

FDA ADVISORY COMMITTEE BRIEFING DOCUMENT

RoxyBond™
(oxycodone hydrochloride) immediate-release tablets

**JOINT MEETING OF THE ANESTHETIC AND ANALGESIC
DRUG PRODUCTS ADVISORY COMMITTEE AND THE DRUG
SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE**

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List of Abbreviations and Definition of Terms

AIDS	acquired immune deficiency syndrome
ADF	abuse-deterrent formulation
AE	adverse event
API	active pharmaceutical ingredient
ASA	American Society of Anesthesiologists
AUC	area under the curve
CDC	Centers for Disease Control and Prevention
CI	confidence interval
C_{max}	maximum plasma concentration
DAAAP	Division of Anesthesia, Analgesia, and Addiction Products
E_{max}	maximum effect
ER	extended-release
FDA	United States Food and Drug Administration
HAP	human abuse potential
HCV	hepatitis C virus
HCl	hydrochloride
HIV	Human Immunodeficiency virus
IDS	Inspirion Delivery Sciences, LLC
IN	intranasal
IR	immediate-release
IV	intravenous
LS	least squares
NDA	New Drug Application
ONDCP	Office of National Drug Control Policy
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
RADARS	Researched Abuse, Diversion and Addiction-Related Surveillance
RLD	reference listed drug
SD	standard deviation
SE	single-entity
SAMHSA	Substance Abuse and Mental Health Services Administration
TE_{max}	time to maximum effect
T_{max}	time to maximum plasma concentration

1 EXECUTIVE SUMMARY

RoxyBond™ is an abuse-deterrent, immediate-release (IR), single-entity (SE) oxycodone hydrochloride (HCl) tablet intended for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. RoxyBond is provided in 3 strengths – 5 mg, 15 mg, and 30 mg tablets for oral administration every 4 to 6 hours. Inspirion Delivery Sciences, LLC (IDS) submitted a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) in October 2016 requesting approval of RoxyBond. In consultation with the FDA's Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), RoxyBond was developed under the 505(b)(2) regulatory pathway using Roxicodone® (NDA 021011; Mallinckrodt, Inc.) as the reference listed drug (RLD).

RoxyBond is formulated using IDS' SentryBond™ abuse-deterrent technology, which imparts multiple physical and chemical barriers that make RoxyBond more difficult and/or less rewarding to manipulate and abuse via the intranasal and intravenous (IV) routes.

- RoxyBond resists particle size reduction (i.e., crushing, cutting, grating, or grinding) with common household tools, creating physical barriers to getting the tablet into an abusable form for intranasal or IV abuse.
- Intact and manipulated RoxyBond tablets resisted extraction for IV abuse across a range of conditions and solvents.
- When manipulated and subjected to a liquid environment, RoxyBond creates a viscous material that is difficult to syringe, creating a considerable barrier to IV abuse.
- Intranasal administration of manipulated RoxyBond led to slower and lower oxycodone absorption and drug liking compared to manipulated intranasal administration of Roxicodone and intact oral administration of RoxyBond.

This briefing document provides data supporting the approval of RoxyBond as an IR opioid analgesic and the labeling of RoxyBond with properties that can be expected to deter the intranasal and IV routes of abuse.

Background on Pain and Opioid Abuse

When other options are inadequate, opioids play a key role in the medical management of pain, particularly in patients with severe cancer pain, intractable nonmalignant conditions, and postsurgical pain (American Society of Anesthesiologists [ASA], 1996; ASA, 2010, ASA, 2012); however, the misuse, abuse, and diversion of these medications have become a considerable public health problem.

As one component of a larger strategy to address the opioid abuse epidemic, the FDA has encouraged the development of abuse-deterrent formulations (FDA, 2013). Initial data support the public health benefit of replacing easily abusable opioid products with abuse-deterrent formulations. Following the reformulation of an extended-release (ER) oxycodone product

(OxyContin®) with abuse-deterrent properties, marked decreases in abuse, doctor-shopping, and overdose fatalities were observed for ER oxycodone (Coplan et al, 2016).

While there are currently 9 approved abuse-deterrent ER opioid formulations, there are no approved IR formulations with abuse-deterrent labeling. In 2016, 93% of all prescriptions for oral opioid analgesics in the United States were for IR products (Symphony Health Solutions PHAST™ PRESCRIPTION Database). Given the greater exposure of IR products in the community, it is not surprising that population-adjusted rates of intentional abuse are 4.6 times greater and rates of drug diversion are 6.1 times greater for IR products than ER products (Iwanicki et al, 2016). For IR oxycodone, specifically, the population-adjusted rates of intentional abuse are 2.9 times higher than that of ER oxycodone and 6.8 times higher than that of ER morphine (Researched Abuse, Diversion, and Addiction-Related Surveillance [RADARS®] System Poison Center Program, 2012).

Snorting and injection are common routes of IR oxycodone abuse among individuals being assessed for substance abuse treatment (RADARS Treatment Center Program, 2016). Intranasal and IV abuse are particularly concerning because these routes are associated with significantly higher relative risks of death or major effects (e.g., overdose) than the oral route (RADARS System Poison Center Program, 2015). Furthermore, IV opioid abuse carries additional health risks above and beyond those directly related to the opioid effects including the potential transmission of blood borne pathogens such as human immunodeficiency disease (HIV) and hepatitis C virus (HCV) (Bruneau et al, 2012; Sullivan et al, 2005).

Considering the above, it stands to reason that the eventual replacement of easily abusable IR opioid formulations with abuse-deterrent formulations would be an important next step in the public health initiative aimed at addressing the opioid epidemic. Imparting abuse-deterrent features in IR opioids, combined with appropriate post-marketing activities, such as incorporating IR opioids into FDA's class-wide Risk Evaluation and Mitigation Strategy (FDA, 2017) to reduce misuse and abuse of opioids, will help ensure the appropriate benefit/risk balance of such formulations.

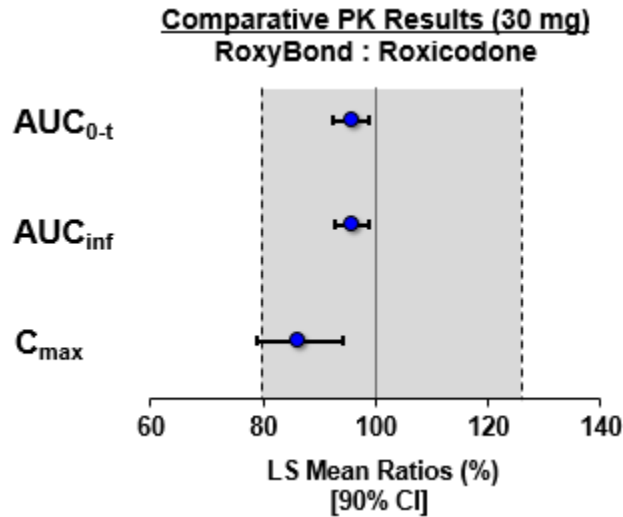
Development of RoxyBond for the Proposed Indication for Use

RoxyBond was developed via the 505(b)(2) regulatory pathway. Its approval is supported by comparable relative bioavailability to Roxicodone, which establishes a scientifically valid bridge to FDA's prior findings of safety and effectiveness to the RLD. Dose proportionality and food effect studies were performed to provide further support for approval. Based on the results of these studies, a Phase 3 efficacy and safety study was not required by the FDA.

The pivotal pharmacokinetic (PK) study compared the PK profile of RoxyBond 30 mg to that of Roxicodone 30 mg in a fasted state (**Figure 1**). RoxyBond met 80% to 125% confidence interval (CI) (i.e., bioequivalence range) for area under the curve (AUC) for plasma drug concentration as a measure of overall exposure. The PK parameter for maximum plasma concentration (C_{max}) had a lower confidence bound (79%) that fell slightly outside the lower bioequivalence limit of 80%. However, given that RoxyBond, like all opioids, will be titrated to effect, Inspirion and the

FDA agreed that the slightly missed lower limit for C_{max} would not be expected to affect the product's efficacy profile.

Figure 1: Comparative PK Results of RoxyBond Relative to Roxicodone under Single-Dose Fasted Conditions – Study O-ARIR-003



Note: gray shaded area reflects bioequivalence range of 80% to 125%.
 AUC = area under the curve; CI = confidence interval; C_{max} = maximum plasma concentration; LS = least squares; PK = pharmacokinetics.

A dose proportionality study of RoxyBond demonstrated the dose proportionality of the 5-, 15-, and 30-mg RoxyBond tablets, and provides support for the approval of all 3 dosage strengths. Finally, clinical PK data determined that there was no clinically significant effect of food on the bioavailability of RoxyBond, demonstrating that it can be taken without regard to food.

Abuse-Deterrent Studies for the Intranasal and IV Routes of Abuse

The in vitro (Category 1) and clinical (Categories 2 and 3) evaluations of RoxyBond's abuse-deterrent properties were consistent with the FDA Guidance "Abuse-Deterrent Opioids – Evaluation and Labeling: Guidance for Industry" issued in 2015. In all studies, 30-mg Roxicodone was used as the non-abuse-deterrent comparator.

Category 1 Studies

Category 1 testing of RoxyBond encompassed a comprehensive evaluation of the effects of physical manipulation, pre-treatment, large volume extraction, syringeability, and small volume extraction. This testing was performed in an iterative manner; at multiple time points during the development and the review processes, IDS incorporated feedback from the Agency to fully characterize RoxyBond's physical and chemical barriers.

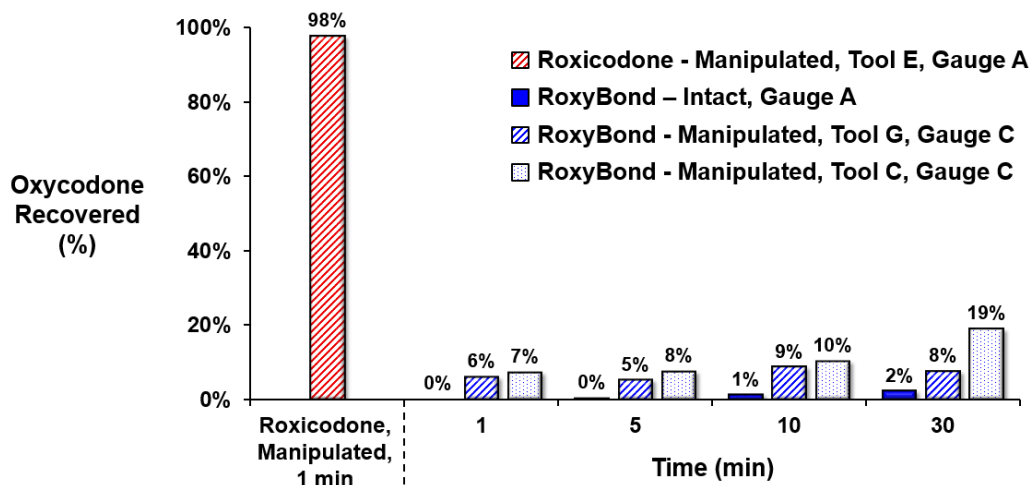
Unlike some abuse-deterrent products that rely primarily on the hardness of the tablet for their abuse-deterrent characteristics, RoxyBond incorporates multiple overlapping physical and

chemical barriers that significantly increase the hurdles required to prepare the tablets for intranasal and IV abuse. As illustrated in the summary of results below, particle size reduction, with or without chemical extraction, does not appreciably increase the release of oxycodone.

Key results from the Category 1 studies include:

- RoxyBond demonstrated resistance to common types of physical manipulation. An electric tool was the only tool able to produce small homogenous particles of RoxyBond amenable for snorting. In comparison, Roxicodone was easily manipulated into a fine powder in seconds with a mechanical tool.
- Pre-treatment of RoxyBond by extreme changes to temperature did not significantly increase the effectiveness of particle size reduction with household tools.
- RoxyBond demonstrated considerable resistance to extraction in large volumes of ingestible and non-ingestible solvents. In comparison, manipulated Roxicodone released 100% of oxycodone within 1 minute in a common solvent under non-stressed conditions.
- The amount of oxycodone recovered in a syringe was low in all conditions for RoxyBond (**Figure 2**) with small volume extraction times ranging from 1 to 30 minutes in Solvent A at Temperature A. For Roxicodone, following 1 minute of extraction, 98% of oxycodone was recovered in an injectable form using the smallest needle gauge evaluated (Gauge A).

