FDA ADVISORY COMMITTEE BRIEFING DOCUMENT

REMOXY™ ER
(EXTENDED-RELEASE OXYCODONE CAPSULES)

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

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Available For Public Release

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List of Abbreviations

Abbreviation	Definition or Explanation
ADF	Abuse-deterrent formulation
ADT	Abuse-deterrent technology
AE	Adverse event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
API	Active pharmaceutical ingredient
AQ	Abuse quotient (C_{max}/T_{max})
AUC	Area under the plasma concentration curve - subscripts that may follow indicate time points [i.e. AUC ∞ means from time zero to infinity]
AUE	Area under the effect curve - subscripts that follow indicate time points
AUE_{tau}	AUC to the end of the dosing period
BA	Bioavailability
BID	Twice a day
BMI	Body mass index
CDC	Center for Disease Control
CE	Continuing education
CI	Confidence interval
C_{max}	Maximum observed plasma drug concentration
C_{min}	Minimum observed plasma drug concentration
CNS	Central nervous system
CRL	Complete Response Letter
DAWN	Drug Abuse Warning Network
DEA	Drug Enforcement Administration
ECG	Electrocardiogram
E_{max}	Maximum effect
ER	Extended-release
FDA	United States Food and Drug Administration
HAP	Human abuse potential
HPLC	High performance liquid chromatography

Abbreviation	Definition or Explanation
HCl	Hydrochloride
IR	Immediate-release
ITT	Intent-to-treat
IV	Intravenous
LA	Long acting (also sometimes called extended release)
N or n	Number
NDA	New Drug Application
NIH	National Institutes of Health
NSAIDs	Non-steroidal anti-inflammatory drugs
NTX	Naltrexone
% PTF	Percentage of peak-trough fluctuation within a dosing interval
PDUFA	Prescription Drug User Fee Act
PD	Pharmacodynamic(s)
PI	Pain intensity
PK	Pharmacokinetic(s)
PSR	Particle size reduction
REMS	Risk Evaluation and Mitigation Strategy
RPC	REMS Program Companies
SF-12	Short Form 12 Question Health Survey
SD	Standard deviation
SPA	Special Protocol Assessment
T_{max}	Time of maximum observed plasma drug concentration
VAS	Visual analog scale
WOMAC	Western Ontario and McMaster University Osteoarthritis Index

This Briefing Document references the following drug products and their trademarks:

REMOXY™ ER (oxycodone) extended-release capsules - *Pain Therapeutics, Inc.*
OxyContin® ER (oxycodone hydrochloride) extended-release tablets - *Purdue Pharma L.P.*
Xtampza® ER (oxycodone) extended-release capsules - *Collegium Pharmaceuticals, Inc.*
Roxicodone™ (oxycodone hydrochloride tablets USP) - *Mallinckrodt Pharmaceuticals, plc*

1 EXECUTIVE SUMMARY

The Sponsor of REMOXY ER prepared this Briefing Document to support a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee. This document aims to provide a useful format to evaluate whether data submitted to the U.S. Food and Drug Administration (FDA) for REMOXY ER in New Drug Application (NDA) 22-324 are sufficient to support labeling of the product with properties that can be expected to deter abuse. The term "Abuse-deterrent" as used in this Briefing Document is not intended to designate a medical claim but rather a general description of properties designed to address the misuse, abuse and diversion of opioids.

The Sponsor is requesting regulatory approval of REMOXY ER as an analgesic with properties that can be expected to meaningfully deter the injection, snorting and smoking routes of abuse. Sponsor does not seek a label claim for oral abuse.

REMOXY ER is the trade name for a new type of abuse-deterrent, extended-release, twice-daily, gel formulation of oral oxycodone. REMOXY ER has physical/chemical properties intended to deter formulation abuse yet provide 12 hours of steady pain relief when properly prescribed and used appropriately. Oxycodone, a potent opioid, is a controlled substance (CII) with high potential for abuse, misuse, overdose, and death. The active ingredient in all opioids, including REMOXY ER, is highly addictive.

Studies were extensive. The clinical efficacy of REMOXY ER was established in a Phase III study conducted under an FDA Special Protocol Assessment (SPA)[1]. In total, over 2,400 subjects were exposed to REMOXY ER in over 30 clinical studies. Nearly 9,000 unique data points were collected from 11 lab studies. The NDA for REMOXY ER provides full reports of all studies, including clinical pharmacology, safety, efficacy, and abuse deterrence. The assessment of REMOXY ER's abuse-deterrent properties is supported by data from FDA Category 1 (lab), Category 2 (pharmacokinetic) and Category 3 (human abuse potential) studies.

[1] SPA is a regulatory process in which the FDA reaches concurrence with a sponsor to ensure that the study conducted under the SPA has the potential to support regulatory requirements for approval.

REMOXY ER's approach to abuse deterrence is markedly different from OxyContin ER or Xtampza ER, which are currently the only two abuse-deterrent ER oxycodone products available in the US.

REMOXY ER has a sticky, high viscosity, hydrophobic, gel formulation that abusers cannot cut, grate, or divide into discrete particle size (Figure 1). Its gel formulation resists syringeability, injection, and rapid extraction. REMOXY ER's high viscosity gel and adhesive properties cause it to stick to tools and equipment used for abuse. When exposed to Temperature I, REMOXY ER releases vapors that irritate the respiratory tract and eyes. REMOXY ER resists dose dumping when challenged by ethanol and common physical and chemical manipulations.

Figure 1 REMOXY ER Formulation Mass – Sticky, High Viscosity, Hydrophobic Gel

The FDA Guidance (U.S. Food and Drug Administration, 2015) states that opioids are often manipulated for purposes of abuse. Therefore, the objective of abuse deterrence is to render drug manipulation more difficult, more time consuming, and less rewarding. The intended effect is to make manipulated opioids less attractive to abusers. The FDA defines abuse-deterrent properties as "those properties shown to meaningfully deter abuse, even if they do not fully prevent abuse" (U.S. Food and Drug Administration, 2015).

