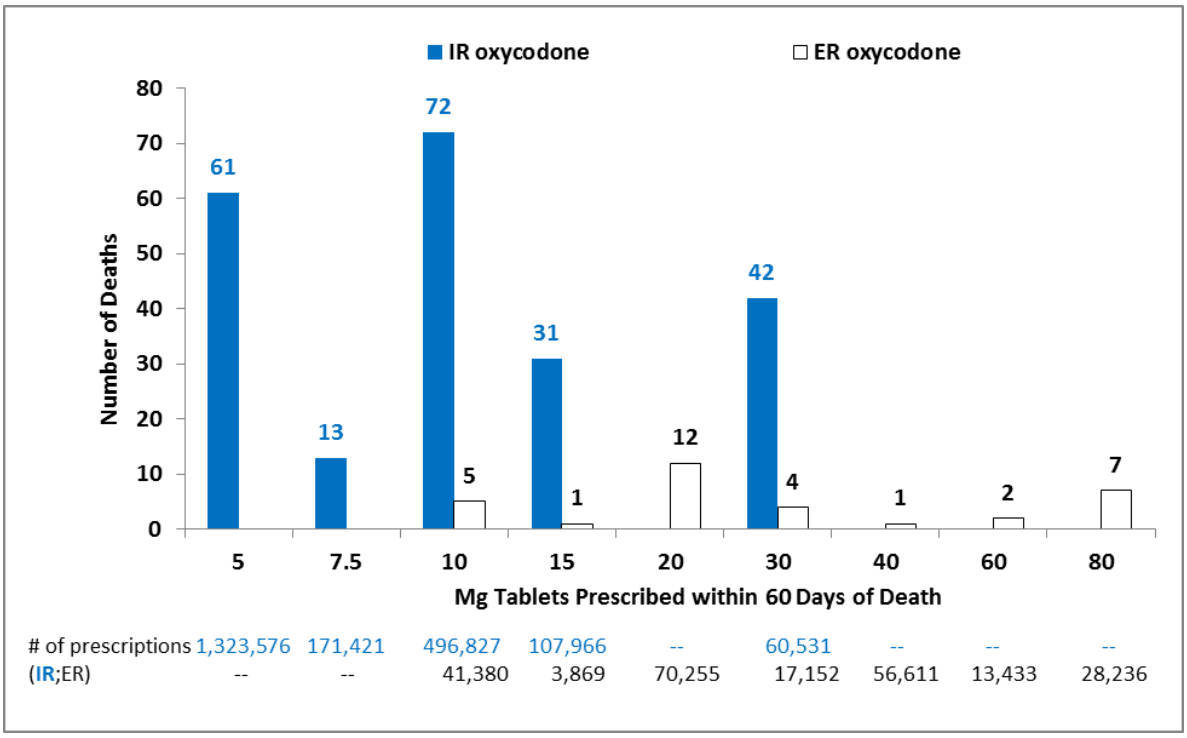
IR oxycodone was associated with a large absolute number of deaths, in addition to a high prescription-adjusted mortality rate. Of 251 deaths associated with oxycodone in the study, 219 deaths were associated with IR oxycodone and 32 deaths were associated with ER oxycodone (Figure 40). The tablet strength associated with the largest number of oxycodone deaths was IR oxycodone 10 mg (n=72 oxycodone deaths).



or

Source: Hirsch 2014

Figure 39 Oxycodone Death Rate per 100,000 Prescriptions for IR Oxycodone by Tablet Strength Compared to ER Oxycodone, North Carolina (2010)



Source: Hirsch 2014

Figure 40 Number of Deaths and Prescriptions Written Within 60 days of Death for IR Oxycodone by Tablet Strength Compared with ER Oxycodone, North Carolina (2010)

6.3.2 Abuse, Addiction/Dependence, and Poisoning/Overdose among Individuals Dispensed IR Single-Entity Oxycodone

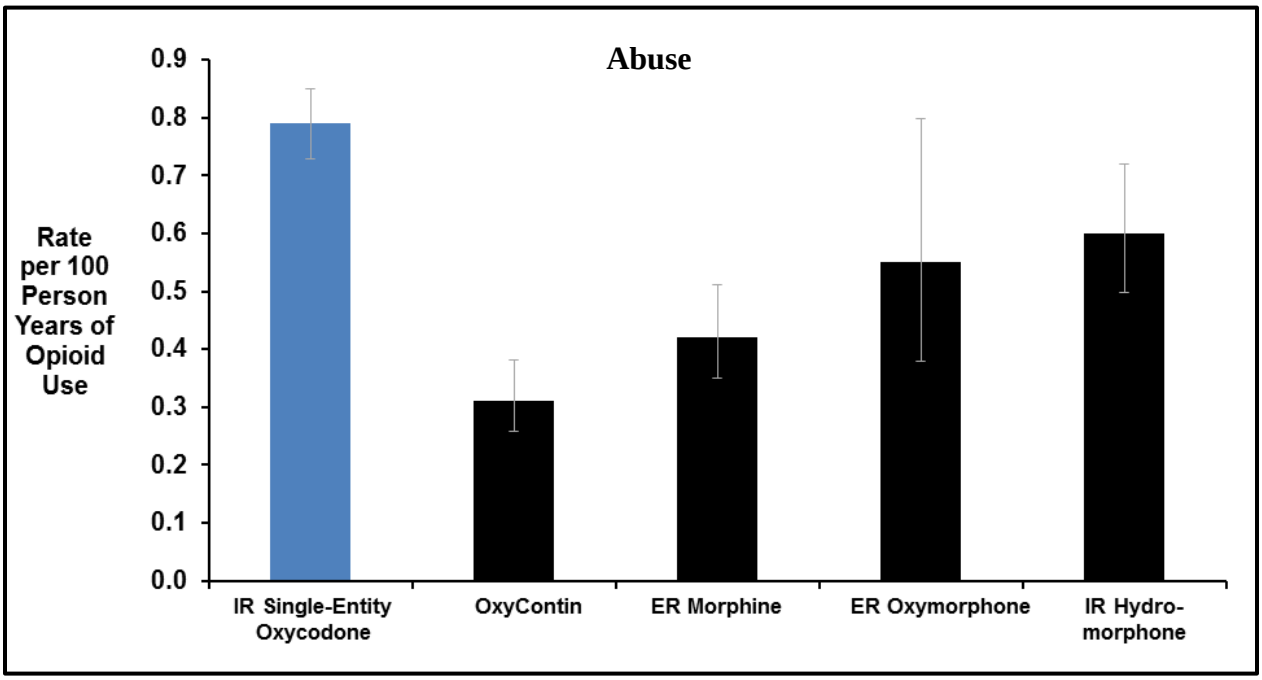
As with fatalities associated with opioids, there are few datasets available to assess overdose/poisonings that also provide information on specific opioid formulations associated with the overdose/poisonings. Data from administrative claims databases on diagnoses for opioid abuse, addiction, and overdose that occur during the time that individuals have received a prescription for an opioid can be used to compare rates for different opioids. A study was conducted using Truven MarketScan commercial insurance data to provide information on rates of diagnosed poisoning/overdose, addiction/dependence, and abuse in relation to the individual's dispensed opioids, utilizing formulation data from pharmacy claims records (ie, prescriptions dispensed to the patient). The MarketScan commercial data are generalizable to the US population covered by employer-sponsored insurance (58% of the US population) and contain eligibility, pharmacy claims, and medical claims data. The dataset covered 100 million individuals between 2009 and 2013.