Figure 2: Percent of Oxycodone Recovered Following Syringeability and Small Volume Extraction

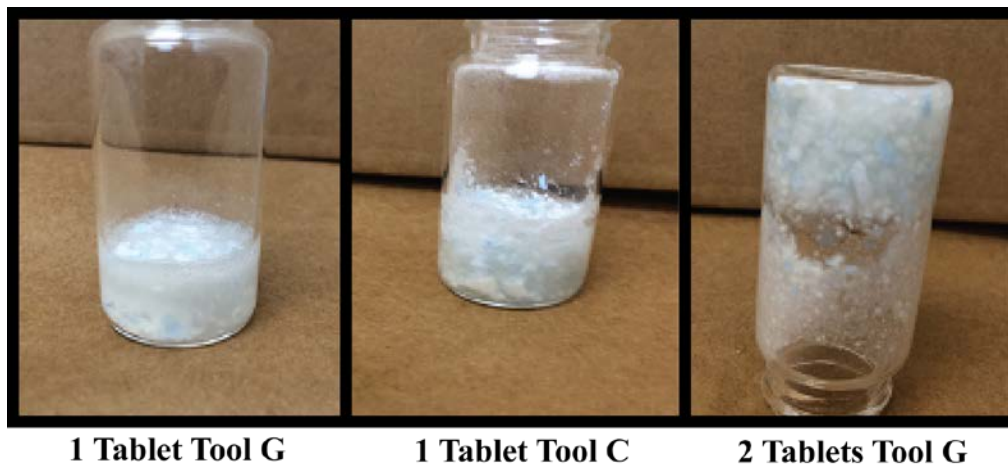


Volume A, Solvent A, Agitation A, Temperature A, Tablet Form A

- Particle size reduction with mechanical Tool C or electric Tool G did not appreciably increase the release of oxycodone for small volume extraction. Furthermore, manipulated RoxyBond tablets immediately formed a viscous material that was difficult to syringe and required the largest needle gauge evaluated (Gauge C), which abusers do not prefer for

IV drug abuse. Finally, the resulting solution contained visible particulate that was not suitable for IV injection (**Figure 3**). Adding additional tablets resulted in a completely non-syringeable material.

Figure 3: Examples of Manipulated RoxyBond with Visible Particulate After 5 Minutes in Solution A, Volume A, Temperature A, and Agitation A



Overall, Category 1 testing demonstrated that RoxyBond creates physical barriers to manipulating the product into an abusable form for intranasal abuse as well as physical and chemical barriers that would make IV abuse very difficult.

Category 2/3 Study

Study O-ARIR-002 was an intranasal human abuse potential (HAP) study (Category 3) with PK evaluations (Category 2). Study O-ARIR-002 was a randomized, double-blind, double-dummy, placebo-controlled, single-dose, 4-way crossover study. The primary objective of this study was to determine the abuse potential of manipulated RoxyBond (Tool G) relative to manipulated Roxycodone (Tool E) when administered intranasally to recreational, nondependent opioid users.

Key findings of the intranasal HAP study include:

- The study met its primary endpoint demonstrating a statistically significantly lower maximum effect (E_{max}) for Drug Liking for manipulated and snorted RoxyBond than manipulated and snorted Roxycodone (83 mm vs. 71 mm, $P < 0.0001$)
- The study met its key secondary endpoints: manipulated and snorted RoxyBond demonstrated statistically significant reductions in Take Drug Again, Overall Drug Liking, and Drug High compared to manipulated and snorted Roxycodone.
- Manipulated and snorted RoxyBond was rated by subjects as significantly more difficult to insufflate and was associated with greater adverse nasal effects than Roxycodone.

- Pharmacodynamic results were consistent with the PK findings. Manipulated and snorted RoxyBond had lower oxycodone concentrations than manipulated and snorted Roxycodone throughout the first 3 hours after administration.
- Consistent with the design of the formulation, manipulated and snorted RoxyBond had significantly slower oxycodone release and Drug Liking than intact RoxyBond when taken as intended orally.

Conclusion

Despite the fact that the population-adjusted rate of abuse of IR products is over 4 times greater than ER products, there are currently no abuse-deterrent IR opioid products approved in the US. IR oxycodone, specifically, is a common target of abuse with relatively high rates of intranasal and IV routes of abuse compared to other opioid products.

RoxyBond is an abuse-deterrent IR SE oxycodone product that provides comparable bioavailability of oxycodone compared to Roxycodone, establishing a scientific bridge to FDA's previous findings of safety and efficacy for the RLD. In addition, a clinical study demonstrated that there was no clinically significant effect of food on the PK of RoxyBond. Overall, RoxyBond can be expected to provide effective analgesia for patients with pain severe enough to require the use of an opioid analgesic and for which alternative treatment options are inadequate.

In vitro experiments demonstrated that RoxyBond's physical and chemical properties provide substantial barriers to particle size reduction for the purposes of getting the drug in an abusable form for intranasal or IV abuse and to extraction of oxycodone. In addition, a series of laboratory evaluations demonstrated that RoxyBond can be expected to make abuse via injection difficult. A clinical HAP study demonstrated that RoxyBond produces clinically relevant reductions in drug liking that can be expected to reduce abuse or misuse via the intranasal route. Overall, the results of the in vitro and clinical studies provide support for abuse-deterrent labeling for the intranasal and IV routes, which pose the greatest health risks and are common routes of abuse for IR SE oxycodone products.

2 PUBLIC HEALTH NEED FOR ABUSE-DETERRENT IR OPIOID ANALGESICS

Summary

- Immediate-release opioids are an important pain relief option for patients with pain severe enough to require an opioid analgesic and for which alternate treatment are inadequate.
- 93% of oral opioid prescriptions dispensed in 2016 were for IR products. The number of IR SE oxycodone prescriptions (17.9 million) exceeded the number of prescriptions for all ER opioids (of any moiety; 12.0 million) by ~5 million.
- Despite the approval of 9 abuse-deterrent ER formulations, there are no approved IR abuse-deterrent opioids in the United States.
- In the 4th quarter of 2015, the population-adjusted rates of intentional abuse and diversion were 4.6 times and 6.1 times higher for IR than ER opioids, respectively.
- The population-adjusted rate of abuse of IR oxycodone is 2.9 times higher than ER oxycodone and 6.8 times higher than ER morphine.
- Each incident of intranasal or IV opioid abuse carries 2 to 3 times the risk of death or a major adverse effect (e.g., overdose) compared to oral abuse.

2.1 Background on IR Opioid Analgesics and Abuse Deterrence Landscape

Immediate-release opioid analgesics are an important pain relief option for patients with moderate to severe pain. In particular settings, such as following a surgery or an injury, patients require an IR opioid when alternative therapies would not provide adequate pain relief.

In 2016, there were 151.4 million prescriptions filled for IR opioids and 12.0 million prescriptions for ER opioids (Symphony Health Solutions PHAST™ PRESCRIPTION Database). This large difference in prescriptions is not surprising since patients are usually only transitioned to an ER product if chronic treatment is needed. However, both ER and IR formulations are subject to high rates of abuse, misuse, and diversion.

The Centers for Disease Control and Prevention (CDC) released a Policy Impact on Prescription Painkiller Overdoses (CDC, 2011) that defined prescription drug overdose as an epidemic in the United States. The CDC reports that there are approximately 12 million annual nonmedical opioid users and more than 16,600 fatal overdoses involving prescription opioids each year (CDC, 2011). Because of these alarming statistics, the White House's Office of National Drug Control Policy (ONDCP), the CDC, and FDA have all initiated programs to help curb misuse, abuse, and diversion of opioid analgesics (White House, 2013; CDC, 2013; FDA, 2013).

Data from the National Survey on Drug Use and Health (Substance Abuse and Mental Health Services Administration [SAMHSA], 2011) show that among nonmedical users of prescription pain relievers:

- 69% obtained them from a friend or family member with a legitimate prescription
- 85% of those friends or family members utilized a single licensed prescriber

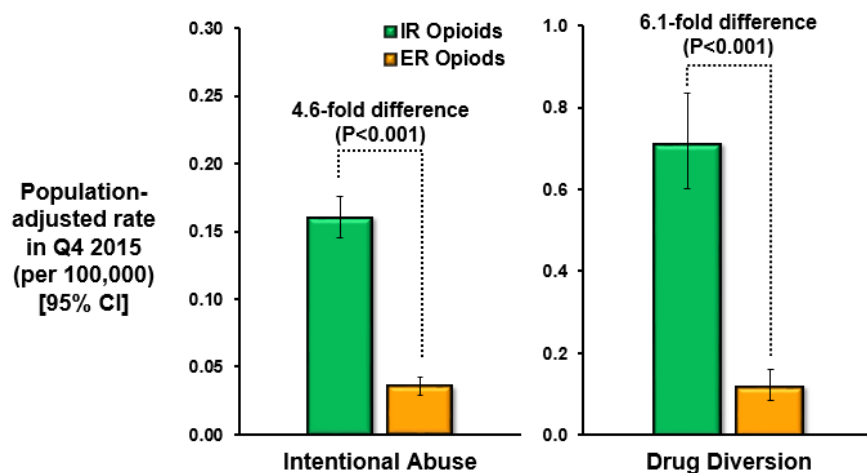
These survey results suggest that most opioid products abused in the United States are diverted from legitimate prescriptions rather than being procured from a dealer on the street, and underscore the potential public health impact of abuse-deterrent formulations.

There are currently 9 FDA-approved abuse-deterrent ER opioid formulations (OxyContin[®], Targiniq[™] ER, Embeda[®], Hysingla[®] ER, MorphaBond ER[™], Xtampza[®] ER, Troxyca[®] ER, Arymo[™] ER, and Vantrela[™] ER). To date, there are no approved IR formulations with abuse-deterrent labeling. Most abusers of opioid products report starting their abuse with IR, not ER products (Budman et al 2009; Lankenau et al, 2012); therefore, it stands to reason that abuse-deterrent IR products offer the opportunity to deter abuse earlier than abuse-deterrent ER formulations.

2.2 Epidemiology of IR Oxycodone Abuse

Data from the RADARS System, which provides data coverage for well over 90% of the US population, illustrate the relative scope of the abuse and diversion problem with IR and ER opioids (Iwanicki et al, 2017; **Figure 4**). In the last quarter of 2015, the population-adjusted rate of intentional abuse of IR opioids was 4.6 times higher than ER opioids, and the rate of drug diversion was 6.1 times higher.

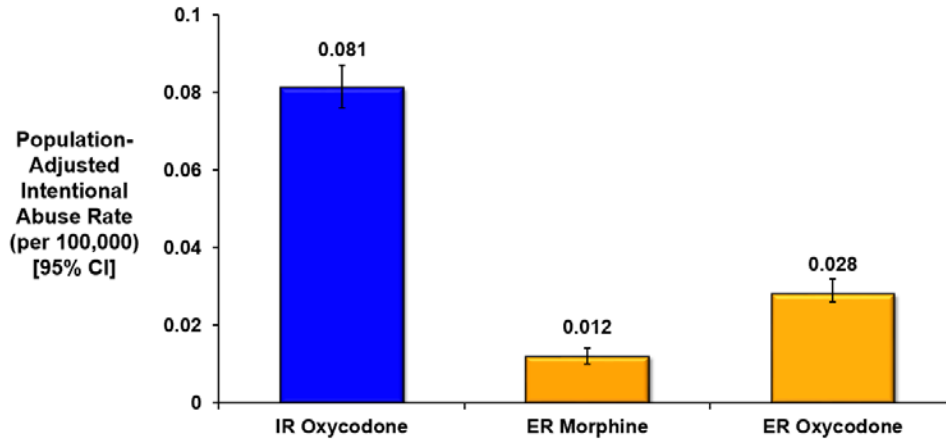
Figure 4: Population-Adjusted Rates of Abuse and Diversion with IR and ER Opioids from RADARS System in Q4 2015



Note: Data from Iwanicki et al. *PLoS One* 2016;11:e0167499.
 CI = confidence interval; ER = extended-release; IR = immediate-release; Q4 = fourth quarter

RADARS data also provides estimated rates of abuse for specific opioid products. Intentional abuse rates from the RADARS Poison Center Program show that the population-adjusted rate of abuse of IR oxycodone is higher than that of several commonly abused products such as ER morphine (6.8 times higher) and ER Oxycodone (2.9 times higher) (**Figure 5**).

Figure 5: Estimated Intentional Abuse Rates of IR Oxycodone, ER Morphine, and ER Oxycodone from RADARS Poison Center Program in 2012



Note: Data from RADARS System Report (2012).
 CI = confidence interval; ER = extended-release; IR = immediate-release; RADARS = Researched Abuse, Diversion and Addiction-Related Surveillance.

IR oxycodone is commonly abused via the intranasal and IV routes of abuse. The RADARS Treatment Center program interviews individuals being evaluated for substance abuse treatment and asks questions about their drugs of abuse and the routes of abuse for each drug. During the period from July 2015 through June 2016, 65% of IR oxycodone abusers reported abuse by the oral route, 36% by the intranasal route, and 17% for IV route (RADARS Treatment Center - 2017, data on file). These figures include both combination and SE IR oxycodone products, which likely underestimates the prevalence of non-oral abuse with IR SE oxycodone since abusers are known to prefer products without acetaminophen for snorting and injection. Nonetheless, the prevalence rates of snorting and injecting for IR oxycodone products is still higher than that of ER oxycodone (28% and 16%, respectively).

The relatively high rates of snorting and injecting of IR oxycodone is particularly concerning given that non-oral routes are the most dangerous routes of abuse. Data from the RADARS system have found that the relative risk of death or a major, life-threatening effect (e.g., overdose) relative to a single instance of oral abuse is 2.2 times greater for each instance of intranasal abuse and 2.6 times greater for each instance of IV abuse (RADARS System Poison Center Program - 2015, data on file).

The intranasal and IV routes of abuse also carry additional risks beyond those typically associated with opioid abuse such as respiratory depression, overdose, and death. Intravenous prescription opioid abuse puts users at risk for many immediate and long-term serious events

such as Hepatitis C (Bruneau et al., 2012; Lankenau et al., 2015; Valdiserri et al., 2014; Zibbell et al., 2014), heart or lung infections (Chong et al, 2009; Ho et al, 2009), blood clots (FDA, 2012), and HIV (Conrad et al, 2015; Surratt et al, 2011). In fact, data from the CDC showed that 6% of diagnoses of HIV and 10% of diagnoses of AIDS in 2015 were attributed to injection drug use (CDC, 2016). Erosion of the nasal cavities and soft palate as well as fungal rhinosinusitis have also been reported in association with chronic insufflation of opioid (Greene, 2005; Yewell et al., 2002).