The toll of illness and death caused by prescription drug abuse is well documented. Opioid overdose deaths exceeded 40,000 in 2016, according to the Center for Disease Control (Center For Disease Control and Prevention, 2017b).

In October 2017, the FDA Commissioner released a public statement in support of several regulatory priorities to help combat the opioid epidemic:

> ***"Since becoming FDA Commissioner, I've made it one of my highest priorities to work on multiple fronts to reduce the scope of the opioid epidemic that's devastating our nation and destroying individual lives and families. In particular, we believe the FDA has a vital role to play in curbing new addiction, reframing how we look at the benefits and risks of opioids as part of our pre- and post-market efforts, and keeping as many people as possible from experiencing the serious adverse effects associated with these medications. The agency is also focused on promoting the development of opioids that are harder to manipulate and abuse."*** (U.S. Food and Drug Administration, October 26, 2017)

REMOXY ER intends to address the public health epidemic related to prescription opioids by advancing the science of abuse deterrence, providing an additional treatment option for physicians and patients, and increasing the range of available abuse-deterrent technologies.

REMOXY ER was developed under the 505(b)(2) regulatory pathway using Roxicodone as the reference product. The Sponsor submitted the NDA for REMOXY ER in February 2018. This NDA has a Prescription Drug User Fee Act (PDUFA) target date of August 7, 2018.

1.1 Proposed Indication and Dosing

Regulatory approval is being requested for 5 mg, 10 mg, 20 mg, 30 mg and 40 mg strength capsules to be administered every 12 hours, twice-daily (BID), by the oral route. The proposed indication is for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

If approved, REMOXY ER 5 mg would provide the lowest ER titration starting dose available to doctors and patients. REMOXY ER 5 mg is intended to encourage responsible prescribing practices and dosing flexibility for patients who may benefit from slow, safe upward titration, or who need to discontinue or taper opioid therapy.

Because of the risks of addiction, abuse and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with ER opioids, it is intended that REMOXY ER should be reserved for use in adult patients for whom alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient pain relief. When opioid use is started, clinicians should always prescribe the lowest dosage strength. REMOXY ER is not to be prescribed or used as an as-needed (prn) analgesic.

REMOXY ER has a unique twice-daily (BID) pharmacokinetic profile and therefore is not a generic drug substitute for OxyContin ER or for Xtampza ER.

REMOXY ER is a Schedule II drug under the Controlled Substances Act, is subject to the class labeling of an ER/long-acting (ER/LA) opioid analgesic, will require a Medication Guide for patients, and is subject to the ER/LA Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS).

1.2 Background on Chronic Pain

Chronic pain is a major health burden affecting more than one-third of the U.S. population, with the incidence expected to rise due to the aging population (Center For Disease Control and Prevention, 2017a). Opioid products have well-known analgesic properties and, when appropriately prescribed, can be used to treat some patients with severe chronic pain. FDA has acknowledged the role of opioids as important components of modern pain management (Gottlieb & Woodcock, 2017).

1.3 Abuse-Deterrence Properties

Abusers often attempt to defeat the time-release mechanism of ER oxycodone formulations. This allows an abuser to ingest, inject, snort or smoke a large dose of oxycodone that was originally intended to release slowly into the bloodstream over 12 hours, resulting in a powerful, and dangerous, euphoric high. Rapid increases in plasma levels of oxycodone can also lead to overdose, addiction or death. One potentially important step towards the goal of creating safer opioid analgesics has been the development of ER opioids with abuse deterrent properties.

REMOXY ER was developed with significant advice from the FDA and experts in the field, particularly in the design of the studies used to evaluate its abuse deterrent properties. Their advice was implemented throughout the drug development program, and studies conducted with REMOXY ER are consistent with the FDA Guidance.

The FDA Guidance refers to pre-market abuse potential studies as Category 1 (lab studies), Category 2 (pharmacokinetic studies) and Category 3 (human abuse potential studies).

Category 1 (lab) studies were performed to evaluate the abuse-deterrent properties of REMOXY ER. The formulation was challenged extensively, including extractions in Solvents S1 – S24; exposure to Temperatures A to I; twelve manipulation methods (RM1 – RM12); and assessments of injectability/syringeability and inhalation (nasal and smoking). Data from these studies demonstrate REMOXY ER resists physical and chemical attempts to extract oxycodone when compared to OxyContin ER, a marketed product with abuse-deterrent label claims. In many cases, *manipulated* REMOXY ER was less than or similar to *intact* OxyContin ER with regard to the amount of oxycodone extracted. Furthermore, attempts to rapidly release oxycodone from REMOXY ER by crushing or physical disruption and mixing with solvents were shown to be unsuccessful. Overall, data from nearly 9,000 unique data points were collected from 11 Category 1 (lab) studies. These data demonstrate that REMOXY ER has meaningful abuse-deterrent properties. These evaluations provide evidence that REMOXY ER has physical/chemical properties that can be expected to meaningfully deter the injection, snorting and smoking routes of abuse.

A Category 3 (human abuse potential) study in the nasal route of abuse met its primary endpoint ($p < 0.0001$) in favor of REMOXY ER versus IR oxycodone. Category 2 (PK) data from this study support abuse deterrence for REMOXY ER relative to oxycodone IR and OxyContin ER. These data demonstrate REMOXY ER has meaningful abuse-deterrent properties relative to OxyContin ER following manipulation and intranasal administration. These evaluations demonstrate REMOXY ER has physical/chemical properties that can be expected to meaningfully reduce abuse against the nasal route.