Before starting the study using Truven MarketScan insurance database, a validation study of the ICD-9 codes used for opioid poisoning/overdose was conducted in a separate database of the Kaiser Permanente Northwest and Northern California region membership population. The validation study was carried out by Kaiser Permanente (KP) Northwest and Northern California

and was funded by Purdue Pharma L.P. The validation study compared diagnoses of opioid overdose/poisoning identified by ICD-9 codes with medical chart reviews by trained chart abstracters and clinical reviewers (data on file; Janoff 2015). The study identified several ICD-9 codes used in previous studies that were not predictive of opioid overdose and identified that opioid poisoning (965.0x) codes did have a high positive predictive value. Of 2,100 poisoning/overdose events identified by 965.0x ICD-9 codes for opioid poisoning/overdose, 96% were verified as opioid overdose/poisoning events; 11.5% of the 2,100 poisoning/overdose events occurred within 3 days of surgery, and, therefore could be related to anesthesia. Excluding postsurgical overdoses/poisonings, 84.6% of the codes were verified as true opioid overdose/poisoning events.

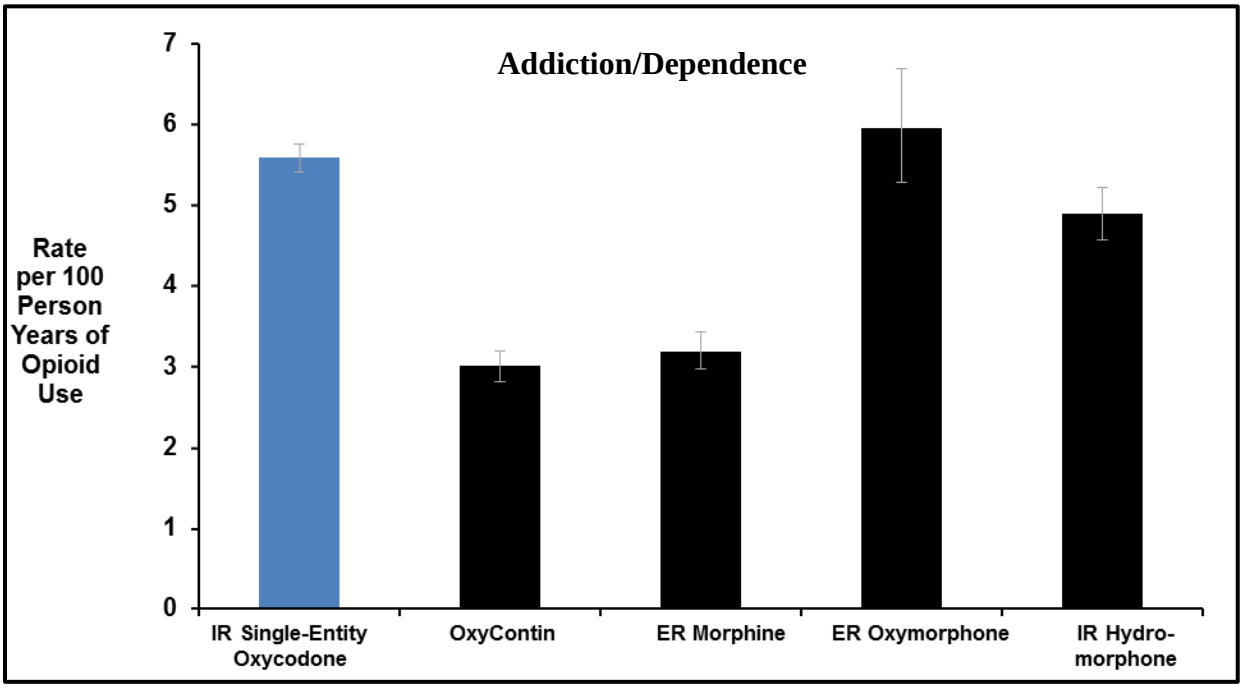
Data from the MarketScan commercial database (November 2010-2013) for individuals age 18 to 64 dispensed single opioids without other concomitant opioids show that the rate of abuse among patients dispensed IR single-entity oxycodone was 0.79 per 100 person-years of opioid use (Figure 41), which was higher than abuse rates for comparator opioids (0.31 per 100 person-years for OxyContin, 0.42 for ER morphine, 0.55 for ER oxymorphone, and 0.60 for IR hydromorphone). The rate of diagnosed addiction/dependence among individuals dispensed IR single-entity oxycodone (5.58 per 100 person years of opioid use) without other opioids was higher than that of other opioids (3.00 for OxyContin, 3.18 for ER morphine, 4.89 for IR hydromorphone) and similar to ER oxymorphone (5.95 per 100 person-years of opioid use) (Figure 42). The rates of diagnosed poisoning/overdose per 100 person-years of opioid use among patients dispensed opioids without other opioids was higher for IR single-entity oxycodone (0.40 per 100 person years) than that associated with reformulated OxyContin (0.28 per 100 person years), but lower than ER morphine (0.51 per 100 person years), ER oxymorphone (0.49 per 100 person years) and IR hydromorphone (0.68 per 100 person years) (Figure 43).

In addition to rates of abuse, addiction, and overdose that adjust for time dispensed opioid, absolute numbers of diagnosed abuse, addiction, and overdose cases for IR SE oxycodone can be compared with that for other opioids. Over the 3 years of the study analysis, there were 613 diagnosed abuse cases associated with IR single-entity oxycodone, which was higher than all other opioids, and the next highest opioid was IR hydromorphone with 114 diagnosed abuse cases. The number of addiction/dependence cases was 4,200 for IR single-entity oxycodone, which was the highest among the opioid groups studied and 4 times more than that of the next highest opioid. In addition, the number of overdose/poisoning cases was 315 for IR single-entity oxycodone, which was the highest among the opioid groups studied. The number of poisoning/overdose, addiction/dependence, and abuse cases, as well as the number of patients and person time (years) are shown in Table 15.



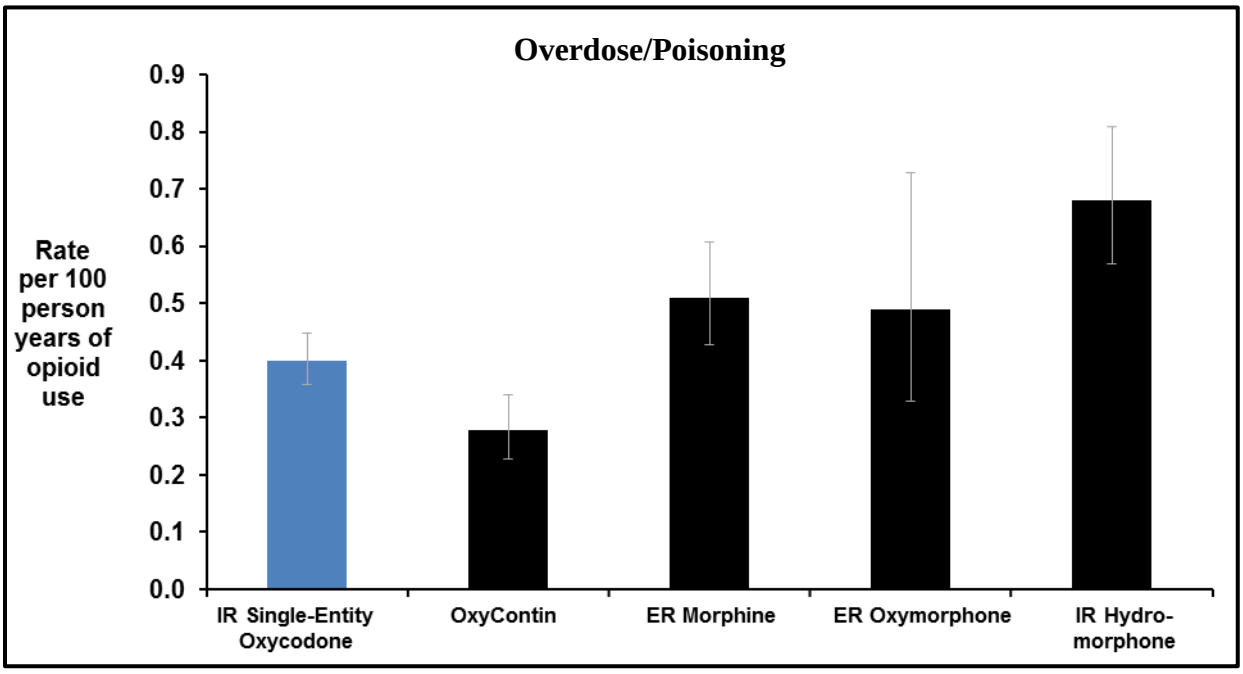
Source: MarketScan Commercial Healthcare Claims Database (November 2010-October 2013)