2.3 Abuse of IR vs. ER Opioids

Immediate- and ER formulations have different release profiles that affect the methods and routes an individual will use to abuse an opioid product (**Table 1**).

Table 1: Key Attributes of ER and IR Opioid Products for Abuse

Attribute	Extended-Release	Immediate-Release
Speed of Release	Slow (over 8-12 hours)	Fast (~80% in 30 minutes)
Impact of Particle Size Reduction on Release	Dose dumping (turn ER into IR)	Little to none (already has IR profile)
Impact of Particle Size Reduction on Abusability	Allows access to intranasal and IV routes	
Rationale for Large Volume Extraction	Faster access to API for oral abuse	None
Rationale for Small Volume Extraction	High yield of opioid in small volume of injectable solvent for IV abuse	
API = active pharmaceutical ingredient; ER = extended release; IR = immediate release; IV = intravenous		

Extended-release opioids are intended to release slowly over 8 to 12 hours and are taken 2 or 3 times daily to provide around-the-clock pain relief. In contrast, IR opioids, are intended to provide patients rapid, acute pain relief. An effective IR product needs to have rapid oral bioavailability and should release approximately 80% of the active pharmaceutical ingredient (API) in the first 30 minutes after dosing.

Particle size reduction of ER products tends to defeat a product’s slow-release properties and transforms it into a high-dose IR product. Therefore, several abuse-deterrent ER products have been designed to resist particle size reduction via physical manipulation. In contrast, particle size reduction for an IR opioid, has little effect on the release, since the product already has an IR profile.

Particle size reduction for ER and IR formulations have the same impact on abusability for non-oral routes. For both ER and IR products, abusers will attempt to reduce the products into a fine powder for the purposes of snorting or preparing the product for injection. Intranasal and IV routes are attractive routes of abuse because they circumvent the gastrointestinal tract thereby allowing abusers to get higher faster, and with less opioid.

Another consideration for ER products is the potential for extraction of the API in large volumes of various solvents for oral abuse. For example, an abuser might try to crush an ER tablet and then attempt to extract it in an alcohol to elicit “dose dumping”. If successful, the abuser could then drink the liquid in order to get a greater and faster high. An IR product is rapidly orally bioavailable by design, so there is little rationale for an abuser to attempt extraction of the product in a large volume (see detailed discussion in Section 5.5).

The rationale for small volume extraction is the same for both IR and ER products where an abuser would attempt to extract a high yield of the opioid in a small, injectable volume of liquid to facilitate the IV route of abuse.

3 ROXYBOND DEVELOPMENT AND FORMULATION

Summary

- RoxyBond is an IR SE oxycodone HCl tablet with a proposed indication for the management of pain severe enough to require an opioid analgesic and for which alternative treatment options are inadequate.
- RoxyBond was developed via the 505(b)(2) regulatory pathway where approval is based, in part, on the demonstration of comparable bioavailability to Roxicodone, the RLD.
- The abuse-deterrent SentryBond™ technology used in RoxyBond is also used in MorphaBond ER™, an FDA-approved abuse-deterrent morphine sulfate tablet.
- A comprehensive series of studies was performed based on FDA guidance and expert input to evaluate the physical and chemical abuse-deterrent properties of RoxyBond intended to address the intranasal and IV routes of abuse.

3.1 Formulation

RoxyBond is an IR SE oxycodone HCl tablet with a proposed indication for the management of pain severe enough to require an opioid analgesic and for which alternative treatment options are inadequate. The proposed indication for RoxyBond is the same as the current indication for the RLD, Roxicodone. The API in RoxyBond, oxycodone HCl, is also the same as Roxicodone. RoxyBond is differentiated from Roxicodone because it is formulated with abuse-deterrent features to deter the intranasal and IV routes of abuse.

RoxyBond tablets will be provided in 5 mg, 15 mg, and 30 mg dosage strengths for oral administration every 4 to 6 hours as needed for the treatment of pain. The same excipients are used for all RoxyBond strengths with the exception of coloring agents. All RoxyBond tablets are approximately the same size as a 200 mg Advil® tablet.

3.2 SentryBond™ Technology

RoxyBond tablets incorporate IDS's proprietary abuse-deterrent SentryBond technology, which is designed to make tablets difficult to manipulate, resist extraction in widely used solvents, and more difficult to abuse via injection. SentryBond technology is also used in MorphaBond ER (morphine sulfate) extended-release tablets, an FDA-approved abuse-deterrent opioid product.

RoxyBond is formulated with inactive ingredients that impart several physical and chemical barriers to make abuse more difficult to prepare for intranasal or IV abuse. These properties are intended to slow the release of oxycodone from manipulated and/or extracted product compared to release in the human body when taken orally intact, as intended. In addition, the excipients in RoxyBond are intended to form a viscous material when manipulated and subjected to a liquid

environment in order to resist passage through a needle and make injection of the product more difficult.

3.3 Overview of Development Program

IDS developed RoxyBond under the 505(b)(2) regulatory pathway using Roxycodone as the RLD. The NDA is supported by comparative bioavailability studies as well as several studies evaluating RoxyBond’s abuse-deterrent properties. During the development program and review process, the FDA provided input and advice on specific aspects of development including:

- Protocol design and statistical analysis of pharmacodynamic (PD) end points
- Demonstration of comparative bioavailability
- Characterization of abuse-deterrent physical and chemical properties
- Evaluation of excipients and impurities

3.4 Clinical PK Studies and Effect of Food

Studies of RoxyBond included evaluation of the PK profile of 30 mg RoxyBond compared to 30 mg Roxycodone, dose proportionality of the 3 RoxyBond tablet strengths, as well as the effect of food (**Table 2**). These clinical PK studies were open-label, randomized, single-dose, naltrexone-blocked crossover studies in healthy volunteers.

Table 2: Overview of Clinical Pharmacokinetic Studies in Healthy Volunteers

Purpose	Study	Subjects	Treatments Compared
Establish comparative bioavailability	O-ARIR-003	58	30 mg RoxyBond (fasted) 30 mg Roxycodone (fasted)
Establish dose proportionality	O-ARIR-006	51	5 mg RoxyBond (fasted) 15 mg RoxyBond (fasted) 30 mg RoxyBond (fasted)
Assess effect of food on pharmacokinetic profile	O-ARIR-003	58	30 mg RoxyBond (fed) 30 mg RoxyBond (fasted)

3.5 Category 1 Studies

IDS performed a comprehensive set of laboratory-based, in vitro manipulation and extraction studies to evaluate the physical and chemical abuse-deterrent features of RoxyBond. Testing was performed based on iterative feedback from FDA to ensure that RoxyBond’s barriers to abuse were well characterized. These studies included physical manipulations and chemical extractions that covered both general and route-specific manipulations. Roxycodone served as the non-abuse-deterrent comparator in all studies.

Particle size reduction experiments were performed, with and without different pre-treatments, to evaluate the ability of a variety of household tools to reduce particle size (i.e., get the drug into an abusable form for non-oral routes). In accordance with the FDA Guidance, large volume extraction studies evaluated the resistance of the product to chemical extraction. IDS also performed several studies specific to the IV route of abuse, including testing of syringeability and small volume extraction.

3.6 Category 2/3 Study

IDS performed a combined Category 2/3 intranasal HAP study to evaluate the PK and PD of manipulated RoxyBond compared to manipulated Roxicodone when administered via the intranasal route.

Study O-ARIR-002 was a randomized, double-blind, double-dummy, placebo-controlled, 4-period crossover study. The study enrolled recreational, nondependent opioid users who were experienced with nasal insufflation of opioids. A total of 31 subjects met inclusion criteria for the study and entered the treatment phase. 29 subjects completed the study. The active treatments in the study were 30 mg dosage strengths of either RoxyBond or Roxicodone.

4 BIOPHARMACEUTICS

Summary

- When taken as intended, RoxyBond demonstrated comparable bioavailability to Roxycodone, which forms the scientific bridge between RoxyBond and the established safety and efficacy profile of the RLD.
- RoxyBond 5 mg, 15 mg, and 30 mg tablets were found to be dose proportional (i.e., with expected oxycodone release at all doses), providing support for approval of all 3 dosage strengths.
- Steady-state modeling demonstrated bioequivalence of RoxyBond and Roxycodone under both 4- and 6-hour dosing schedules.
- There was no clinically significant effect of food on the bioavailability of oxycodone when RoxyBond was administered as intended in fed and fasted states.

4.1 Comparable Bioavailability to Roxycodone

IDS evaluated the relative bioavailability of the highest strength RoxyBond tablets (30 mg) with the RLD (Roxycodone 30 mg tablets). Study O-ARIR-003 was an open-label, single-dose, randomized, 3-period, crossover study in healthy adult subjects. The three treatments included:

- RoxyBond 30 mg dosed intact in a fasted state
- Roxycodone 30 mg dosed intact in a fasted state
- RoxyBond 30 mg dosed intact in a fed state (with a high-fat/high-calorie meal)

All subjects were administered naltrexone to minimize the opioid's PD effects. There was a 4-day washout between each study period. A total of 75 subjects enrolled in the study, and 58 subjects completed the study and comprised the PK population for the study.

A summary of the comparative PK parameters for Roxycodone and RoxyBond is shown in **Table 3**. RoxyBond met the bioequivalence limits for overall exposure as assessed by the AUCs for plasma drug concentration, which are the most relevant PK parameters for analgesia. The AUC values for RoxyBond were well within the bioequivalence limits of 80% to 125% for the 90% CI (**Table 4**). The mean ratio for C_{max} had a lower confidence bound of 79%, which is slightly below the lower 80% bioequivalence limit. Although the median time to maximum plasma concentration (T_{max}) for RoxyBond and Roxycodone differed by approximately 45 minutes, the ranges were nearly identical. Considering that RoxyBond, like all opioids, will be titrated to effect, Inspirion and the FDA concluded that the modest differences in these parameters are not expected to impact the efficacy profile of RoxyBond.

Table 3: Summary of PK Parameters for RoxyBond 30 mg and Roxicodone 30 mg Administered in a Fasted State – Study O-ARIR-003

Parameter	Roxicodone 30 mg (fasted state)	RoxyBond 30 mg (fasted state)
C_{max} (ng/mL), mean (%CV)	67.7 (35.1%)	57.8 (31.1%)
AUC_{0-t} (ng•h/mL), mean (%CV)	300.3 (22.9%)	287.4 (22.9%)
$AUC_{0-\infty}$ (ng•h/mL), mean (%CV)	305.4 (22.9%)	292.7 (23.0%)
T_{max} (h), median (range)	1.0 (0.5, 5.0)	1.8 (0.8, 5.0)

AUC = area under the curve; C_{max} = maximum plasma concentration; CV = coefficient of variance; T_{max} = time to maximum plasma concentration

Table 4: PK Comparison of RoxyBond and Roxicodone in a Fasted State – Study O-ARIR-003

Parameter	LS Mean Ratio	90% CI
C_{max} (ng/mL)	86%	79% - 94%
AUC_{0-t} (ng•h/mL)	96%	93% - 99%
$AUC_{0-\infty}$ (ng•h/mL)	96%	93% - 99%

AUC = area under the curve; CI = confidence interval; C_{max} = maximum plasma concentration; LS = least squares

4.2 Dose Proportionality

To support approval of all 3 doses of RoxyBond, IDS evaluated the dose proportionality of RoxyBond under fasted conditions in healthy subjects (Study O-ARIR-006). This was an open-label, randomized, single-dose, 3-treatment, 3-period, crossover study. All subjects received a single 15-mg dose of RoxyBond in period 1. Subjects were then randomized to receive the 5- or 30-mg doses of RoxyBond in periods 2 and 3. There was a 2-day washout between periods. A total of 54 subjects were enrolled in the study and 51 provided PK data.

The dose proportionality of log-transformed C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ values for oxycodone were explored and dose proportionality was to be concluded if the 90% CI around the slope fell within a predefined range of 0.8755 to 1.1245. All parameters passed successfully (**Table 5**), demonstrating that RoxyBond tablets were dose proportional over the range of 5 to 30 mg.