Category 2 (PK) and Category 3 (human abuse potential) data from an oral study demonstrated statistical significance in favor of chewed REMOXY ER versus an IR oxycodone in the early time points (0 - 2 hours, post-dose), when abusers seek a euphoric high. Data from this oral study did not demonstrate a statistically significant difference between REMOXY ER and the IR comparator for all four co-primary endpoints. Overall, this oral study met 2 of 4 co-primary endpoints with statistical significance. Xtampza ER was not a comparator drug in this oral study; however, *chewed* REMOXY ER has a C_{max} similar to the published C_{max} of *intact* Xtampza ER (Collegium Pharmaceutical Inc., 2015). More importantly, *chewed* REMOXY ER has a C_{max} similar to *intact* REMOXY ER at steady state, which indicates absence of dose dumping when REMOXY ER is chewed.

In summary, data generated from Categories 1, 2 and 3 studies demonstrate the abuse-deterrent properties of REMOXY ER in support of the proposed prescribing information.

1.4 Non-clinical Safety

The non-clinical testing program for REMOXY ER was designed to: 1) examine the safety profile of oxycodone as formulated in REMOXY ER; and 2) affirm the safety of the excipients in the formulation. Studies were designed and conducted in accordance with FDA guidelines and discussions with FDA and included testing and studies in multiple species under acute, sub-chronic, and chronic dosing conditions.

The non-clinical testing program affirmed the safety of the pharmaceutical excipients in the REMOXY ER formulation, as well as the safety of the complete final formulation itself.

1.5 Clinical Efficacy and Safety

REMOXY ER has been studied clinically in an extensive development program that includes clinical pharmacology studies as well as efficacy and long-term safety studies. The overall clinical safety database for REMOXY ER includes approximately 2,400 unique individuals exposed to REMOXY ER. Importantly, no new or unexpected treatment-emergent adverse events were observed in clinical studies with REMOXY ER.

The clinical efficacy of REMOXY ER was demonstrated in a multi-center, randomized, placebo-controlled, 12-week study, conducted under a Special Protocol Assessment (SPA). Analgesic efficacy was compared to placebo during the 12-week treatment period. REMOXY ER met the primary endpoint ($p = 0.007$).

The long-term clinical safety of REMOXY ER was demonstrated in >400 patients treated for 6 months and >300 patients treated for one year. No new or unexpected treatment-emergent adverse events were observed in the long-term clinical safety program with REMOXY ER.

A comprehensive Phase I pharmacokinetic program was completed for REMOXY ER and included, among other tests, assessments at steady-state kinetics and confirmation of dose proportionality between dosage strengths.

1.6 Benefit/Risk Assessment

REMOXY ER has demonstrated a favorable benefit/risk balance, as summarized below:

- Oxycodone, the active pharmaceutical ingredient in REMOXY ER, is marketed in the US. The analgesic efficacy of oxycodone in the treatment of chronic pain is well established.

- The nonclinical testing program affirms the safety of the excipients in the REMOXY ER formulation, as well as the safety of the complete final formulation itself.

- The safety profile of REMOXY ER is consistent with other ER oxycodone drugs. No new or unexpected treatment-emergent adverse events were observed in the long-term clinical safety program with REMOXY ER.

- The analgesic efficacy of REMOXY ER was confirmed in a pivotal 12-week randomized, double-blind, placebo-controlled study in subjects with moderate to severe chronic pain due to osteoarthritis of the hip or knee.

- If approved, REMOXY ER 5 mg would be the lowest ER titration starting dose for opioid-naïve patients with a need to safely initiate opioid therapy.

- Category 1 (lab) studies demonstrate that REMOXY ER has meaningful abuse-deterrent properties relative to one or both marketed ER oxycodone drugs.

- Category 2 (PK) studies in recreational opioid abusers confirmed REMOXY ER's abuse-deterrent properties relative to oxycodone IR and OxyContin ER

- Category 3 (human abuse potential) studies in recreational opioid abusers confirmed REMOXY ER's abuse-deterrent properties relative to oxycodone IR.

- These studies indicate REMOXY ER can be expected to meaningfully deter abuse, and, consistent with FDA Guidance, is not expected to completely prevent abuse.

2 INTRODUCTION

2.1 Non-medical Use of Opioids

It is well known that opioids can produce both analgesia and euphoria. The non-medical use and abuse of prescription opioid products has led to a serious and persistent public health crisis. According to the National Institute of Health (NIH), an estimated 2.1 million people suffered from disorders associated with opioid analgesics, with increasing evidence that the non-medical use of opioid analgesics is related to heroin abuse (Volkow, 2014). In 2016, opioid drug overdoses accounted for over 40,000 deaths (Center For Disease Control and Prevention, 2017b).

Opioid abusers seek a rapid euphoric high. Specifically, abusers seek to absorb a maximum amount of drug in the shortest amount of time. A survey reported the majority of abusers are willing to spend 10 minutes or less tampering with opioid products (Sellers, Perrino, Colucci, & Harris, 2013). Abusers intentionally defeat a drug's extended-release mechanism to convert it to an immediate release (IR) form. The resultant IR dosage form allows an abuser to ingest, inject, snort, or smoke a large dose of oxycodone that was intended to slowly release. This practice provides abusers with a powerful, and dangerous, euphoric high. It is well established that rapid increases in plasma levels of oxycodone can lead to overdose or death.

Oral opioid abuse is prevalent, although abuse by unapproved routes of administration, such as snorting, inhalation, and injection is widespread (Figure 2) (Gasior, Bond, & Malamut, 2016). Snorting, inhalation and injection avoids first pass hepatic metabolism (which occurs via oral administration), thus contributing to a more rapid, maximum euphoric high. Studies and surveys show opioid addicts progress from oral ingestion to more dangerous non-oral routes, predominantly snorting and injection (Figure 3) (Katz et al., 2011).

Figure 2 Route of Abuse of Prescription Opioids in the US (Gasior et al., 2016).