Figure 41 Abuse Diagnosis Rates among Patients Dispensed One Opioid Analgesic



Source: MarketScan Commercial Healthcare Claims Database (November 2010-October 2013)

Figure 42 Addiction/Dependence Diagnosis Rates among Patients Dispensed One Opioid Analgesic



Source: Truven MarketScan Commercial Healthcare Claims Database (November 2010-October 2013)

Figure 43 Overdose/Poisoning Diagnosis Rates among Patients Dispensed One Opioid Analgesic

Table 15 Diagnosed Overdose, Addiction, and Abuse Cases, Patients, and Person Years for IR Single-Entity Oxycodone and Comparator Opioids

	Cases	Patients	Person-years of opioid use[1]
Overdose/Poisoning			
IR SE oxycodone	315	509,376	77,820
OxyContin	90	190,629	32,388
ER morphine	133	192,089	25,927
ER oxymorphone	24	32,320	4,908
IR hydromorphone	129	219,732	18,914
Addiction/Dependence			
IR SE oxycodone	4,200	509,376	75,248
OxyContin	943	190,629	31,390
ER morphine	800	192,089	25,135
ER oxymorphone	279	32,320	4,687
IR hydromorphone	902	219,732	18,456
Abuse			
IR SE oxycodone	613	509,376	77,748
OxyContin	102	190,629	32,399
ER morphine	109	192,089	25,963
ER oxymorphone	27	32,320	4,906
IR hydromorphone	114	219,732	18,929

Source: Truven MarketScan Commercial Healthcare Claims Database (November 2010-October 2013)
SE=single-entity
[1]Calculated from time covered by prescribed and dispensed opioids

Rates of diagnosed abuse, addiction/dependence, and overdose/poisoning in individuals prescribed IR single-entity oxycodone concomitantly with OxyContin, an ER oxycodone product, were compared to that for OxyContin alone (Table 16) in the same cohort. There was a large number of opioid cases for all 3 outcomes (overdose/poisoning, addiction/dependence, and abuse) among patients prescribed ER oxycodone in conjunction with IR single-entity oxycodone, and both the number of cases and the rate per 100 person-years exceeded that of ER oxycodone alone. Thus, prescribing a nonabuse-deterrent IR single-entity oxycodone product along with an ER opioid with abuse-deterrent properties (eg, ER oxycodone) increases the risk of overdose/poisoning, addiction/dependence, and abuse. This highlights the need for an IR single-entity oxycodone product with abuse-deterrent properties, as IR opioids are frequently used for breakthrough pain in conjunction with around-the-clock ER opioids.

Table 16 Rates of Diagnosed Abuse, Addiction/Dependence, and Overdose/Poisoning per 100 Person Years of Opioid Use Among Individuals Dispensed IR Single-Entity Oxycodone with ER Oxycodone (OxyContin) vs ER Oxycodone Alone

	Cases	Person-years of opioid use[1]	Rate per 100 person-years of opioid use
Abuse			
OxyContin + IR SE oxycodone	292	23,173	1.26
OxyContin alone	102	32,399	0.31
OxyContin + IR oxycodone combo	159	16,267	0.98
Addiction/ Dependence			
OxyContin + IR SE oxycodone	2,624	21,854	12.01
OxyContin alone	943	31,390	3.00
OxyContin + IR oxycodone combo	1,436	15,588	9.21
Overdose/Poisoning			
OxyContin + IR SE oxycodone	283	23,178	1.22
OxyContin alone	90	32,388	0.28
OxyContin + IR oxycodone combo	126	16,275	0.77

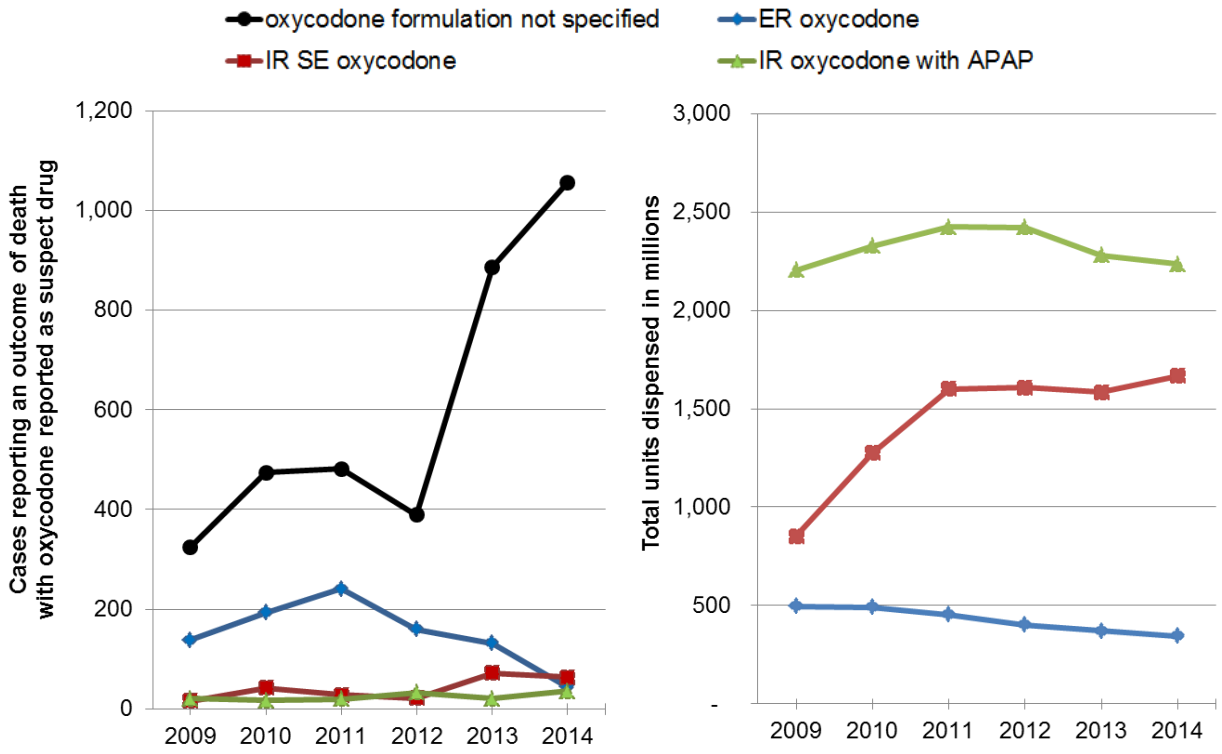
SE=single-entity
Source: MarketScan Commercial Healthcare Claims Database (November 2010-October 2013)
[1]Calculated from time covered by prescribed and dispensed opioids

6.3.3 Deaths Reported to FDA Adverse Event Reporting System (FAERS) Associated with Oxycodone

A source of national data on opioid deaths that provides opioid-specific information is the FDA Adverse Event Reporting System (FAERS). However, FAERS has the limitation of relying on spontaneously reported deaths to FDA or the manufacturer. FAERS data were used for an analysis of the number of deaths reported for IR single-entity oxycodone over time relative to the number of prescriptions for IR single-entity oxycodone in the same period, as compared with that for other oxycodone products and all oxycodone products. Data from FAERS and IMS Health (IMS) were extracted from the years encompassing 2009 through 2014.