Table 5: Dose Proportionality Analysis – Study O-ARIR-006

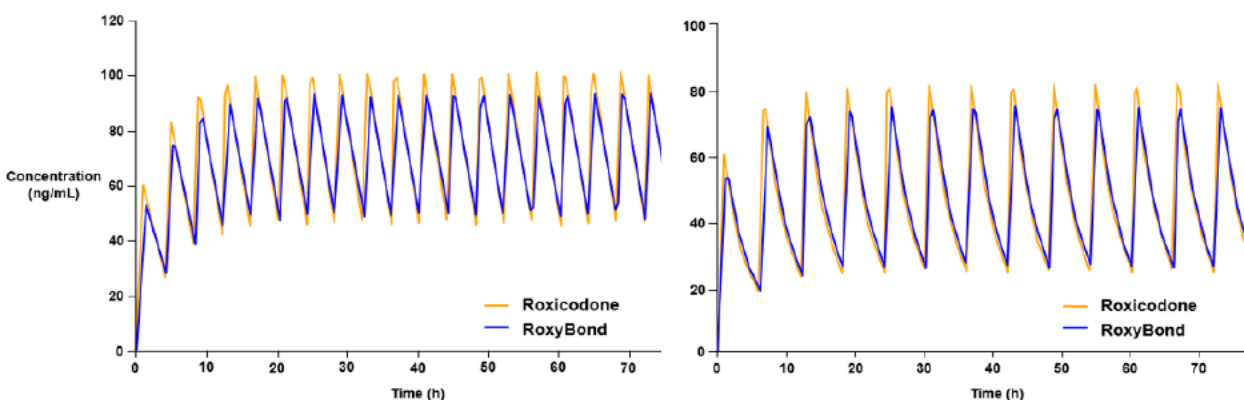
Parameter (Units)	Slope	90% CI	Acceptance Limits
AUC _{0-t} (ng•h/mL)	1.0081	0.9888 – 1.0273	0.8755 – 1.1245
AUC _{0-∞} (ng•h/mL)	0.9799	0.9608 – 0.9991	0.8755 – 1.1245
C _{max} (ng/mL)	0.9769	0.9514 – 1.0024	0.8755 – 1.1245

AUC = area under the curve; CI = confidence interval; C_{max} = maximum plasma concentration.

4.3 Pharmacokinetic Modeling at Steady State

Pharmacokinetic modeling was conducted to evaluate the comparative PK of RoxyBond and Roxicodone at steady state. The PK model was constructed using the data from the single-dose relative bioavailability study (Study O-ARIR-003) to simulate and predict steady-state plasma levels of oxycodone. Both 4 and 6-hour dosing regimens were bioequivalent on steady-state parameters (**Figure 6**).

Figure 6: PK Steady-State Modeling for 4- (Left) and 6-Hour (Right) Dosing



4.4 Effect of Food on Bioavailability

As part of the pivotal relative bioavailability study (Study O-ARIR-003), IDS included arms for administration of RoxyBond in both fed and fasted states. In the fasted arm, a single oral dose of RoxyBond 30 mg was administered to subjects following a 10-hour overnight fast. In the fed arm, a single oral dose of RoxyBond 30 mg was administered to subjects within 30 minutes of starting and completing a high-fat/high-calorie meal which was preceded by a 10-hour overnight fast (**Table 6**).

The results indicated that C_{max} values were approximately 19% higher and AUC values were approximately 24% higher in the fed state (Table 7). The differences in the PK parameters of oxycodone following administration of RoxyBond in fasted and fed states are not expected to be clinically significant. As a point of comparison, AUC was increased following administration of Roxicodone in the fed state versus fasted state by 27% and increased the T_{max} from 1.25 hours to 2.54 hours (Roxicodone Prescribing Information, 2016), which is comparable to the 24% increase observed for RoxyBond. The Roxicodone label does not have an instruction with regard to taking the product with or without food.

Table 6: Summary of Pharmacokinetic Parameters for RoxyBond 30 mg Administered in Fed and Fasted States – Study O-ARIR-003

Parameter	RoxyBond 30 mg (fed state)	RoxyBond 30 mg (fasted state)
C_{max} (ng/mL), mean (%CV)	68.0 (29.5%)	57.8 (31.1%)
AUC_{0-t} (ng•h/mL), mean (%CV)	354.2 (23.3%)	287.4 (22.9%)
$AUC_{0-\infty}$ (ng•h/mL), mean (%CV)	361.9 (23.9%)	292.7 (23.0%)
T_{max} (h), median (range)	2.0 (1.0 – 6.1)	1.8 (0.8 – 5.0)

AUC = area under the curve; C_{max} = maximum plasma concentration; T_{max} = time to maximum plasma concentration.

Table 7: Pharmacokinetic Comparison of RoxyBond Fed versus Fasted States – Study O-ARIR-003

Parameter	LS Mean Ratio	90% CI
C_{max} (ng/mL)	118.5%	108.6% - 129.4%
AUC_{0-t} (ng•h/mL)	123.0%	119.1% - 127.0%
$AUC_{0-\infty}$ (ng•h/mL)	123.5%	119.7% - 127.4%

AUC = area under the curve; CI = confidence interval; C_{max} = maximum plasma concentration; LS = least squares.

Note: LS Mean Ratio calculated as ratio of Least squares geometric means for fed over fasted states

5 CATEGORY 1 STUDIES

Summary

Particle Size Reduction Studies

- The rationale for an abuser to physically manipulate an IR product is to get the product into an abusable form (i.e., fine powder for intranasal abuse or for extraction in a small volume for IV injection).
- Roxicodone was easily manipulated into a fine powder with a mechanical Tool E.
- RoxyBond was difficult to manipulate with mechanical household tools. Electric Tool G was required to produce a consistent particle sizes amenable for snorting.
- Ultimately, particle size reduction with electric Tool G did not appreciably increase the release of oxycodone in large or small volume extractions

Large Volume Extraction Studies

- There is no rationale for an abuser to attempt a large volume extraction of an IR opioid product for oral abuse as they might for ER products since IR products are rapidly bioavailable by design.
- Manipulated Roxicodone released 100% oxycodone at 1 minute after extraction in a common ingestible solvent (Solvent A) under non-stressed conditions.
- Manipulated and intact RoxyBond tablets demonstrated considerable resistance to extraction in ingestible and noningestible solvents under a variety of temperature, agitation, and tablet conditions.

Syringeability and Small Volume Extraction Studies

- After 1 minute of extraction with Solvent A under non-stress conditions, 98% of oxycodone could be syringed and recovered from Roxicodone with the smallest needle gauge evaluated.
- For intact RoxyBond tablets in Solvent A, 0% to 2% of oxycodone was recovered at Temperature A after up to 30 minutes of extraction. Temperature B did not appreciably increase oxycodone recovery (range, 1% to 21%).
- Manipulated RoxyBond tablets formed a viscous material that was difficult to syringe. The resulting material contained large particulate would not be suitable for injection. At Temperature A in Solvent A, 5% to 19% oxycodone could be recovered but only with the largest needle gauge evaluated. Temperature B did not appreciably increase recovery (range, 7% to 33%).
- Extreme cases were evaluated with Pre-treatment D, Agitation B, long extraction times, and solvents that would require neutralization or back-extraction in order to be injectable. Despite the considerable effort required, the maximum yield was 66%.

5.1 Overview

A series of laboratory-based in vitro manipulation and extraction studies were performed to evaluate the physical and chemical abuse-deterrent properties of RoxyBond. The studies were consistent with the FDA Guidance “*Abuse-Deterrent Opioids – Evaluation and Labeling: Guidance for Industry*”, and were designed through iterative consultation with the FDA and abuse deterrence experts.

Category 1 studies included both general manipulations (e.g., particle size reduction) and route-specific manipulations (e.g., syringeability and small volume extraction). At the request of FDA, all Category 1 testing was performed using the highest 30 mg tablet strength of RoxyBond. Roxycodone was the non-abuse-deterrent comparator for all studies.

Initial particle size reduction studies were performed to characterize and understand the feasibility and difficulty of using household tools to get RoxyBond tablets into an abusable form for non-oral routes of abuse. Subsequent studies further examined physical manipulation for understanding tool optimization as well as the effect of pre-treatments. Chemical manipulation studies included both large and small volume extractions. Syringeability and small volume extractions were studied to assess the potential for abuse via the IV route of administration.

In accordance with the FDA Guidance, the Category 1 studies were designed to test the abuse-deterrent features of RoxyBond to failure. Therefore, these studies encompassed both realistic abuser scenarios as well as extreme sophisticated laboratory manipulations that would be very unlikely to be attempted in the real world.

5.2 Particle Size Reduction Studies

Prescription opioid abusers often physically manipulate ER opioid tablets to increase the speed of drug release and/or to get the drug into an abusable form for alternative routes. For IR opioids, the primary rationale of an abuser to physically manipulate a tablet is to get it into an abusable form for snorting or IV injection. RoxyBond is formulated with overlapping physical and chemical barriers; so while RoxyBond is difficult to physically manipulate, particle size reduction does not defeat its abuse-deterrent properties for the intranasal or IV routes.

The difficulty of physical manipulation of RoxyBond was assessed in a series of in vitro tests employing seven common household tools. The tools selected for the studies were chosen to be representative of the different methodologies an abuser could attempt to achieve particle size reduction, including crushing, cutting, grating, and grinding. The difficulty of manipulation was rated by laboratory technicians on a scale of 1 (“very easy”) to 10 (“impossible”), and the time required to significantly adulterate the tablet or to the greatest amount possible within 5 minutes were measured for each tool. Following physical manipulation, sieve analysis was used to determine the particle size distribution.

Roxycodone was easily manipulated with Tool E resulting in 100% of small particles (<2000 microns) that would be amenable for insufflation. In contrast, RoxyBond was not easily

manipulated using Tools A, B, C, D, E or F, with median difficulty scores ranging from 6 to 10 (Table 8). Four of the tools took the full 300 seconds without successfully adulterating the tablet.

Tool G produced the highest percentage of small particles for RoxyBond. Tool G was rated a median score of 1 for difficulty of manipulation and required a median of 31 seconds of manipulation because it was an electric tool. The optimal tools for particle size reduction for each product were brought forward to other Category 1 studies – Tool E for Roxycodone and Tool G for RoxyBond.

Table 8: Results of Initial Particle Size Reduction Study for RoxyBond

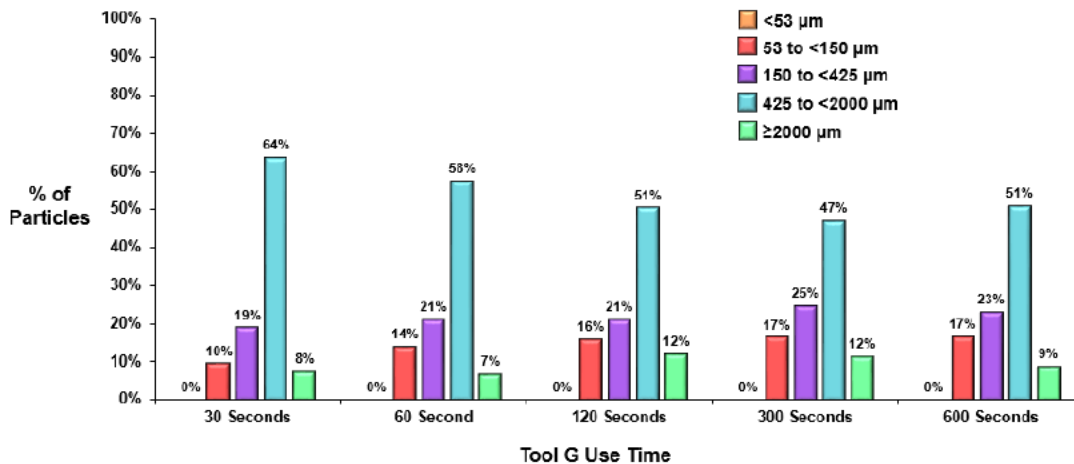
Outcome	Tools						
	A	B	C	D	E	F	G
Median Manipulation Time (sec)	300	300	300	60	118	300	31
Median Manipulation Difficulty (1-10)	10	9	7	6	7	8	1
Mean % Particles < 2000 Microns	0%	9%	25%	44%	64%	79%	92%

Note: Results are shown for n=5 replicates for each tool

5.3 Optimization of Particle Size Reduction for RoxyBond

Tool G was further studied using a range of manipulation times ranging from 30 seconds up to 600 seconds (10 minutes). Longer manipulation times did not meaningfully alter the particle size distribution (Figure 7).

Figure 7: Particle Size Distribution Results for Varying Use Times with Tool G

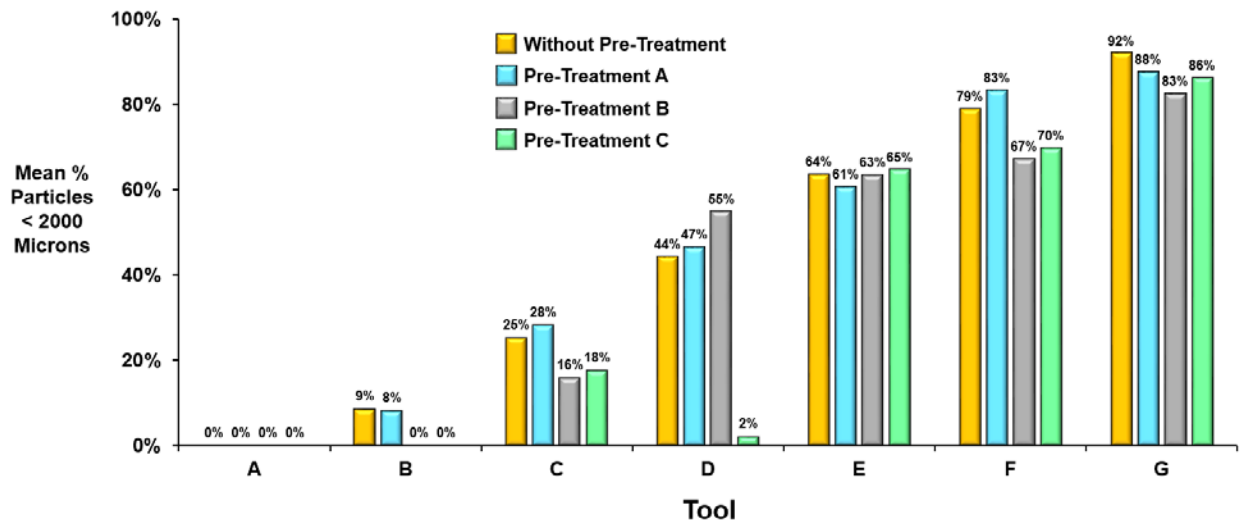


5.4 Effect of Pre-Treatment on Particle Size Reduction

The effect of pre-treatments applied before physical manipulation were conducted to further evaluate RoxyBond’s resistance to particle size reduction. Overall, pre-treatment of tablets with extreme temperatures did not substantially increase the yield of small particles for each tool (Figure 8). Consistent with non-pretreated results, Tool G was the only household tool that yielded a consistent output of small particles amenable to intranasal insufflation.