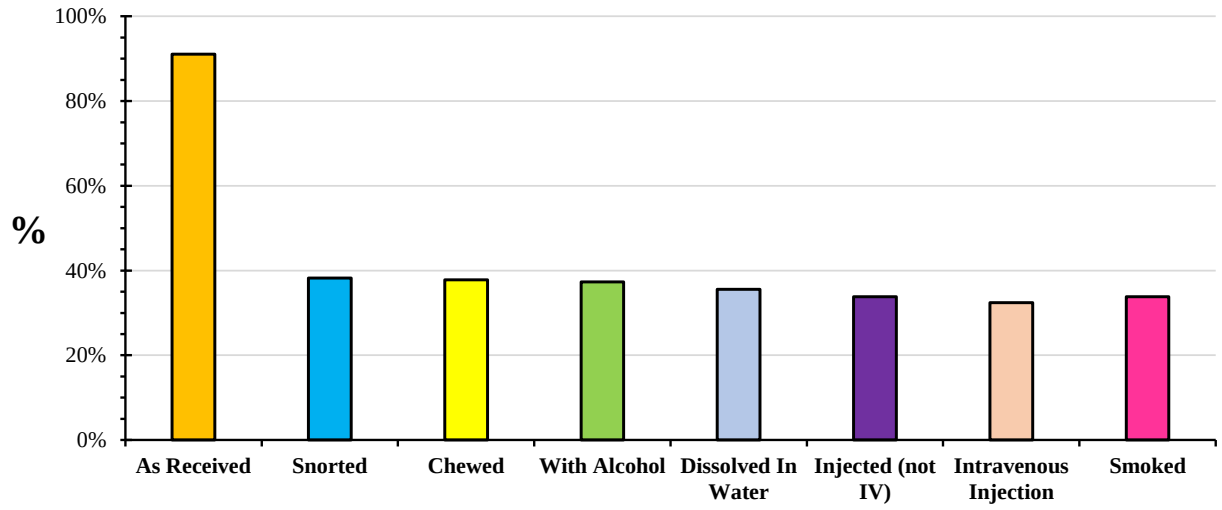
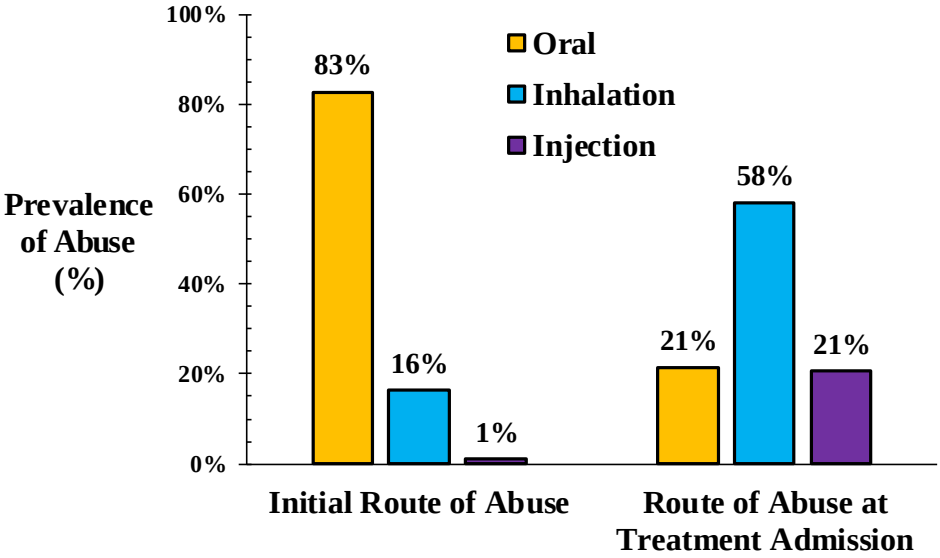


Figure 3 Route of Abuse Progression (Katz et al., 2011).



In a survey of 251 participants from the US National Health and Wellness survey who reported prescription opioid abuse, over half reported tampering with their opioid to get high and approximately 40% of the respondents reported chewing, snorting, or injecting the opioid (Vietri, Joshi, Barsdorf, & Mardekian, 2014).

Abusers are known to adapt to abuse-deterrent technologies and discover methods to defeat them. A 2015 survey reported that ~33% of those who abused the non-abuse-deterrent formulation of OxyContin ER continued to inject and snort the reformulated (abuse-deterrent) OxyContin ER formulation (Cicero & Ellis, 2015).

Published data also suggests that abuse by non-oral routes of administration is associated with more serious negative health consequences. Poison center data show that opioid exposures involving an unintended route were 63% more likely to be associated with death or major medical outcomes than oral ingestion. Death or major medical outcomes occurred in 13% of inhalation and in 13% of injection cases compared to 7% of cases with oral ingestion (Bartelson et al., 2015).

The risks of opioid abuse demand new abuse-deterrent technologies and mechanisms.

2.2 Abuse-deterrent Formulations

One important step towards the goal of creating safer opioid analgesics has been the development of formulations that incorporate technology to deter formulation abuse. These are commonly referred to as 'abuse-deterrent formulations'. Abuse-deterrent technologies address the need to make ER formulations more difficult to abuse, yet provide 12 hours of steady pain relief when properly prescribed by physicians and used appropriately by patients.

FDA considers the development of abuse-deterrent formulations a high public health priority and continues to strongly support the development of more effective abuse-deterrent features as one of several ways to combat the abuse epidemic (Califf, Woodcock, & Ostroff, 2016). As noted in the FDA Guidance, "the objective of abuse deterrence is to render drug manipulation more difficult and less rewarding, thereby making manipulated ER opioid drugs less attractive to drug abusers" (U.S. Food and Drug Administration, 2015).