Figure 44 displays the number of death cases reported to FAERS with oxycodone as the suspect drug, as well as the corresponding number of units dispensed for oxycodone products obtained from IMS Health. Reported deaths with IR single-entity oxycodone as the suspect drug were a small proportion of the total reported deaths for oxycodone, even though the number of dispensed units for IR single-entity oxycodone was a large proportion of the dispensed units of all oxycodone products. The number of dispensed units of IR single-entity oxycodone rose from 2009 to 2014, but the number of reported deaths associated with IR single-entity oxycodone did not increase substantially as a proportion of total reported oxycodone deaths. In contrast, the number of oxycodone deaths reported to FAERS that were attributed to oxycodone but no specific oxycodone formulation or product rose dramatically between 2009 and 2014. In 2014, the large majority of reported oxycodone deaths was not associated with any product or

formulation. It is not clear what oxycodone formulation caused these deaths,, but some proportion of the oxycodone deaths with no formulation reported are presumably due to IR single-entity oxycodone.



Source: FDA Adverse Event Reporting System (FAERS) (deaths); IMS Health NPA (units dispensed)
SE=single-entity

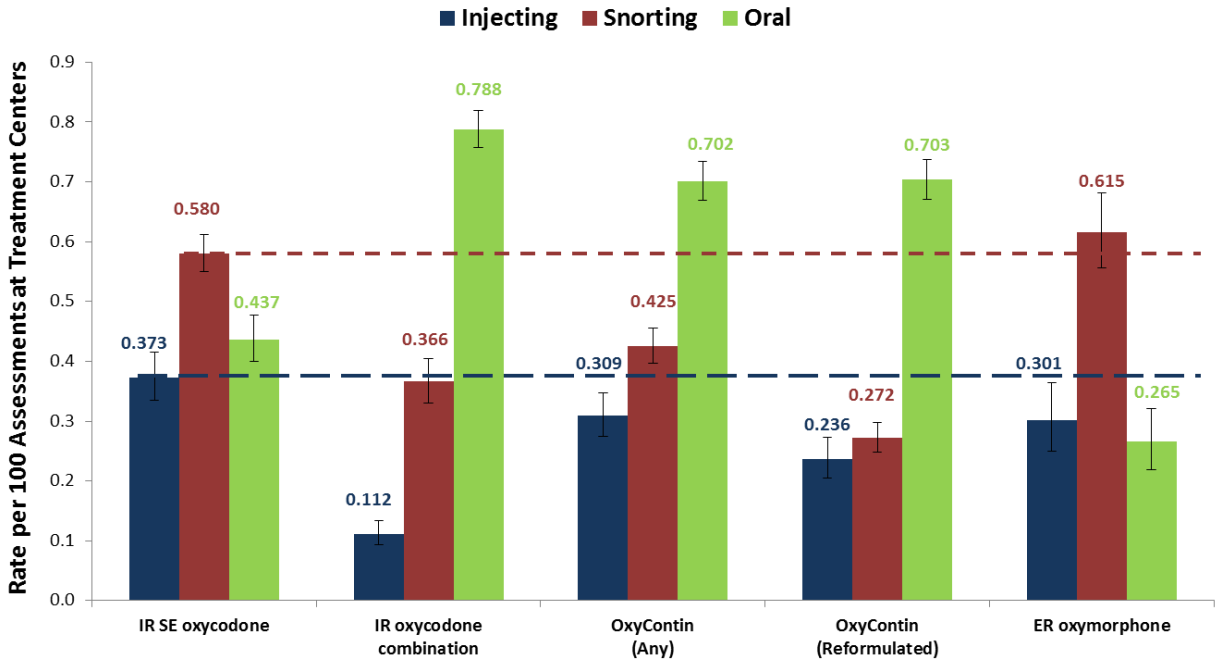
Figure 44 Number of IR Single-Entity Oxycodone Deaths vs Number of Unknown Oxycodone Deaths Reported to FDA and Increase in IR Single-Entity Oxycodone Prescriptions during the Same Time Period (2009-2014)

6.4 Snorting and Injecting IR Single-Entity Oxycodone

IV and IN administration are typically more prevalent in experienced users, while oral abuse is generally more common among new abusers; (Butler 2010; Hays 2003; Hays 2004; Katz 2011). Progression of opioid abuse from oral routes to injection or snorting is common and concerning (Hays, 2003). As the IN and IV routes have a significant increased risk of negative health outcomes, eg, blood-borne bacterial and viral infection (including HIV), nasal/palatal necrosis and perforation, overdose, addiction, and death, these routes are important targets in the development of formulations with abuse-deterrent properties (Katz 2011; Surratt 2011).

An important indicator of abuse in the community is patterns of abuse among individuals assessed upon entry into substance abuse treatment programs. The NAVIPPRO® Addiction Severity Index-Multimedia Version (ASI-MV) system collects data in real time on overall abuse of specific drugs (legal and illegal) and abuse by routes of administration in the past 30 days

among individuals assessed in a network of several hundred substance abuse treatment centers across the US. Among individuals reporting abuse of IR single-entity oxycodone, snorting was the most commonly endorsed route of abuse, followed by oral abuse and injecting (Figure 45). The rate of injecting IR single-entity oxycodone was higher than for the other opioids evaluated. Additionally, the rate of snorting IR single-entity oxycodone was higher than for all comparator opioids except ER oxymorphone. Because these individuals are entering substance abuse treatment programs, they may be more serious abusers than the population of individuals abusing drugs as a whole.

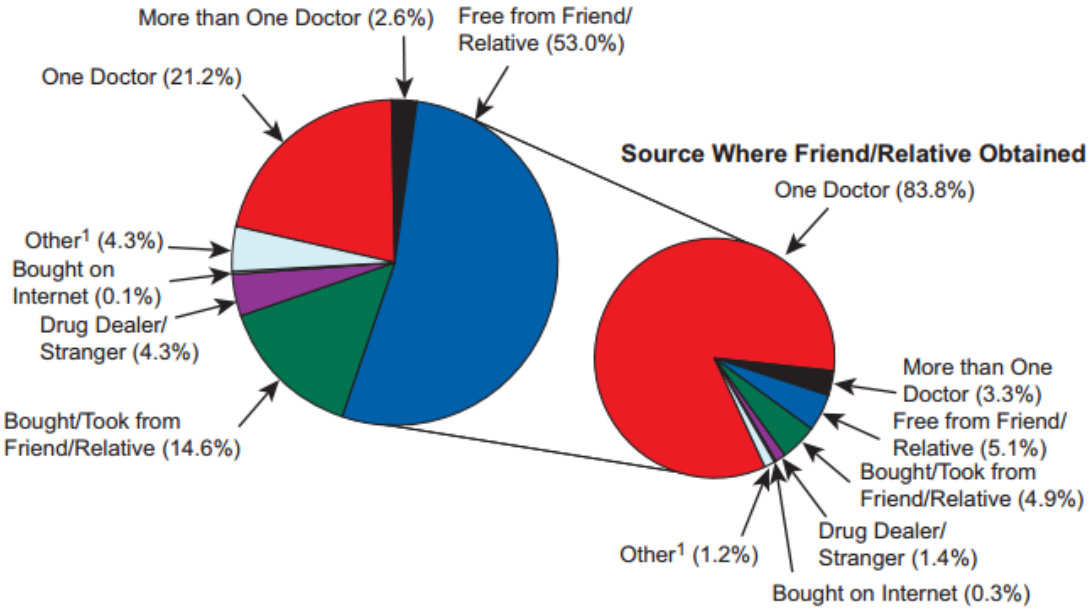


Source: NAVIPPRO Addiction Severity Index-Multimedia Version® (ASI-MV); 1Q2011-4Q2013
SE=single-entity