Results for other tools showed relatively little impact for the pre-treatments. One exception was for with Pre-Treatment C prior to manipulation with Tool D. However, this combination made particle size reduction less effective as it produced even larger particles than tablets without pre-treatment.

Figure 8: Effect of Pre-Treatment on Particle Size Distribution Following Physical Manipulation



Additional study of the effects of Pre-Treatments D, E, and F was performed. Tools E, F, and G were used in these assessments. Pre-Treatments E and F produced charred tablets not suitable for further testing. Pre-Treatment D produced similar particle size distributions to tablets without pre-treatment.

5.5 Large Volume Extraction

The rationale for large volume extraction of ER opioid products is to accelerate the release of API in solution, thereby facilitating oral abuse. This is less relevant for IR products since they must be rapidly orally bioavailable when taken as intended to achieve their clinically anticipated therapeutic effect. The lack of clinical relevance of large volume extraction for oral abuse of IR opioid products is illustrated in the Prescribing Information for Roxicodone which shows no advantage in the onset or speed of drug release for Roxicodone as an oral solution compared to an intact tablet (Table 9).

Table 9: Pharmacokinetic Parameters of Roxicodone 15 mg Tablets and 15 mg Oral Solution

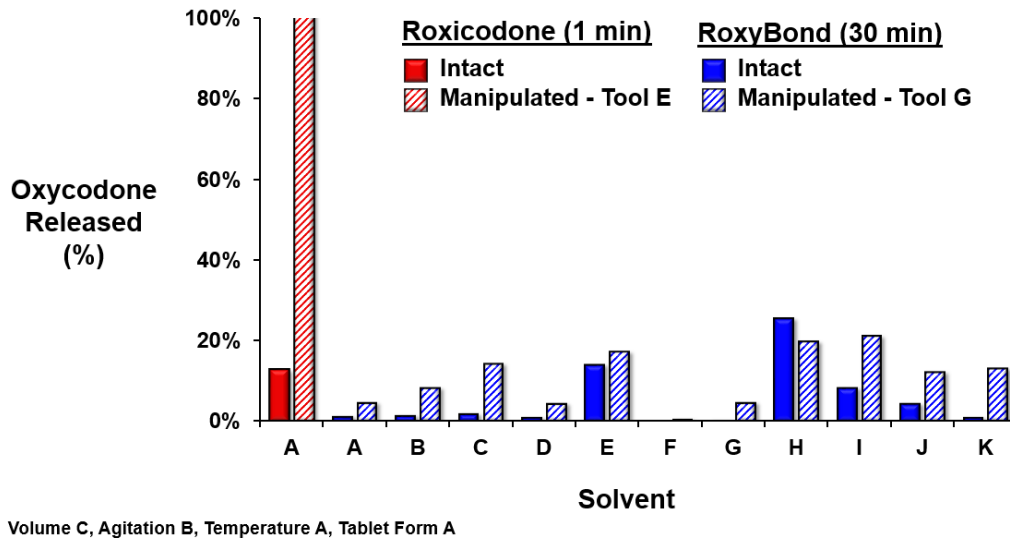
Parameter	Roxicodone 15 mg tablet	Roxicodone Liquid Concentrate 15 mg oral solution
C_{max} (ng/mL), mean (SD)	22.2 (7.6)	21.1 (6.1)
AUC (ng•h/mL), mean (SD)	128.2 (35.1)	130.6 (34.7)
T_{max} (h), mean (SD)	1.4 (0.7)	1.9 (1.5)
<p>AUC = area under the curve; C_{max} = maximum plasma concentration; T_{max} = time to maximum plasma concentration.</p> <p>Note: Data from Roxicodone Prescribing Information.</p>		

Nonetheless, a series large volume extraction studies were carried out based on The FDA Guidance to fully characterize RoxyBond’s resistance to chemical extraction.

Intact and manipulated (using Tool G) RoxyBond tablets were added to commonly available solvents at Volume C to evaluate whether any could induce rapid extraction of oxycodone. Solvents included both ingestible and non-ingestible varieties and a range of pH values.

In these large volume extractions, manipulated Roxicodone tablets (using Tool E) released 100% of oxycodone within 1 minute in Solvent A at Temperature A under Agitation B (**Figure 9**). Due to the observation of complete extraction under non-stressed conditions, Roxicodone was not examined in additional solvents. In contrast, none of the solvents extracted an appreciable amount of oxycodone from RoxyBond. RoxyBond released almost no oxycodone from any solvent at 1 minute; therefore, results in **Figure 9** reflect 30-minute results. Even at long time points, particle size reduction does not appreciably affect the release of oxycodone from RoxyBond in any of the solvents evaluated.

Figure 9: Results of Large Volume Extraction at Temperature A



Additional combinations of solvents, agitation, temperature manipulation, and extraction times were evaluated to determine their effect on the release of oxycodone from RoxyBond tablets.

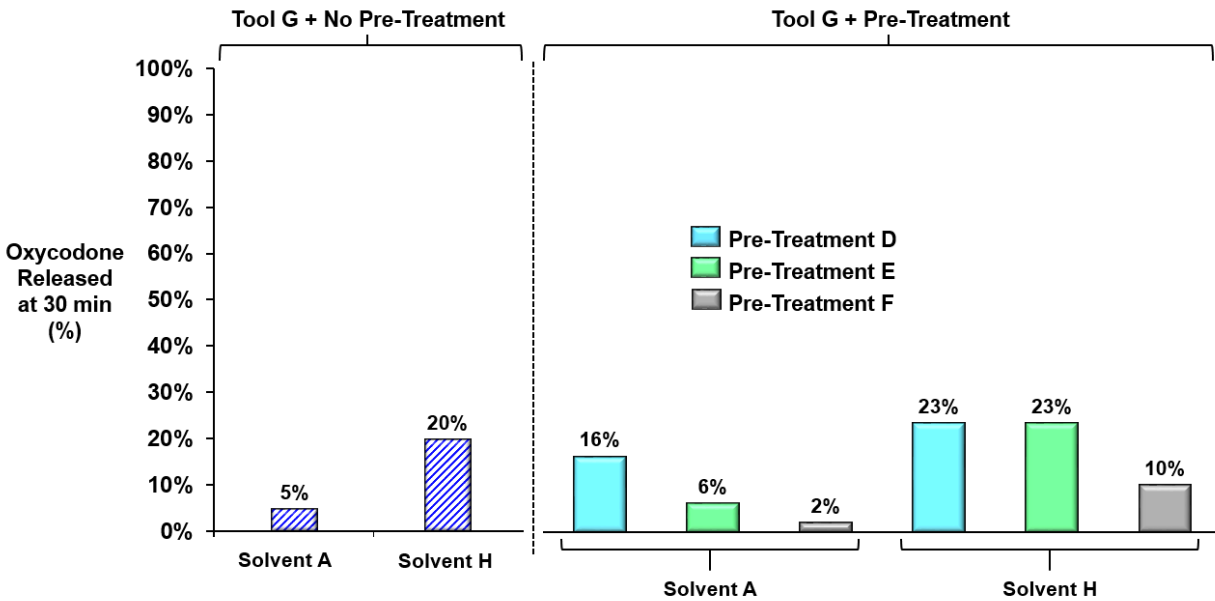
Effect of Temperature Modifications

As expected, Temperature B increased the extraction of oxycodone in most solvents. However, given there is no advantage of large volume extraction of an IR opioid (**Table 9**), there is little rationale for an abuser to attempt this manipulation.

Effect of Additional Pre-Treatments

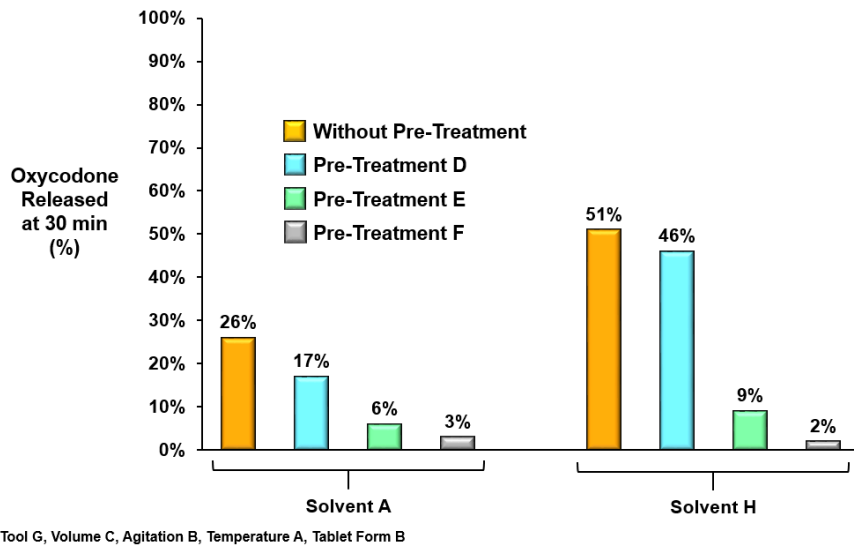
A series of additional large volume extractions were performed to evaluate the effect of Pre-Treatment on oxycodone release from RoxyBond. Extractions were assessed at 30 minutes and were based on physical manipulation with Tool G, chemical manipulation with Solvents A and H, Agitation B, as well as Pre-Treatments D, E, and F (**Figure 10**). Consistent with other results, RoxyBond demonstrated resistance to chemical extraction despite Pre-Treatment.

Figure 10: Effect of Additional Pre-Treatments of RoxyBond in Large Volume Extraction at 30 Minutes



Tablet Form B was also tested without pre-treatment and with Pre-Treatments D, E, and F, and subject to 30 minutes of extraction in Volume C of Solvents A and H under Agitation B (**Figure 11**). The highest percentage of oxycodone released at 30 minutes was 51% for Solvent H with no pre-treatment at Temperature A. This particular extraction required a series of complex steps (producing Tablet Form B, followed by extraction in Solvent H under Agitation B for 30 minutes).

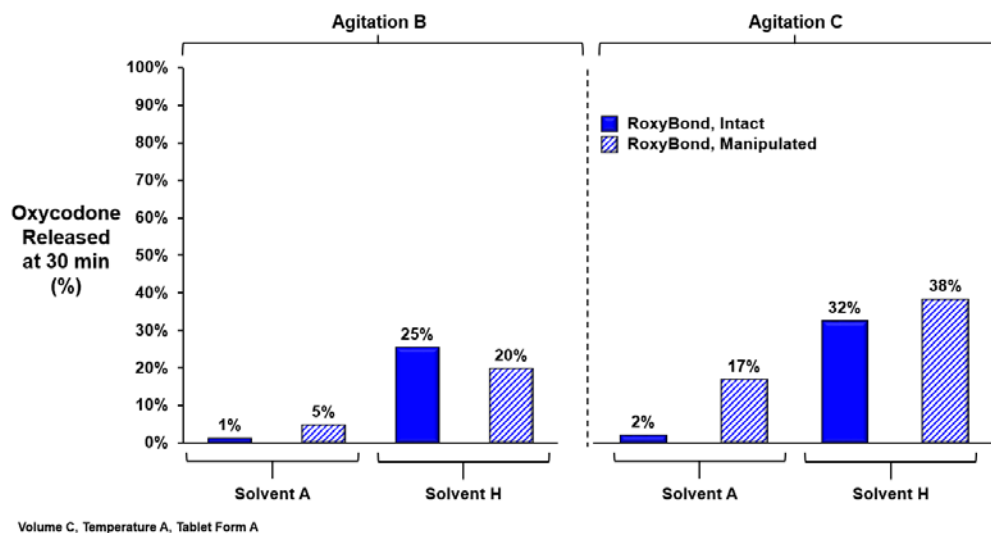
Figure 11: Effect of Pre-Treatment on Tablet Form B of RoxyBond in Large Volume Extraction at 30 Minutes



Effect of Additional Agitation Conditions

Finally, Agitation C was evaluated for intact and manipulated samples (using Tool G) in Volume C with Solvents A and H (**Figure 12**). There was a slightly higher rate of oxycodone release with Agitation C compared to Agitation B in both solvents.

Figure 12: Effect of Additional Agitation Conditions with RoxyBond in Large Volume Extraction at 30 Minutes



In summary, although there is a lack of clinical relevance of large volume extraction for oral abuse of IR opioid products, results from these extraction studies demonstrate that RoxyBond offers considerably greater barriers against chemical extraction compared to Roxicodone.