The FDA Guidance defines abuse-deterrence as "those properties shown to meaningfully deter abuse, even if they do not fully prevent abuse". The cardinal feature of abuse deterrence is to make ER formulations more difficult to defeat. However, abuse-deterrent never means "abuse proof". Furthermore, abuse-deterrent technology does not address the numerous, complex clinical or

behavioral factors associated with opioid use and abuse, such as tolerance, rewarding effects, physical dependence, craving, withdrawal, drug diversion, risk-taking behavior, or addiction.

The FDA Guidance describes three categories of pre-market studies to obtain a full and scientifically rigorous understanding of the impact of a product's abuse-deterrent properties and abuse potential:

Category 1 – Laboratory Manipulation and Extraction Studies;
Category 2 – Pharmacokinetic Studies; and
Category 3 – Human Abuse Potential Studies.

According to the FDA Guidance, label claims for abuse-deterrence should describe the product's specific abuse-deterrent properties as well as the specific routes of abuse that the product has been developed to deter. When data predict or show that a product's potentially abuse-deterrent properties can be expected to result in a significant reduction in that product's abuse potential, these data, together with an accurate characterization of what the data mean, may be included in product labeling.

The science of abuse deterrence is still evolving. Only two ER oxycodone drugs are currently available to patients in the US: OxyContin ER and Xtampza ER [2]. Both drugs have label claims on abuse deterrence. OxyContin ER uses a hardened polymer to deter abuse, while Xtampza ER relies on wax microspheres. Each approach may deter abuse to a certain extent (Butler, 2013; Havens, Leukefeld, DeVeaugh-Geiss, Coplan, & Chilcoat, 2014). However, oxycodone abuse has not been eliminated. OxyContin ER tablets remains particularly vulnerable to quick, simple manipulations that enable extraction of high levels of oxycodone. Instructions on how to defeat OxyContin ER are available on internet forums that cater to drug abusers. There is evidence that continued abuse of OxyContin ER is explained in part by "successful efforts to defeat the abuse-deterrent formulation mechanism, leading to a continuation of inhaled or injected use" (Collegium Pharmaceutical Inc., 2017).

[2] Targiniq® ER (oxycodone HCl/naloxone HCl) from Purdue Pharma, and Troxyca®/ALO-02 (oxycodone HCl/naltrexone) from Pfizer, are both FDA approved products but are not marketed in the US.

New technologies can advance the science of abuse deterrence. These may also overcome limitations of currently marketed drug products, and provide improved protection against abuse, while ensuring that patients that are suffering from chronic pain have access to safe and effective products to treat that pain.

To meet these goals, the Sponsor has developed REMOXY ER, a new type of abuse-deterrent technology.

2.3 Product Overview

REMOXY ER is an abuse-deterrent, extended-release, twice-daily, gel formulation of oral oxycodone. REMOXY ER capsules contain a high viscosity, sticky, hydrophobic formulation that an abuser cannot crush, cut, grate, grind or divide into discrete particle size. REMOXY ER resists syringeability, injection, and rapid extraction. The gel's extreme stickiness results in high (20-30%) loss of mass when manipulated with tools and equipment. When exposed to Temperatures G, H and I, REMOXY ER releases vapors that irritate the respiratory tract and eyes. REMOXY ER resists dose dumping when challenged by common physical manipulations and chemical extractions, many of which were shown to compromise OxyContin ER.

Results of studies conducted with REMOXY ER are reported later in this briefing document. All studies were conducted according to pre-specified instructions; were carried out by third-parties in independent facilities; and employed reliable, quantitative measures that were well documented.

The assessment of REMOXY ER's abuse deterrent properties is supported by studies from all three categories referenced in the FDA Guidance (U.S. Food and Drug Administration, 2015). Based on these assessments, the sponsor of REMOXY ER is requesting label claim that the product deters abuse via the routes of injection, snorting and smoking.

REMOXY ER capsules shells are filled from a common formulation to achieve five dose strengths: 5 mg, 10 mg, 20 mg, 30 mg and 40 mg. The various product strengths are differentiated by capsule size, color and print content on the capsules.

2.4 Development Program Overview

The development program for REMOXY ER incorporates significant advice from the FDA and experts in the field. Studies conducted with REMOXY ER are consistent with the FDA Guidance.

The REMOXY ER development program consists of clinical pharmacology studies conducted in healthy volunteers; over 11 laboratory manipulation and extraction studies that generated nearly 9,000 unique data points; 2 human abuse potential studies in non-dependent recreational opioid users; a Phase III safety & efficacy study; and a long-term safety study in subjects with chronic pain. Overall, approximately 2,400 subjects have been exposed to REMOXY ER.

Summaries of key studies are presented in this Briefing Document. Due to the large quantity of data available for REMOXY ER and space limitations, only a representative amount is presented in this Briefing Document. All data was submitted to the FDA in the NDA for REMOXY ER. Manipulation methods, solvents and other key parameters of abuse are coded in this document to avoid informing drug abusers.

Since 2015, Pain Therapeutics has been, and continues to be, the sole Sponsor and responsible party for REMOXY ER. Prior to 2015, the development program for REMOXY ER was conducted at various times by Pfizer, Inc., King Pharmaceuticals, Inc., or Pain Therapeutics, Inc.

2.5 Regulatory History

REMOXY ER is the subject of prior regulatory reviews by the FDA's Division of Anesthesia, Analgesia and Addiction Products. Deficiencies in commercial manufacturing and evolving non-clinical requirements were topics of discussions in prior Complete Response Letters (CRLs). The safety and efficacy of REMOXY ER were never questioned in prior regulatory reviews. A chronological regulatory history of REMOXY ER follows.

The initial NDA was submitted by the Sponsor in June 2008, and a CRL was issued in December 2008. Deficiencies noted in the initial CRL were primarily around commercial manufacturing issues and non-clinical support. Subsequently, King Pharmaceuticals, Inc. assumed sole responsibility for REMOXY ER and resubmitted the NDA in December 2010.

A second CRL was issued in June 2011 on the King resubmission. The deficiencies identified were primarily regarding commercial manufacturing issues and non-clinical support.