Figure 45 Injecting and Snorting Abuse for IR Single-Entity Oxycodone Compared With Other Opioids in the NAVIPPRO ASI-MV System

6.5 Potential Diversion of Opioids from Patients to Nonpatients for Purposes of Abuse

There is potential for access to these opioid analgesics for abuse both by patients prescribed the opioid as well as by others who may obtain the opioid from the patient, either with or without their knowledge. Among persons aged 12 or older in 2011-2012 who used pain relievers nonmedically in the past year, 53% reported receiving pain relievers for free from a friend or relative and 14.6% purchased or took them from a friend or relative (SAMHSA 2014; Figure 46). Of note, while these data represent nonmedical use of opioids, nonmedical use is a proxy for abuse. Younger populations in particular are more likely to experiment with medications received from a friend or relative (Inciardi 2009).



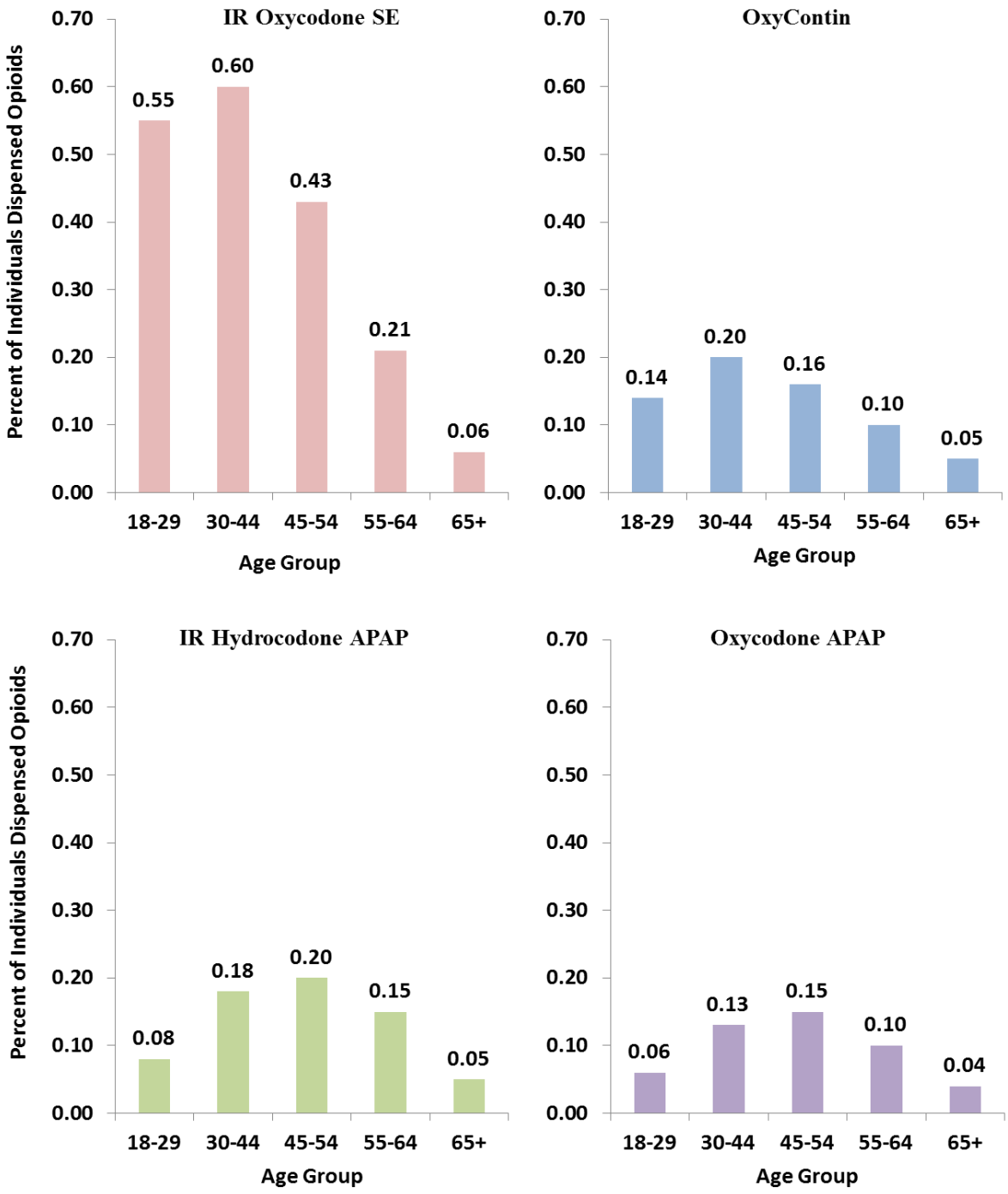
[1]The Other category includes the sources "Wrote Fake Prescription," "Stole from Doctor's Office/Clinic/Hospital/Pharmacy," and "Some Other Way."

Note: The percentages do not add to 100 percent due to rounding.

Source: SAMHSA 2014

Figure 46 Proportion of Opioids Used Nonmedically And Obtained from Diverted Sources

Doctor/pharmacy shopping is a means of obtaining prescriptions from multiple prescribers and/or pharmacies for personal abuse or distribution to others who intend to abuse the drugs, and generally involves multiple overlapping prescriptions from more than one prescriber and multiple pharmacies (Cepeda 2013). Rates of doctor shopping are highest for IR single-entity oxycodone (Chilcoat 2015) (Figure 47). For IR single-entity oxycodone, rates of doctor shopping decline with age, with the highest rates of doctor shopping observed in the youngest individuals.



Source: IMS LRx (2011-2Q2013)
Abbreviations: APAP=acetaminophen; SE=single-entity

Figure 47 Doctor-Shopping Rates by Age Group for IR Single-Entity Oxycodone and Comparator Opioids

The availability of an IR single-entity oxycodone formulation with abuse-deterrent properties could decrease the desirability for abuse, and, as a result, the product may be less likely to be diverted from patients to nonpatients for purposes of abuse/nonmedical use. Further, another potential benefit of a formulation with abuse-deterrent properties is that even if the drug is diverted, regardless of source, there is a reduction in the ability to abuse it via riskier nonoral routes.

6.6 Conclusions

IR single-entity oxycodone is the most commonly prescribed Schedule II opioid without acetaminophen, and is prescribed long-term and at high doses (>100 mg/day morphine equivalent dose) more frequently than ER oxycodone. IR single-entity oxycodone is also highly abused, with high rates of fatalities reported in both a state study (North Carolina 2010) and in FDA data, the only national data source to differentiate oxycodone formulations. Additionally, IR single-entity oxycodone was associated with high rates of poisoning/overdose, addiction/dependence, and abuse among patients dispensed IR single-entity oxycodone (without other concomitant opioids) in commercially insured individuals. IV and IN abuse of IR single-entity oxycodone is common. As IN and IV routes have a significant increased risk of serious negative health outcomes, these routes are important targets in the development of abuse-deterrent formulations (Katz 2011; Surratt 2011). Further, like other opioids, IR single-entity oxycodone is subject to potential diversion from patients to nonpatients for purposes of abuse, and a formulation with abuse-deterrent properties is likely to decrease desirability of the product for diversion. Overall, these factors support the medical and public health importance of an IR single-entity oxycodone product with abuse-deterrent properties.