5.6 Syringeability and Small Volume Extractions

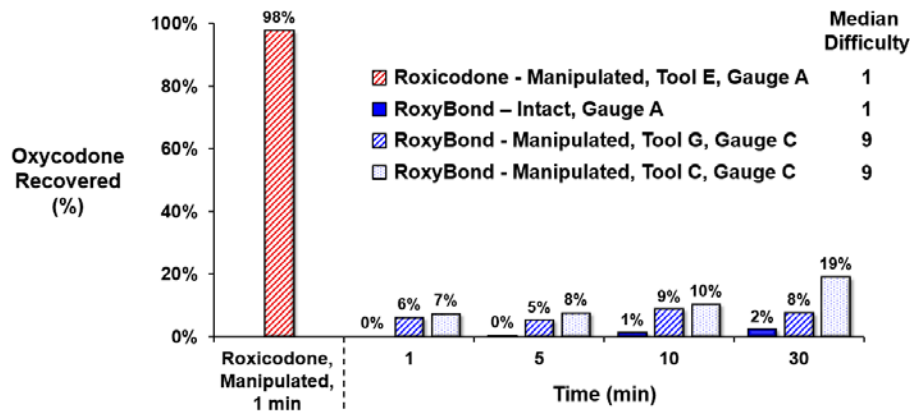
IV opioid abuse requires the ability to extract a high yield of opioid into a small volume of liquid that can be syringed for injection. Consistent with the FDA Guidance, intact and physically manipulated RoxyBond tablets were incubated in small volumes under combinations of temperature and agitation conditions, and attempts were made to draw the resulting mixture into a syringe. Initial studies evaluated small volume syringeability of Solvent A under various conditions: Volumes A and B; intact and manipulated tablets (Tools C and G); Agitation A and B; and Temperature A and B; and incubation times from 1 to 30 minutes.

At each time point, attempts were made to draw the mixture into 10 cc syringes fitted with different gauge needles (A, B, and C) and the difficulty of each attempt was assessed on a scale of 1 to 10 (“very easy” to “impossible”). Notably, Needle Gauge C is a large needle that is not preferred by abusers. After each syringeability assessment, the volume of syringeable liquid was recorded and the liquid was assayed for oxycodone content.

Manipulated Roxicodone extracted for 1 minute in Solvent A was easily drawn into a syringe through the smallest needle gauge evaluated with a 98% yield of injectable oxycodone (**Figure**

13). Intact RoxyBond was easily syringed but resisted oxycodone extraction (with a yield of 0% to 2%) even after 30 minutes of extraction. Manipulated RoxyBond (Tool C or G) immediately formed a viscous material in Solvent A that was difficult to syringe (median difficulty of 9), even with the largest needle gauge evaluated, and did not contain an appreciable amount of oxycodone. It is important to note that despite particle size reduction, manipulated RoxyBond did not release high levels of oxycodone in syringeable liquid even after 30 minutes of extraction.

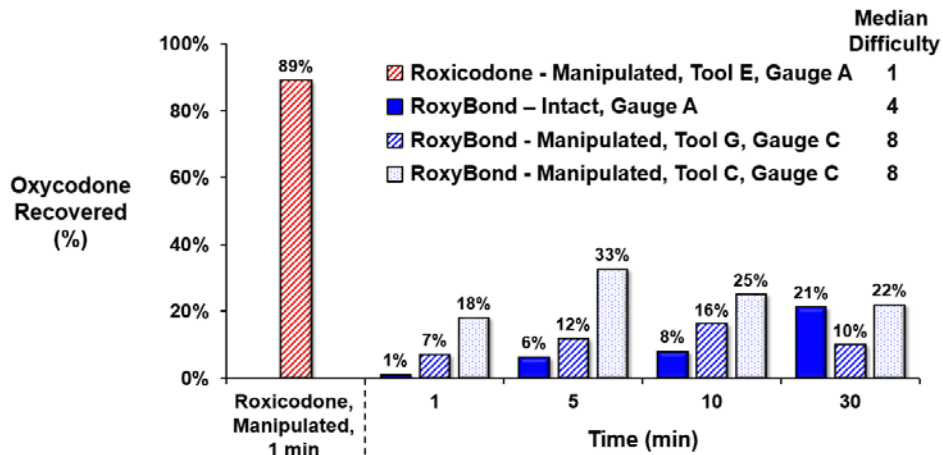
Figure 13: Recovery of Oxycodone from Syringeable Liquid Following Small Volume Extractions in Solvent A at Temperature A



Volume A, Solvent A, Agitation A, Temperature A, Tablet Form A

Extraction was repeated under the same conditions under Temperature B (Figure 14). Similar to the results at Temperature A, relatively low amounts of oxycodone were recovered at Temperature B from either intact or manipulated tablets at any time through the extended 30-minute time point. Furthermore, the conditions required the use of the largest needle gauge and were rated as very difficult to syringe (median difficulty score of 8).

Figure 14: Recovery of Oxycodone from Syringeable Liquid Following Small Volume Extractions in Solvent A at Temperature B

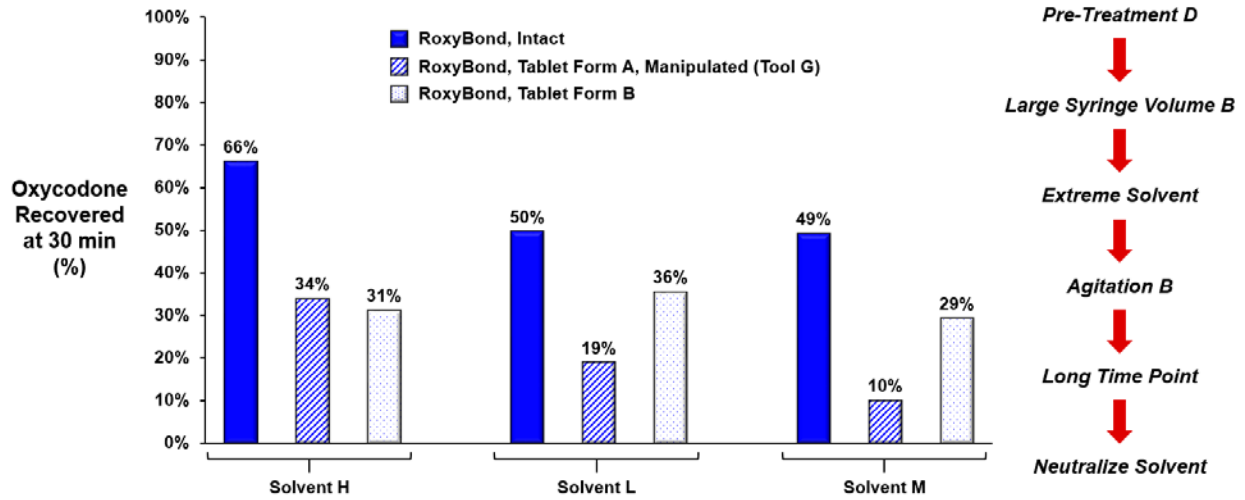


Volume A, Solvent A, Agitation A, Temperature B, Tablet Form A

In general, other conditions tested (e.g., Volume B, Agitation B, addition of another tablet to the extraction) resulted in a lower percentages of oxycodone recovery than the conditions presented above.

Additional syringeability and small volume extraction experiments were conducted at Volume B with Pre-Treatment D and Agitation B for intact tablets, tablets manipulated using Tool G, and tablets in Tablet Form B using Solvents H, L, and M (**Figure 15**). In these studies, manipulated tablets and tablets in Tablet Form B released less oxycodone relative to intact tablets. These particular extractions required (1) Pre-Treatment D, (2) large syringe Volume B, (3) Agitation B, (4) 30 minutes of extraction, and (5) and solvents that are not suitable for direct injection. These particular conditions would require pH neutralization or back-extraction in order to get the solution into an injectable form, requiring considerably time, effort, and chemistry knowledge on the part of an abuser.

Figure 15: Recovery of Oxycodone from Syringeable Liquid Following Small Volume Extraction after Pre-Treatment D in Solvents H, L, and M



Volume B, Pre-Treatment D, Temperature A, Agitation B

In summary, RoxyBond demonstrated considerable resistance to extraction and preparation for IV injection relative to Roxycodone. The yield of oxycodone from intact tablets was low in all conditions except those involving a multi-step process with extreme solvents that would not be readily injectable. Furthermore, manipulated RoxyBond tablets resisted extraction in addition to forming a viscous solution that was difficult to syringe.

6 CATEGORY 2 AND CATEGORY 3 INTRANASAL HUMAN ABUSE POTENTIAL STUDY

Summary

- The primary endpoint was met with significantly lower Drug Liking E_{max} for manipulated intranasal RoxyBond than for manipulated intranasal Roxycodone.
- Drug Liking through the first 3 hours was consistently lower for manipulated intranasal RoxyBond than for manipulated Roxycodone.
- Subjects reported that they were significantly less likely to take manipulated RoxyBond again and had a lower overall drug liking compared to manipulated Roxycodone via the intranasal route.
- Manipulated intranasal RoxyBond produced a significantly lower drug high, was rated as more difficult to snort, and was associated with more adverse nasal effects than manipulated intranasal Roxycodone.
- Pharmacokinetic results were consistent with the pharmacodynamic results. Intranasal administration of manipulated RoxyBond resulted in a significant reduction in early oxycodone concentrations compared to manipulated Roxycodone.
- Consistent with the formulation properties, manipulation and intranasal administration of RoxyBond slowed the absorption of oxycodone compared to intact oral dosing.

6.1 Study Design

Study O-ARIR-002 evaluated the relative bioavailability and abuse potential of intranasally administered RoxyBond compared to Roxycodone among nondependent recreational opioid users who were experienced in nasal insufflation. The study was a prospective, randomized, double-blind, double-dummy, active- and placebo-controlled, single-dose, four-way crossover study.

The study population consisted of opioid experienced, nondependent healthy volunteers aged 18 to 55 years. The study included a Qualification Period, Treatment Period, and Follow-up Period. The Qualification Period consisted of an inpatient, double-blind qualifying session during which a Naloxone Challenge Test and Drug Discrimination Test were administered. The Naloxone Challenge Test ensured that subjects were not opioid dependent and the Drug Discrimination Test determined whether they could distinguish intranasally administered active drug from placebo as well as high from low active intranasal dosages, and tolerate the treatments.

In the Treatment Period for O-ARIR-002, study treatments were randomized in a four-way crossover, double-blind, double-dummy design. In each of the four treatment periods (**Table 10**) participants insufflated a nasal preparation and swallowed an oral tablet. Treatment periods were administered in a randomized order. Placebo treatments consisted of a tablet matching

RoxyBond, a manipulated placebo RoxyBond tablet, “RoxyBond Placebo,” and a powder (microcrystalline cellulose) matching manipulated Roxicodone. The placebo arm was included to demonstrate a difference between Roxicodone and placebo, thereby supporting the internal validity of the study. Active treatments included RoxyBond or Roxicodone at the 30 mg dosage strength. Due to the different sizes of the tablets, treatments included preparations with different volumes, both low volume (100 mg, Periods 2 and 4) and high volume (587 mg, Periods 1 and 3). Nasal preparations were prepared using the most effective particle size reduction methods identified in Category 1 testing. RoxyBond tablets and RoxyBond placebo were manipulated with Tool G, and Roxicodone was manipulated with Tool E.

Table 10: Randomized Treatment Periods - Intranasal HAP Study O-ARIR-002

Period	Nasal Preparation	Oral Tablet
1	RoxyBond placebo, manipulated	RoxyBond placebo, intact
2	Roxicodone, manipulated	RoxyBond placebo, intact
3	RoxyBond, manipulated	RoxyBond placebo, intact
4	Roxicodone placebo, manipulated	RoxyBond, intact

Note: Active treatment arms are bolded.

The inpatient Treatment Period encompassed an 11-night stay for dosing, followed with a minimum 72-hour washout separating each treatment. A post-treatment Follow-up Period was performed 7-10 days after the last dose of the treatment period and consisted of safety assessments.

The primary endpoint of the study was Drug Liking E_{max} through 24-hours (i.e., maximum of all time points from each subject).

Key secondary endpoints included:

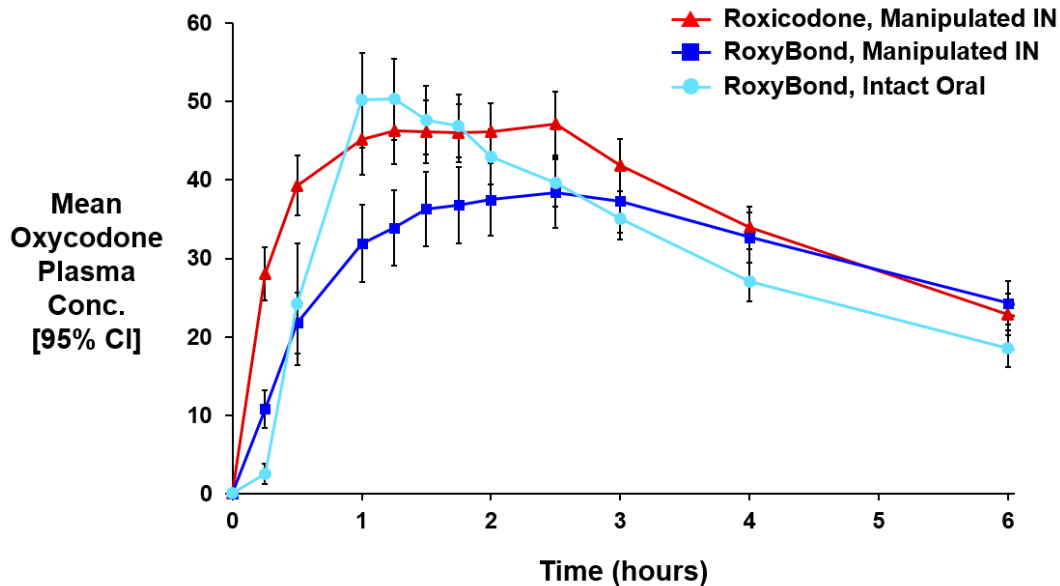
- Take Drug Again
- Overall Drug Liking
- Drug Effects Questionnaire
- Ease of Snorting Assessment
- Nasal Effect Assessment

6.2 Results

Pharmacokinetics

Mean plasma concentrations of oxycodone for the first 6 hours after administration are displayed in **Figure 16**. Intranasal administration of manipulated RoxyBond resulted in a significant reduction in early oxycodone absorption compared with manipulated Roxicodone.