Subsequently, Pfizer, Inc. acquired King Pharmaceuticals and assumed sole responsibility for the development of REMOXY ER. Pfizer successfully completed work designed to address commercial manufacturing issues. However, Pfizer divested away from neuroscience drug development. In April 2015, the Sponsor reassumed sole responsibility for REMOXY ER and submitted the NDA in March 2016.

In September 2016, a CRL was issued, citing the need to conduct a Category 3 (human abuse potential) study via the nasal route of abuse, and to generate additional data from Category 1 (lab) studies.

The Sponsor and FDA met in February 2017 to ensure a clear understanding of the 2016 CRL, and to gain agreement on the specific new information needed to resolve deficiencies. The Sponsor and FDA met again in November 2017 to confirm that the data to be included in the REMOXY ER NDA resubmission would constitute a complete response. All questions were addressed and summarized in final meeting minutes issued by the FDA. There were no unresolved discrepancies following receipt of final meeting minutes.

As a result, in February 2018, the Sponsor resubmitted to the FDA the NDA for REMOXY ER.

The NDA was accepted for filing by FDA and is assigned a Prescription Drug User Fee Act (PDUFA) date of August 7, 2018.

3 ABUSE DETERRENCE EVALUATIONS

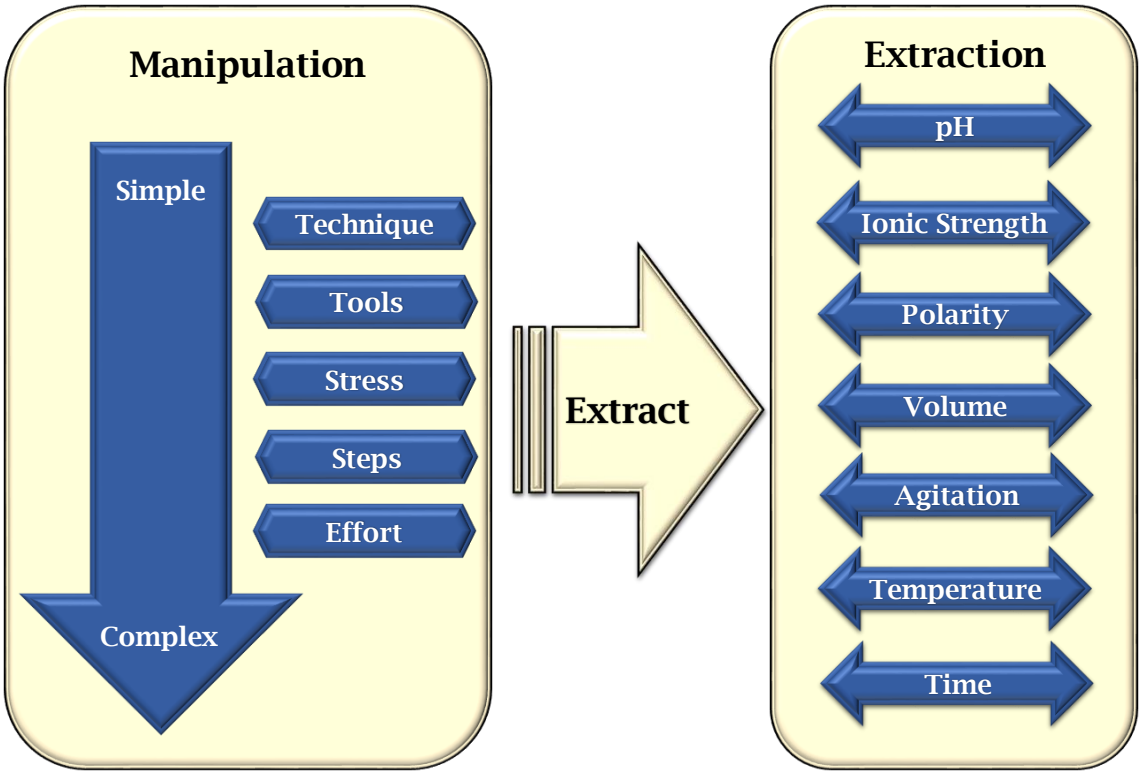
3.1 Category 1 Studies

3.1.1 Overview, Methodology and Rationale for Studies

The objective of Category 1 (laboratory) studies for REMOXY ER was to characterize its abuse-deterrent properties and to explore the degree of effort required to defeat its ER properties.

REMOXY ER was evaluated in a comprehensive battery of Category 1 (lab) studies (Figure 4). Studies were conducted with scientific rigor. Category 1 (lab) studies for REMOXY ER included the use of comparator drugs, sampling times that extend to Time O, and the use of HPLC methods to provide a robust, accurate assay of oxycodone. Outside laboratories performed all the studies under highly-controlled conditions, including good manufacturing practices and good laboratory practices.

Figure 4 Overview of Category 1 (lab) Strategy for REMOXY ER



Study methodologies were informed by three principal sources:

i) Knowledge of the physical/chemical properties of the REMOXY ER formulation;
ii) Specific input from FDA, experts in the field and prescription opioid abusers; and
iii) Consideration for known methods of abuse of marketed opioid formulations.

Oxycodone extraction was assessed using methods that simulated various routes of abuse: oral ingestion; Volume A - C extractions for IV administration; and smoking / inhalation. These studies simulated both intentional abuse and unintentional (accidental) abuse. In some cases, the simulations required more time, expertise, equipment, effort and overall expense than a casual drug abuser might employ.

The studies were extensive. They assessed simple and sophisticated mechanical and chemical procedures to investigate the effects of time, temperature, pH, polarity, volume, and agitation rate, representing 75 different parameters evaluated (Table 1). Manipulated and non-manipulated (intact) states were both evaluated. Studies were conducted for up to Time O, far longer than the 10 minute time frame the majority of abusers are willing to spend tampering with opioids (Sellers et al., 2013). In total, data collected from 11 Category 1 (lab) studies represent about 9,000 unique data points, providing a body of data that exceeds the recommendations in the FDA Guidance.