7 RISK EVALUATION AND MANAGEMENT

Opioids, as a class, have a number of known risks, including misuse, abuse, addiction, respiratory depression, hypotension and overdose, as well as AEs such as constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and asthenia. Purdue will monitor these well-characterized risks using standard pharmacovigilance to detect any differences in event type or frequency from that expected for an IR oxycodone product.

To monitor the safety (potential clinical implications) of patients who do not take Avridi as prescribed, Purdue proposes to conduct enhanced pharmacovigilance. The pharmacovigilance plan will include a targeted questionnaire, expedited reporting, quarterly analyses (presented in the Periodic Adverse Drug Experience Reports (PADERs)), and a final comprehensive analysis after 3 years, of all overdose, respiratory depression ,and accidental injury postmarket AEs, regardless of outcome, related to taking Avridi with meals (less than one hour prior to or less than two hours after eating). If any unknown risks are detected, these will be reported, further evaluated, and, if appropriate, additional studies will be undertaken to better characterize their frequency and distribution.

Several additional risk management techniques will be used to manage the potential risks of Avridi tablets, including those related to the food effect. This multifaceted approach will include tools such as labeling, prescriber and pharmacist communications, and patient information, as well as a postmarketing research program and an additional study, described below. The label for Avridi tablets will include a statement about the food effect, as well as formulation-specific patient counseling information stating, "Avridi should be taken on an empty stomach, at least one hour prior to, or two hours after eating." Communications with prescribers and pharmacists to ensure appropriate prescribing and dosing will be undertaken.

In accordance with the FDA Guidance to Industry: *Abuse-Deterrent Opioids – Evaluation and Labeling* April 2015, we propose conducting a postmarketing research program to assess levels of abuse of Avridi relative to existing formulations of IR single entity oxycodone products without abuse-deterrent properties, as well as other opioid analgesics. The epidemiologic program will compare rates of overall abuse via any route of administration, as well as through nonoral routes targeted by Avridi's formulation (specifically IN and IV), for Avridi vs other IR single-entity oxycodone products without abuse-deterrent properties. Secondary comparators (IR oxycodone combination products, IR hydrocodone-acetaminophen products, and ER oxycodone with abuse-deterrent properties) will be used to allow assessment of historical trends in oxycodone abuse.

In addition, a study will be conducted to explore the occurrence of adverse outcomes associated with Avridi vs other IR single-entity oxycodone products to assess the potential risk associated with Avridi's food effect. Safety data for Avridi tablets will be compared with other IR single-entity oxycodone products, particularly in relation to timing/dosing patterns. While PK modeling under a variety of dosing scenarios have shown that plasma oxycodone concentrations after administration of Avridi under fed and fasting conditions are comparable with those after administration of the currently available IR oxycodone product, Roxicodone under the same conditions, the proposed study will be conducted in the setting of real-world clinical practice.

These studies will include large-scale surveillance systems of exposures reported to poison centers as well as overdoses captured via healthcare claims data for patients with commercial and Medicaid insurance. Supportive data will be provided through systematic monitoring of reports on drug diversion and street price from law enforcement officials, as well as crowd-sourced reports of street price. Because it is expected that the number of prescriptions for Avridi will be relatively low immediately following launch and then increasing over time, it will be necessary to adjust for number of prescriptions, as well as examining numbers and population-adjusted rates of abuse, where applicable. Through this conservative risk evaluation and management program, Purdue will be able to evaluate the safety of Avridi, including when the dosing instructions in the label are not followed, as well as assess trends in abuse of Avridi compared with nonabuse-deterrent IR single-entity oxycodone products and other prescription opioid analgesics.

8 BENEFITS AND RISKS

Avridi is an IR single-entity oxycodone HCl formulation with abuse-deterrent properties (gelling and aversive components) designed to deter abuse via the IV and IN routes. Avridi, like all medicines, has benefits and risks. The efficacy and safety of oxycodone in the management of acute and chronic pain are well established, with currently marketed IR oxycodone products widely prescribed for these pain conditions. As a single-entity IR oxycodone, Avridi tablets have a similar efficacy and safety profile as other currently approved IR single-entity oxycodone products, including the reference drug, Roxicodone, when taken as directed. Under fasted conditions, Avridi is bioequivalent to Roxicodone.

The risks associated with the administration of the active component of Avridi tablets, oxycodone, are those consistent with the opioid analgesic class of products. The inclusion of gelling agents and sodium lauryl sulfate in Avridi tablets does not increase any of the known risks associated with oxycodone. The most commonly observed AEs associated with the use of oxycodone in clinical trials are constipation, nausea, drowsiness, dizziness, vomiting, and pruritus. Other notable known AEs include misuse, abuse, addiction, and their consequences of overdose and death. The physiologic effects from opioid overdose are respiratory depression, CNS depression, and hypotension. In addition, gastrointestinal effects are a class effect of opioids.

The proposed indication for Avridi tablets is for the management of acute and chronic moderate to severe pain where the use of an opioid analgesic is appropriate. As such, Avridi provides an appropriate treatment option for patients requiring the use of an opioid on a PRN basis, on an around-the-clock (every 4- to 6-hours) regimen, and PRN in conjunction with an around-the-clock ER opioid analgesic regimen. Furthermore, the availability of Avridi tablets in 5 dosage strengths (5 mg, 10 mg, 15 mg, 20 mg, and 30 mg), provides prescribers the flexibility to individualize the dose specific to their patients' needs.

The need for an IR single-entity oxycodone formulation with abuse-deterrent properties is demonstrated by IR oxycodone's high prescription utilization, the rate of abuse in the community, and the consequences of this abuse, particularly when administered by the IV and IN routes. With approximately 16 million prescriptions for IR single-entity oxycodone per year in the US, any impact on abuse, particularly by the more dangerous IV and IN routes, could result in an important population health impact. For example, the serious consequences of abuse are shown in the North Carolina data (Figure 47) where, after adjusting for the number of prescriptions dispensed, IR single-entity oxycodone 30-mg tablets were associated with more than double the risk of overdose death than was observed for OxyContin 80 mg tablets (Hirsch 2014). These data indicate that deterrence of abuse of IR single-entity oxycodone products could have a significant public health impact.

Avridi tablets provide an appropriate alternative to existing nonabuse-deterrent IR oxycodone products (including Roxicodone [the reference drug] and generic equivalents), and are expected to have an important public health benefit by reducing IV and IN abuse.

A series of studies have been conducted to assess the abuse-deterrent properties of Avridi, consistent with evaluations described in FDA Guidance to Industry: *Abuse Deterrent Opioids – Evaluation and Labeling*, April 2015. These assessments include laboratory-based *in vitro* manipulation and extraction studies (defined as Category 1 studies per the FDA Guidance) and clinical abuse potential studies (Category 3). The premarket data indicate that Avridi is formulated with physicochemical barriers to IV abuse and that Avridi is expected to result in a meaningful reduction in the abuse potential of oxycodone via the IN route.