Figure 16: Mean Plasma Concentration - Intranasal HAP Study O-ARIR-002



CI = confidence interval; Conc = concentration; HAP = human abuse potential; IN = intranasal.

Compared to manipulated intranasal Roxicodone, manipulated RoxyBond had significantly lower C_{max} , significantly lower partial AUC at all time points through 6 hours, as well as a longer T_{max} . The profile for intact oral RoxyBond exhibited a profile consistent with an oral IR product.

Results also indicate a lower maximum oxycodone concentration and lower exposure from 0 to 2 hours for manipulated intranasal RoxyBond than for intact oral RoxyBond. This finding was consistent with the intended formulation characteristics of manipulation and non-oral administration leading to slower oxycodone absorption than intact oral dosing.

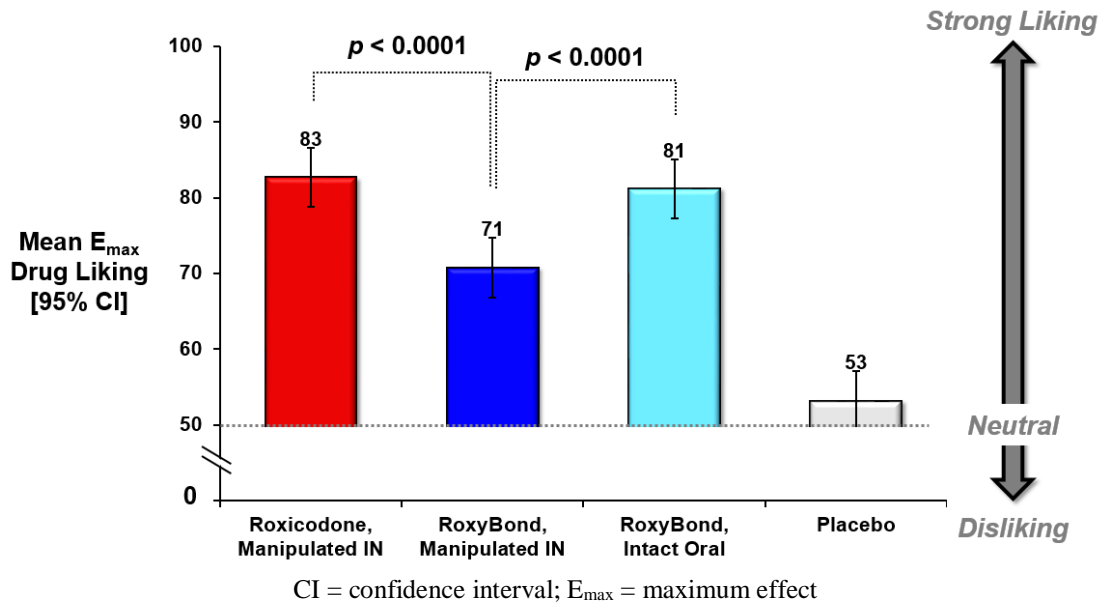
Pharmacodynamics

Drug liking was measured with a 100-point bipolar visual analog scale. A score of 0 denotes “strong disliking”, a score of 50 denotes a neutral response, and a score of 100 denotes “strong liking”.

The PK findings were consistent with the PD results (**Figure 17**). The primary endpoint of Drug Liking E_{max} yielded a statistically significant 12 mm difference between manipulated Roxicodone (83) and manipulated RoxyBond (71) ($P < 0.0001$).

In addition, Drug Liking E_{max} was also significantly lower for manipulated intranasal RoxyBond compared to intact oral dosing, consistent with intranasal insufflation leading to lower oxycodone absorption when RoxyBond is manipulated and administered via this non-oral route.

Figure 17: Mean Drug Liking E_{max} - Intranasal HAP Study O-ARIR-002

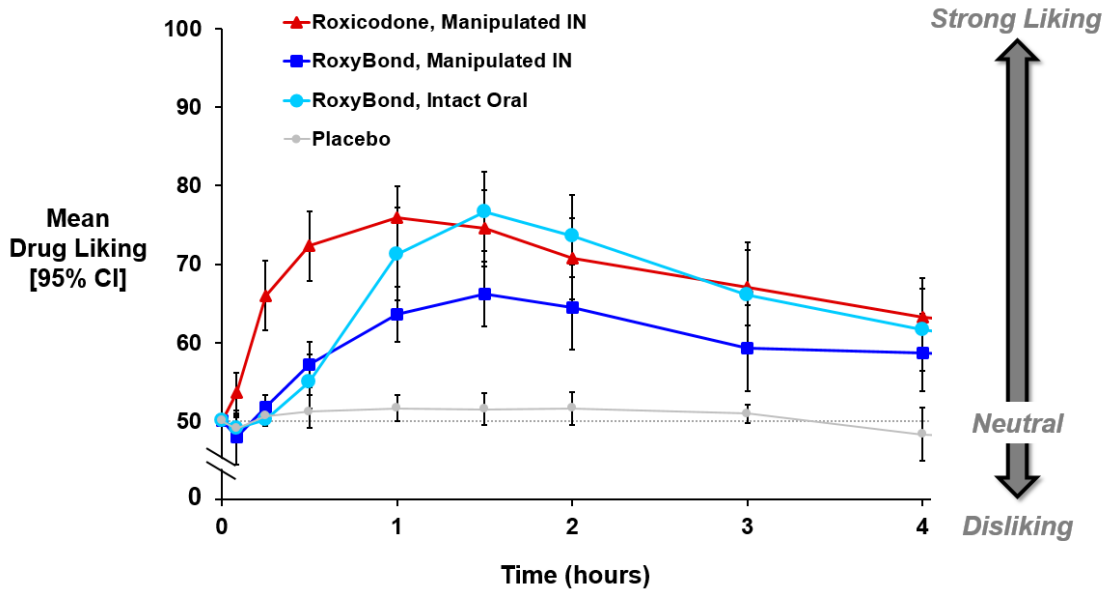


Most subjects experienced a reduction in Drug Liking E_{max} with manipulated intranasal RoxyBond compared with manipulated intranasal Roxicodone. Twenty-five subjects (86%) had a reduction in Drug Liking E_{max} for manipulated RoxyBond compared with manipulated Roxicodone, and in exploratory analysis, seventeen subjects (59%) had at least a 30% reduction.

Assessments of mean Drug Liking over time are provided in **Figure 18**. There was a rapid rise in drug liking for manipulated intranasal Roxicodone with a lower and delayed rise in Drug Liking with manipulated intranasal RoxyBond. The median time to E_{max} (TE_{max}) was significantly longer for manipulated RoxyBond than manipulated Roxicodone by approximately 0.5 hours ($p=0.015$).

In addition, the results are consistent with expectation of intranasal versus oral administration of an IR opioid. Manipulated intranasal Roxicodone was associated with significantly higher drug liking than intact oral RoxyBond at early time points, consistent with the motivation for snorting IR opioid products (i.e. a fast high).

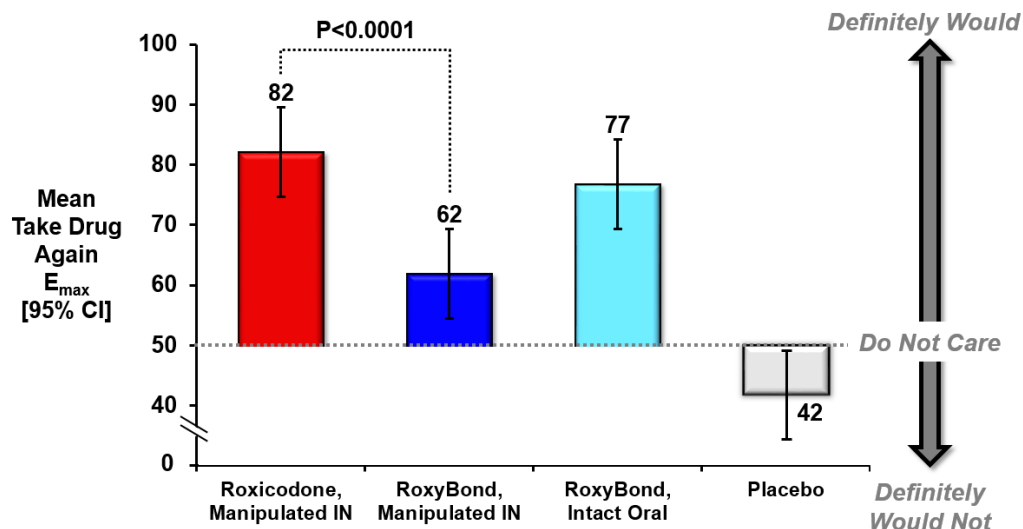
Figure 18: Mean Drug Liking Time Course - Intranasal HAP Study O-ARIR-002



CI = confidence interval; E_{max} = maximum effect.

Figure 19 displays results for the Take Drug Again endpoint, which provides additional clinical context into the primary Drug Liking results. For this endpoint, subjects are asked whether they would take the drug again if given the opportunity; a score of 0 would indicate that they “definitely would not”, a score of 50 indicates that they “wouldn’t care one way or another” and a score of 100 means that they “definitely would”. Take Drug Again E_{max} was significantly lower for manipulated intranasal RoxyBond than manipulated intranasal Roxycodone ($p < 0.0001$) and lower for intranasal RoxyBond than intact oral RoxyBond ($p = 0.001$).

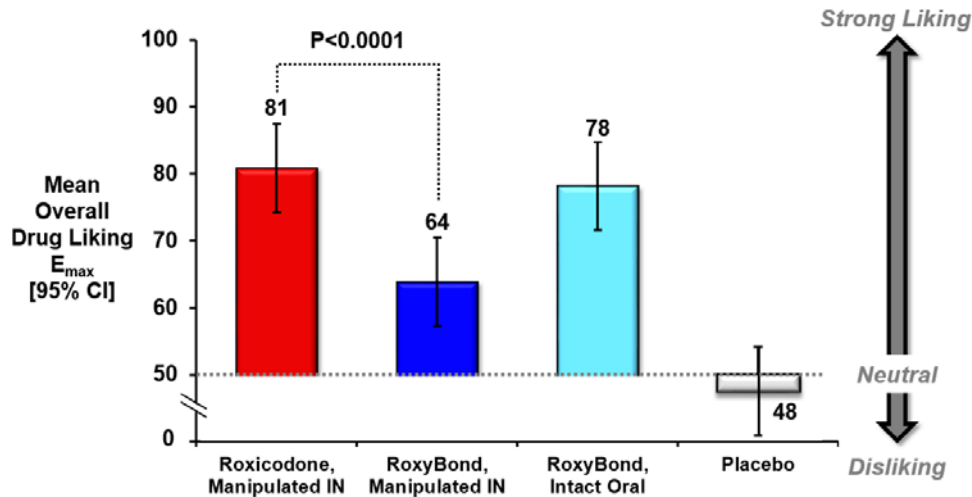
Figure 19: Mean Take Drug Again E_{max} - Intranasal HAP Study O-ARIR-002



CI = confidence interval; E_{max} = maximum effect.

Overall Drug Liking is assessed at 12 and 24 hours post-dose in order to allow the subject to reflect on the entire drug-taking experience. Similar to the other endpoints, the mean Overall Drug Liking E_{max} score of manipulated intranasal RoxyBond (64) was significantly lower than that of either manipulated intranasal Roxicodone (81; $P < 0.0001$) or intact RoxyBond (78; $P = 0.0004$) (**Figure 20**). The difference of 17 mm between manipulated intranasal Roxicodone and RoxyBond may be translated into a clinically relevant reduction in abuse (see Section 6.3).

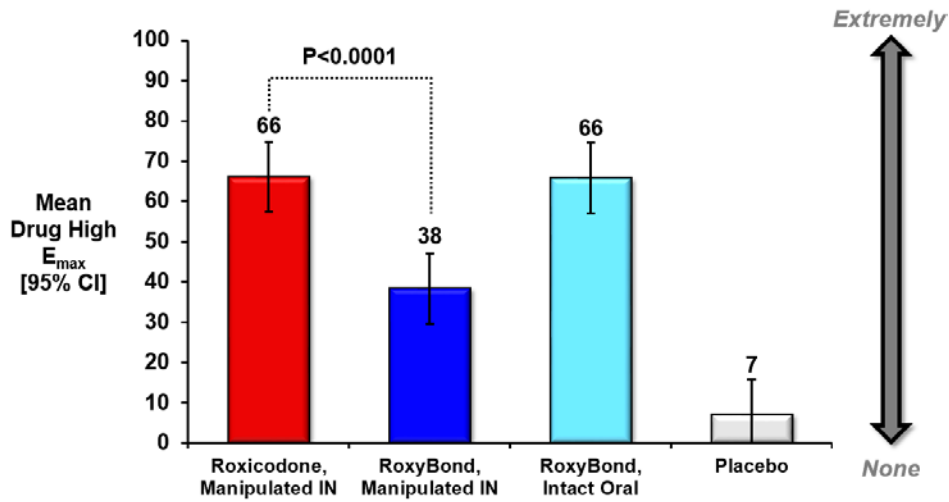
Figure 20: Mean Overall Drug Liking E_{max} - Intranasal HAP Study O-ARIR-002



CI = confidence interval; E_{max} = maximum effect.