Table 1 Category 1 (lab) Study Parameters Evaluated

Category 1 Study Parameters	# Evaluated
Manipulation methods	12
Manipulation Tools	24
Stress Conditions	3
Solvents	24
Solvent Volumes	4
Agitation Methods	4
Extraction Temperatures	4
Total	**75**

The entire content (by weight) of a REMOXY ER capsule was used in studies. In practice, manipulating a single REMOXY ER capsule results in a 20-30% loss of the formulation mass due to its stickiness and high viscosity.

Category 1 (lab) studies used the highest strength of REMOXY ER, i.e., 40 mg. Comparator drugs were OxyContin ER, Xtampza ER, or Roxicodone IR.

Category 1 (lab) studies with REMOXY ER began with "Conventional Practices", i.e., those based on common tools, and progressed to "Complex Practices", i.e., those that require more sophisticated tools, Solvents S1 – S24, greater effort, or employ multistep procedures using laboratory equipment (Table 2).

Table 2 Category 1 (lab) Studies with REMOXY ER

		Experiment	Objective
Manipulations	**Physical**	Alter morphology	Investigate simple and complex tools and techniques to increase drug release.
	Chemical	Extraction	Quantify drug extraction into multiple solvents under different conditions.
Route Specific	**Oral**	Manipulation & Volume D Extractions	Evaluate drug extraction in Solvents S1 – S16.
	IV	Direct Injection	Assess ability to directly inject.
		Manipulation & Volume A - C Extractions	Evaluate drug extraction into Solvents S19 - S24.
	Smoking	Simulated Smoking	Quantify drug vaporized after heating.

All data was submitted to the FDA in the NDA for REMOXY ER. Due to the large quantity of data for REMOXY ER, and space limitations, only a representative amount is presented in this

Briefing Document. The data reported below are for simple manipulations and "worst-case" complex manipulations.

3.1.2 Physical Manipulation Outcomes

Summary

- REMOXY ER was evaluated using 12 different manipulation methods.
- Subjecting REMOXY ER to Temperatures G, H and I releases irritating vapors, causes oxycodone degradation, and can catch fire.
- The use of tools to manipulate and abuse REMOXY ER causes significant (20-30%) loss of mass, due to the gel formulation's stickiness and high viscosity.
- Abusers have no visual cues to indicate if or when REMOXY ER has been compromised or defeated. In contrast, manipulation of OxyContin ER tablets has clear visual cues that the drug has been defeated and is ready for abuse.
- A single step can defeat OxyContin ER into a readily abusable form. In contrast, multiple steps, tools, and extraction procedures were required to defeat REMOXY ER.
- Based on study results, REMOXY ER is expected to be less attractive to abusers and have a meaningful impact on abuse via physical and chemical manipulation methods.

An abuser faces practical difficulties handling the sticky, high viscosity, gel formulation. Manipulation methods RM2 and RM8, for example, resulted in >25% loss of the REMOXY ER formulation mass before extraction attempts could even begin. Low oxycodone extraction from REMOXY ER after physical manipulation is intended to contribute to REMOXY ER's abuse deterrence.

There are no visual cues to alert an abuser that REMOXY ER might be defeated or compromised. Lacking visual clues, an abuser must rely on guesswork, trial-and-error or sophisticated laboratory measurement equipment, such as an HPLC, to gauge the success or failure of various manipulation methods. An abuser would also need to record various experimental manipulation methods, tools,

solvents, etc. to ideal identify conditions for REMOXY ER abuse. The complexity, frustration and tools needed to abuse REMOXY ER are intended to contribute to its abuse deterrence.

3.1.3 Simulated Oral Ingestion: Volume D Extractions

Summary

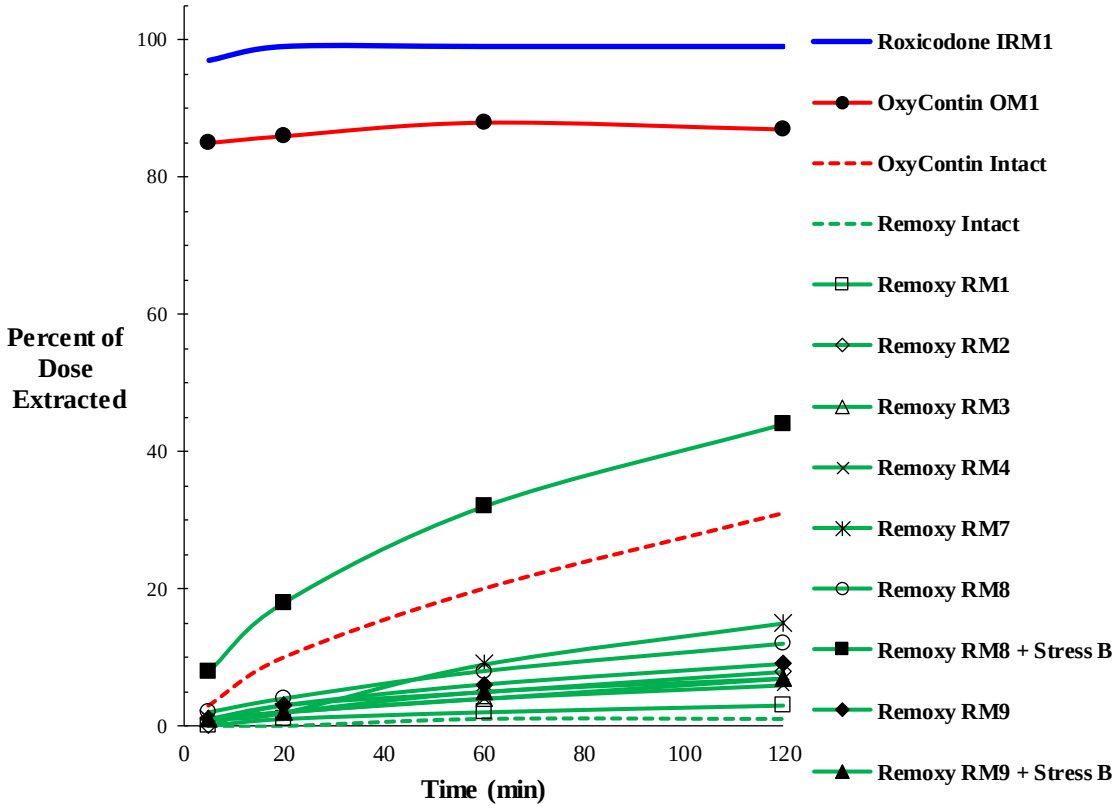
- REMOXY ER was not rendered into an IR dosage form after most physical and chemical manipulations.
- OxyContin ER is easily, quickly defeated into an abusable form.
- Popular methods used to abuse OxyContin ER do not work for REMOXY ER.
- Several methods of abuse *reduced* extraction of oxycodone from REMOXY ER, compared to the intact dosage form.
- Oxycodone extraction from manipulated REMOXY ER was slower than manipulated OxyContin ER in Solvents S1, S2, S3 and S5. Solvent S4 is a poor solvent for both.
- One method of abuse required 5 tools and 6 steps to defeat REMOXY ER.
- Manipulation of OxyContin ER has visual cues that the tablet is dissolved and is ready for abuse. In contrast, there are no visual cues to indicate if REMOXY ER is ready for abuse.
- Based on study results, REMOXY ER is expected to be less attractive to abusers and meaningfully reduce abuse using Volume D with Solvents S1 – S5.