The potential to reduce abuse of Avridi tablets via IN routes of administration was assessed in a clinical abuse potential study which employed a VAS scale of "drug liking right now" and used maximum (peak) effects as the primary measure of abuse liability. Maximum effects were decreased by up to 40% after IN insufflation of crushed Avridi. Subjects reported much higher frequencies of nasal discomfort (some severe) than seen with IN insufflation of crushed Roxicodone tablets or placebo. These nasal/oropharyngeal AEs were considered highly unpleasant by experienced opioid users and led to substantial decreases in "drug liking" VAS scores. None of these AEs was considered serious, and none led to injury of the nasal mucosa. Since Avridi is to be administered orally, these effects are not relevant to patients using the drug as prescribed; they only affect those attempting to misuse or abuse Avridi through the IN route.

The potential to reduce abuse of Avridi tablets via IV routes of administration was assessed by comprehensive *in vitro* studies. The potential for IV abuse with crushed tablets dissolved in small amounts of aqueous media was reduced with Avridi compared with Roxicodone. This was demonstrated in the reduced syringeability of the viscous gel that resulted from such manipulation of the Avridi tablet. The gel effectively blocked any significant possibility of IV administration of the oxycodone thus obtained.

Due to the gelling agents of the Avridi formulation that deter IV abuse, when Avridi is administered with a high-fat meal, lower peak concentrations and a delay in reaching peak concentrations were observed compared with the reference listed drug, Roxicodone. This may, result in delayed analgesia for some patients. In the PK study involving fasted subjects, Avridi was bioequivalent to Roxicodone with regard to rate and extent of absorption, and thus therapeutically equivalent.

To ensure that administration of Avridi tablets produces oxycodone concentrations that are therapeutically equivalent to those resulting from Roxicodone administration, Avridi should be administered in the fasted state. Proposed Avridi labeling and dosing instructions will advise patients to take Avridi on an empty stomach, at least one hour prior to or two hours after eating. Additionally, as included in other oxycodone product labeling under instructions for patients, Avridi labeling will state:

1. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
2. Patients should be advised not to adjust the dose of Avridi without consulting the prescribing professional.

When Avridi is taken with food, the delayed Tmax and lower Cmax may lead to multiple or repeated doses taken by the patient in response to a possible delay of the analgesic effect. This scenario is more likely in the patient taking Avridi on a PRN basis or taking Avridi intermittently for breakthrough pain rather than on an around-the-clock regimen since a patient taking Avridi around-the-clock would have reached steady-state oxycodone plasma concentrations. Generally, when steady-state plasma concentrations of a drug are achieved, so are adequate plasma concentrations of the drug to produce the intended clinical effects.

Recognizing the possibility that a patient may not comply with the instructions in the labeling regarding administration of Avridi in the fasted state, Purdue conducted PK modeling of the potential consequences of various Avridi dosing scenarios with food (PRN use, steady-state around-the-clock dosing, PRN use in conjunction with an around-the-clock ER opioid regimen) to project resulting oxycodone vs time profiles and corresponding distributions for individual subject PK parameters (eg, Cmax, Tmax). In each case, comparisons were made between the PK profiles and PK parameter distributions associated with Avridi dosing and those for the reference drug, Roxicodone, using the same mg dose and dosing conditions. The scenarios indicate that when Avridi is taken under fasting conditions followed by a dose with food or exclusively under fed conditions, the range of oxycodone concentrations, including the maximum concentration, remain within the range for routine use of Roxicodone. These results suggest that Avridi's food effect does not represent a clinically significant safety concern.

Purdue plans to closely monitor the rates of abuse of Avridi relative to other comparable opioid products. The proposed Avridi label provides appropriate guidance for avoiding/managing all of these risks. The management of risk is described in the warnings and precautions related to the established and understood risks of μ-opioid agonists and dosing instructions to ensure proper use of the product. In addition, dosing instructions to take Avridi on an empty stomach will be included in the Dosing and Administration section as well as the patient information section of the label.

The proposed Avridi labeling will be the first IR oxycodone product to include specific dosing instructions related to meals. As such, there is a potential risk that healthcare professionals may not recognize the need to review the specific Avridi labeling and instruct the patient to take Avridi on an empty stomach. Therefore, proposed risk evaluation and mitigation strategies, in addition to labeling, incorporate healthcare provider and patient education, including specific dosing information aimed at pharmacists. Additionally, enhanced pharmacovigilance and specific epidemiologic research are proposed.

In summary, Avridi is expected to provide a favorable benefit-risk profile that is at least as good as that of existing currently approved IR single-entity oxycodone products:

- similar analgesic benefits;
- no notable increased safety risk related to misuse based on the anticipated food effect;
- anticipated meaningful impact on reducing abuse by the high-risk IV and IN routes of administration.

9 CONCLUSIONS

IR single-entity oxycodone is among the most commonly prescribed Schedule II opioids for the management of acute and chronic moderate to severe pain; however, the high prevalence of abuse by injecting and snorting is accompanied by a substantially increased risk of serious negative health outcomes relative to oral administration. Avridi tablets incorporate technology designed to deter IV and IN abuse while providing similar safety and efficacy as currently available nonabuse-deterrent IR single-entity oxycodone products such as Roxicodone tablets. Studies meeting FDA-defined standards for abuse deterrence support the potential impact of the technology, demonstrating that Avridi presents barriers to physicochemical manipulations that are expected to deter abuse by the IV and IN routes. Additionally, the clinical abuse potential study of IN use has shown substantial reductions as compared with Roxicodone in parameters such as "drug liking" and the interest by recreational opioid users to "take drug again". A known food effect with Avridi may result in a delay in analgesia when taken with food, but PK modeling supports that, for those patients who do not follow the dosing instructions and take Avridi without regard to food, the safety risk is likely not be clinically significant. In summary, Avridi tablets will provide an alternative treatment option relative to nonabuse-deterrent IR single-entity oxycodone products that addresses an important need and has a favorable benefit-risk profile with the proposed labeling and other proposed risk evaluation and mitigation strategies.

10 REFERENCES

Blackwell DL, Lucas JW, Clarke TC. Summary health statistics for U.S. adults: National Health Interview Survey, 2012. National Center for Health Statistics. *Vital Health Stat* 10(260). 2014.

Butler SF, Black RA, Grimes Serrano JM, Wood ME, Budman SH. Characteristics of prescription opioid abusers in treatment: Prescription opioid use history, age, use patterns, and functional severity. *J Opioid Manag*. 2010 Jul-Aug;6(4):239-41, 246-52.

Butler SF, Cassidy TA, Chilcoat H, Black RA, Landau C, Budman SH, Coplan PM. Abuse rates and routes of administration of reformulated extended-release oxycodone: initial findings from a sentinel surveillance sample of individuals assessed for substance abuse treatment. *J Pain*. 2013;14(4):351-8.

Cepeda MS, Fife D, Vo L, Mastrogiovanni G, Yuan Y. Comparison of opioid doctor shopping for tapentadol and oxycodone: a cohort study. *J Pain*. 2013;14(2):158-164.

Chilcoat H, Coplan P, Sessler N, Harikrishnan V. Changes in age-specific rates of doctor-shopping for opioids following introduction of reformulated OxyContin. Presented at the College on Problems of Drug Dependence 77th Annual Meeting, Phoenix, AZ, June 13-16, 2015.

Cicero TJ, Ellis MS. Abuse-deterrent formulations and the prescription opioid abuse epidemic in the United States: Lessons learned from OxyContin. *JAMA Psychiatry*. 2015 May;72(5):424-30. doi: 10.1001/jamapsychiatry.2014.3043.

Ciuchta HP, Dodd KT. The determination of the irritancy potential of surfactants using various Methods of assessment. *Drug and Chemical Toxicology.* 1978; 1(3): 305-324.