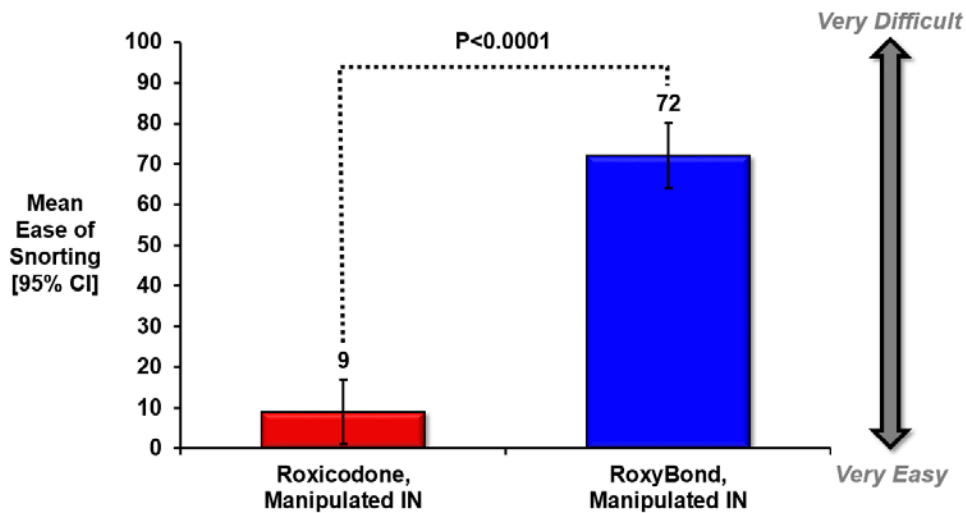
Drug High was evaluated on a unipolar visual analog scale where a score of 100 indicated “extremely” and 0 indicated “none.” Mean Drug High E_{max} for manipulated intranasal RoxyBond (64) was significantly lower than both manipulated intranasal Roxicodone (81; $P < 0.0001$) and intact RoxyBond (78; $P < 0.0001$) (**Figure 21**). The 28 mm reduction between manipulated intranasal Roxicodone and manipulated intranasal RoxyBond may translate to clinically significant reductions in drug-taking behavior (see Section 6.3).

Figure 21: Mean Drug High E_{max} - Intranasal HAP Study O-ARIR-002



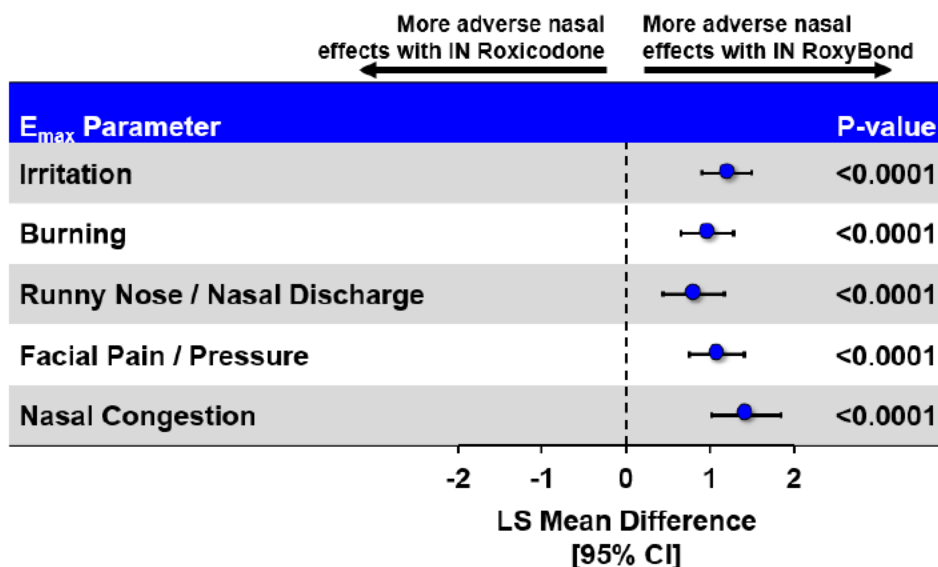
Ease of snorting was measured on a unipolar visual analog scale with a score of 0 corresponding to “very easy” and 100 corresponding to “very difficult”. As shown in **Figure 22**, manipulated RoxyBond was significantly more difficult to snort than manipulated Roxicodone ($p<0.0001$).

Figure 22: Mean Ease of Snorting - Intranasal HAP Study O-ARIR-002



In addition to Ease of Snorting, adverse nasal effects specific to insufflation (e.g., irritation, burning) were assessed with the Nasal Effects Assessment on a four point Likert scale (0 = none, 1=mild, 2=moderate, 3=severe). RoxyBond was associated with significantly more adverse nasal effects than Roxicodone for all parameters (all $p<0.0001$) (**Figure 23**).

Figure 23: Adverse Nasal Effects - Intranasal HAP Study O-ARIR-002



CI = confidence interval; HAP = human abuse potential; IN = intranasal;

In general, all treatments were well tolerated in this study with most adverse events (AEs) being mild or moderate in severity and typical of opioid related AEs or associated with intranasal administration of a drug (Table 11). The most frequently occurring treatment-related AE were pruritus generalized, nausea, vomiting, and pruritus. There were no other AEs that occurred in more than 2 subjects (6.7%) with any treatment.

Table 11: Treatment Emergent Adverse Events - Intranasal HAP Study O-ARIR-002

Adverse Event	Manipulated Roxicodone Intranasal (N = 30)	RoxyBond Manipulated Intranasal (N = 30)	RoxyBond Intact Oral (N = 31)	Placebo (N = 29)
Generalized Pruritus	23.3%	6.7%	12.9%	0.0%
Nausea	13.3%	13.3%	6.5%	0.0%
Vomiting	6.7%	10.0%	6.5%	0.0%
Pruritus	0.0%	0.0%	12.9%	0.0%

HAP = human abuse potential; N = number of subjects.

6.3 Clinical Relevance

In addition to achieving success on the pre-specified statistical comparisons, the treatment differences observed in this study between manipulated intranasal Roxicodone and RoxyBond for Overall Drug Liking and Drug High are relevant in terms of their likelihood of reducing intranasal abuse based on published literature.

A recent meta-analysis using the 2010 National Survey on Drug Use and Health examined the association between subjective drug liking and non-medical use rates (White et al., 2015). In this paper, regression modeling of clinical HAP studies of oxycodone products was used to evaluate the statistically significant association between Overall Drug Liking E_{max} with the expected reductions in rates of non-medical use. According to their calculations, a 5 mm reduction in Overall Drug Liking with an abuse-deterrent ER formulation would translate to an estimated 10% decrease in the rate of non-medical use. If applied directly to the 17 mm difference observed in Study O-ARIR-002, the same model produces an estimated 34% predicted decrease in the rate of non-medical use. Limitations of this calculation include possible differences between ER and IR formulations, and the lack of control in the meta-analysis for the specific route of abuse.

Laboratory and treatment trial data of sustained-release naltrexone were used to determine clinically important differences in Drug High (Eaton et al., 2012). Using both distribution-based and anchor-based methods, their study indicated that differences of 8 to 10 mm in Drug High E_{max} would be expected to lead to clinically significant changes in drug-taking behavior. Thus, the three-fold higher (28 mm) difference in Drug High E_{max} for RoxyBond compared to Roxycodone observed in this study provides support that RoxyBond has a lower abuse potential than Roxycodone for the intranasal route of abuse.

7 CLINICAL PERSPECTIVE

7.1 Comparable Bioavailability of RoxyBond to Roxicodone

Clinical PK studies demonstrated that RoxyBond had comparable bioavailability to Roxicodone, and can be expected to have an efficacy and safety profile equivalent to Roxicodone. In addition, the fact that food does not have a clinically significant impact on the bioavailability of oxycodone with RoxyBond means that patients will not have to remember whether they need to eat (or not eat), or for how long, before they take their medicine.

Overall, the data demonstrate that RoxyBond would be an effective medication for patients requiring an opioid analgesic for pain severe enough to require an opioid analgesic and for which alternative treatment options are inadequate. RoxyBond is not expected to pose any additional risks beyond currently marketed IR SE oxycodone products.

7.2 Abuse-Deterrent Properties for the IV Route of Abuse

Surveillance data from drug treatment centers found that 17% of abusers of IR oxycodone products abuse via the IV route. This route of abuse is likely more common for SE products like Roxicodone than combination products like Percocet[®] due to the absence of acetaminophen. Nonetheless, IV opioid abuse is particularly dangerous. The relative risk of death or a major effect (e.g., overdose) is 2.6 times greater for every instance of IV abuse compared to oral abuse. Furthermore, IV opioid abuse also carries the additional risks of HIV or Hepatitis C transmission, heart or lung infection, and thrombosis.

The Category 1 in vitro studies demonstrated multiple barriers to IV abuse for the RoxyBond tablets, including resistance to particle size reduction in preparation for extraction, difficulty of syringing the highly viscous material produced by manipulation, and resistance to extraction. With Roxicodone, nearly 100% of oxycodone could be recovered in a syringe under non-stressed conditions in the most common injectable solvent. In contrast, RoxyBond provided considerable resistance to extraction across the various common and extreme conditions evaluated. Furthermore, when manipulated and prepared for injection, RoxyBond formed a viscous material with particulate that was difficult to syringe, contained low recoveries of oxycodone, and required the largest needle gauge evaluated.

Overall, the physical and chemical abuse-deterrent properties of RoxyBond can be expected to make abuse by the IV route more difficult.

7.3 Abuse-Deterrent Properties for the Intranasal Route of Abuse

The intranasal route is a common route of abuse of IR oxycodone products with a prevalence of 36% reported at substance abuse treatment centers. Similar to the IV route, intranasal abuse is likely even more common among IR SE oxycodone than IR oxycodone combination products due to the lower volume of powder (i.e., each tablet of Percocet contains 325 mg of acetaminophen for every 2.5 mg to 10 mg of oxycodone). Like IV injection, intranasal abuse is a

more dangerous route of abuse – each instance of intranasal abuse is associated with 2.2 times the relative risk of death or a major adverse effect compared to oral abuse.

RoxyBond's resistance to particle size reduction is a physical barrier to obtaining an abusable form of the product. However, because RoxyBond is formulated to slow the absorption of oxycodone when manipulated and/or extracted for non-oral abuse compared to intact oral administration, an intranasal HAP study found that manipulated intranasal RoxyBond led to lower and slower oxycodone absorption than manipulated intranasal Roxicodone as well as intact oral administration of RoxyBond.

Manipulated intranasal RoxyBond had significantly lower Drug Liking, willingness to Take Drug Again, and Ease of Snorting compared to manipulated intranasal Roxicodone and intact oral RoxyBond. The differences between RoxyBond and Roxicodone on these key PD endpoints were not only statistically significant, but they also exceeded published clinical meaningful thresholds identified in the scientific literature as clinically meaningful.

Overall, the in vitro testing and results of the intranasal HAP study, demonstrated that RoxyBond can be expected to make abuse by the intranasal route more difficult and less rewarding.

7.4 Abuse-Deterrent IR Opioids as a Part of the Public Health Strategy

Abuse-deterrent formulations are abuse *deterrent*, not abuse *proof*. Therefore, abuse-deterrent formulations can only be one component of the overall public health strategy to address prescription opioid abuse. The FDA has recognized that abuse-deterrent formulations must be employed in the context of other solutions, including prescribing guidelines, risk management strategies (e.g., prescription drug monitoring programs), physician and patient education, broader access to treatment for addiction, and safe disposal programs to limit the risk of diversion (FDA 2016). At the recommendation of this Joint Advisory Committee, FDA announced expansion of the Risk Evaluation and Mitigation Strategy requirements for opioid analgesics to IR products (FDA, 2017) as part of an update to the agency's broader Opioid Action Plan.

The full impact of abuse-deterrent technologies on the prescription opioid epidemic cannot be realized until all opioids prescribed in the country are abuse deterrent. The FDA has approved 9 ER abuse-deterrent formulations; however, there are currently no IR products with abuse-deterrent labeling. Extending the safety advantages of abuse-deterrent technologies to IR products, and for IR SE oxycodone products in particular, affords several important opportunities:

- Immediate-release opioids are abused at 4.6 times the rate of ER products. Therefore, replacement of easily abusable IR opioids with abuse-deterrent products could have a substantive impact on overall opioid abuse.
- Most opioid abusers report starting their abuse with IR products. Therefore, IR abuse-deterrent products may offer an opportunity to deter abuse at earlier time points.

- Intranasal and IV abuse of IR oxycodone is common. Therefore, a product like RoxyBond that makes such abuse more difficult and less rewarding offers the potential to substantially reduce the most dangerous forms of abuse of this class of products.

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