Coplan PM, Kale H, Sandstrom L, Landau C, Chilcoat HD. changes in oxycodone and heroin exposures in the national poison data system after introduction of extended-release oxycodone with abuse-deterrent characteristics. *Pharmacoepidemiol Drug Saf.* 2013;22(12):1274-1282.

Dart RC, Surratt HL, Cicero TJ, Parrino MW, Severtson SG, Bucher-Bartelson B, et al. Trends in Opioid Analgesic Abuse and Mortality in the United States. *N Engl J Med.* 2015;372(3):241-8.

DeVeaugh-Geiss A, Kadakia A, Chilcoat H, Alexander L, Coplan P. A Retrospective Cohort Study of Long-term Immediate-release Hydrocodone/Acetaminophen Use and Acetaminophen Dosing Above the FDA Recommended Maximum Daily Limit among Commercially Insured Individuals in the United States (2008-2013). *J Pain*. 2015; 16 (6): 569-579.

Final report on the safety assessment of sodium lauryl sulfate and ammonium lauryl sulfate . *J Am Coll Toxicol*. 1983; 2(7).

Food and Drug Administration. FDA Briefing Document: Drug Safety and Risk Management Advisory Committee (DSaRM) Meeting. October 29-30, 2012a.

Food and Drug Administration Background Materials: Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC), Zohydro ER. December 7, 2012b.

Hall AJ, Logan JE, Toblin RL, Kaplan JA, Kraner JC, Bixler D, Crosby AE, Paulozzi LJ. Patterns of Abuse Among Unintentional Pharmaceutical Overdose Fatalities. *JAMA*. 2008;300(22):2613-2620.

Harris SC, Perrino PJ, Smith I, Shram MJ, Colucci SV, Bartlett C, Sellers EM. Abuse potential, pharmacokinetics, pharmacodynamics, and safety of intranasally administered crushed oxycodone HCl abuse-deterrent controlled-release tablets in recreational opioid users. *J Clin Pharmacol*. 2014;54:468-477.

Havens JR, Leukefeld CG, DeVeaugh-Geiss A, Coplan P, Chilcoat HD. Changes in opioid abuse in rural Kentucky after the reformulation of extended release oxycodone. *Drug and Alcohol Depend*. 2014;139(June):9-17.

Hays L, Kirsh KL,Passik SD. Seeking drug treatment for OxyContin abuse: a chart review of consecutive admissions to a substance abuse treatment facility in Kentucky. *J Natl Compr Canc Netw*. 2003;1(3):423-428.

Hays LR. A profile of OxyContin Addiction. *J Addict Dis*. 2004;23(4):1-9

Hirsch A, Proescholdbell SK, Bronson W, Dasgupta N. Prescription histories and dose strengths associated with overdose deaths. *Pain Med*. 2014;15: 1887-1195

Inciardi JA, Surratt HL, Cicero TJ, Kurtz SP, Martin SS, Parrino MW. The "black box" of prescription drug diversion. *J Addict Dis*. 2009 Oct;28(4):332-47

Janoff S, Coplan P, Perrin N, Campbell C, Shuster E, Ray T, Roberts M, Chilcoat H, Green C. Detection of opioid overdoses and poisonings in electronic medical records as compared to medical chart reviews. Presented at the College on Problems on Drug Dependence 77th Annual Meeting, Phoenix, AZ, June 13-16, 2015.

Kalso E. Proceedings of the Symposium "Updates of the Clinical Pharmacology of Opioids with Special Attention to Long-Acting Drugs." *J Pain Symptom Manage.* 2005; 29(S5):S47-S56.

Katz N, Dart RC, Bailey E, Trudeau J, Osgood E, Paillard F. Tampering with prescription opioids: Nature and extent of the problem, health consequences, and solutions. *Am J Drug Alcohol Abuse.* 2011; 37:205–217.

Kirson NY, White AG, Birnbaum, HG, Ben-Joseph R, Rossiter, LF, Michna E. Societal economic benefits associated with an extended-release opioid with abuse-deterrent technology in the United States. *Pain Medicine.* 2014; 15:1450–1454.

Kokki H, Kokki M, Sjövall S. Oxycodone for the treatment of postoperative pain. *Expert Opin Pharmacother*. 2012;13:1045-1058.

LaRochelle MR, Zhang F, Ross-Degnan D, Wharam JF. Rates of opioid dispensing and overdose after introduction of abuse-deterrent extended-release oxycodone and withdrawal of propoxyphene. *JAMA Intern Med*. 2015;175(6):978-987. doi:10.1001/jamainternmed.2015.0914

Ordóñez Gallego A, González Barón M, Espinosa Arranz E. Oxycodone: a pharmacological and clinical review. *Clin Transl Oncol*. 2007;9:298-307.

Raffa RB, Pergolizzi JV, Jr. Opioid formulations designed to resist/deter abuse. *Drugs.* 2010;70:1657-1675.

Rice JB, Kirson NY, Shei A, Cummings AK, Bodnar K, Birnbaum HG, Ben-Joseph R. Estimating the costs of opioid abuse and dependence from an employer perspective: a retrospective analysis using administrative claims data. *Appl Health Econ Health Policy*. 2014; 12(4):435–446.

Riley J, Eisenberg E, Müller-Schwefe G, Drewes AM, Arendt-Nielsen L. Oxycodone: a review of its use in the management of pain. *Curr Med Res Opin*. 2008; 24(1):175-192.

Romach MK, Schoedel KA, Sellers EM. Update on tamper-resistant drug formulations. *Drug Alcohol Depend*. 2013;130:13-23.

Rossiter LF, Kirson NY, Shei A, White AG, Birnbaum HG, Ben-Joseph R, Michna E. Medical cost savings associated with an extended-release opioid with abuse-deterrent technology in the US. *J Med Econ*. 2014 Apr;17(4):279-287.

Roxicodone® Package Insert, Xanodyne Pharmaceuticals, Inc., March, 2009.

Schaeffer T. Abuse-deterrent formulations, an evolving technology against the abuse and misuse of opioid analgesics. *J Med Toxicol*. 2012; 8: 400–407.

Sessler NE, Downing JM, Kale H, Chilcoat HD, Baumgartner TF, Coplan PM. Reductions in reported deaths following the introduction of extended-release oxycodone (OxyContin) with an abuse-deterrent formulation. *Pharmacoepidemiol Drug Saf.* 2014;23(12):1238-1246.

Severtson SG, Bartelson BB, Davis JM, Muñoz A, Schneider MF, Chilcoat H, Coplan PM, Surratt H, Dart RC. Reduced abuse, therapeutic errors, and diversion following reformulation of extended-release oxycodone in 2010. *J Pain*. 2013;14(10):1122-30.

Substance Abuse and Mental Health Services Administration, Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-48, HHS Publication No. (SMA) 14-4863. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2014.

Surratt H, Kurtz SP, Cicero TJ. Alternate routes of administration and risk for HIV among prescription opioid abusers. *J Addict Dis*. 2011;30(4):334-341.

U.S. Department of Health and Human Services Food and Drug Administration. Draft Guidance for Industry: Applications Covered by Section 505(b)(2), October 1999.

U.S. Department of Health and Human Services Food and Drug Administration. Draft Guidance for Industry: Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies, December, 2002.

U.S. Department of Health and Human Services Food and Drug Administration. Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling, April, 2015.

U.S. Environmental Protection Agency, Washington, DC 20460. August 5, 2009 Memorandum Subject: Sodium Lauryl Sulfate. Human Health Risk Assessment to Support Proposed Exemption from the Requirement of a Tolerance When Used as an Inert Ingredient in Pesticide Formulations.