'Volume D Extraction' evaluations determine how an abuser might attempt to extract oxycodone from an ER formulation. These evaluations simulate oral ingestion abuse.

In these lab studies, REMOXY ER and two comparator drugs, OxyContin ER and Roxicodone IR, were subjected to various representative physical and mechanical manipulation techniques, including Stress B & C. The resulting materials were subjected to an extraction procedure with sampling times from Time A to Time O. Oxycodone extraction was determined using high performance liquid chromatography (HPLC).

Representative data from intact and manipulated REMOXY ER and comparators in Solvent S1 is provided in Figure 5.

Figure 5 Oral Abuse: Percent Oxycodone Extracted in Solvent S1

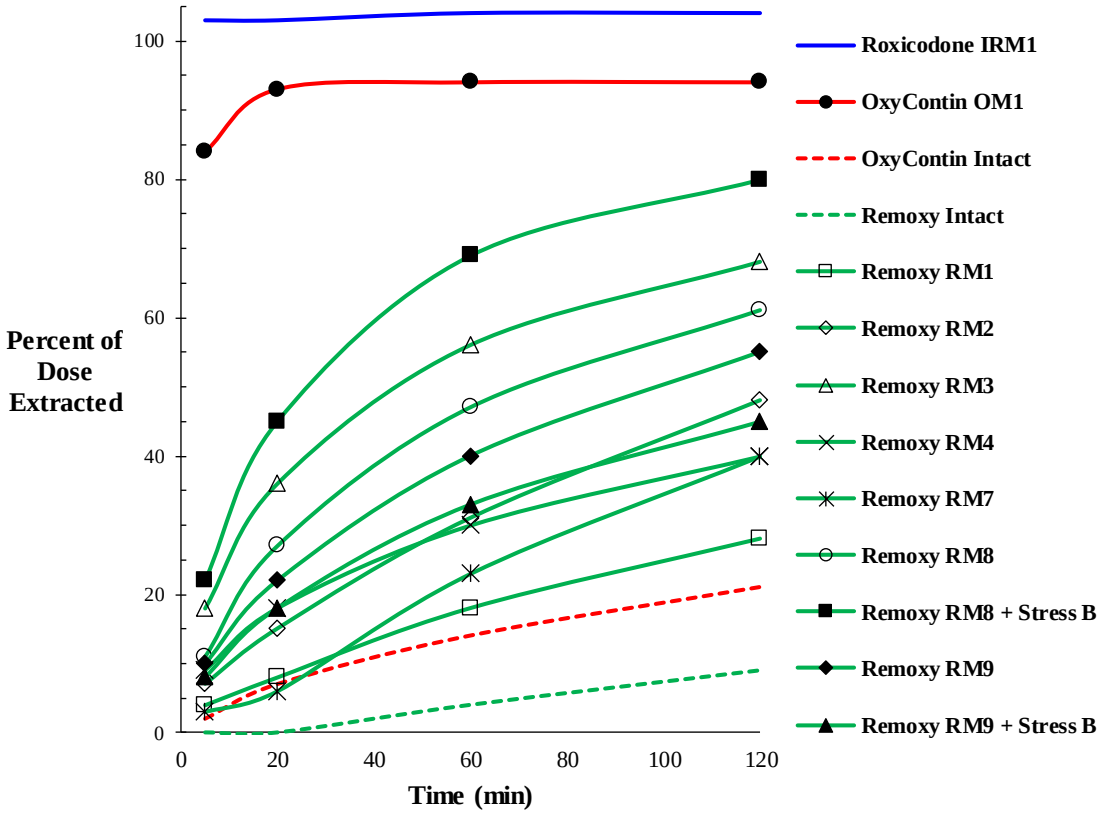


M# refers to Manipulation Method number

REMOXY ER was not rendered into an IR dosage form after manipulation with common tools and methods intended for abuse. Eight of nine manipulation methods in Solvent S1 resulted in less than 20% of the oxycodone dose extracted from REMOXY ER after 2 hours. Manipulated OxyContin ER was defeated in 5 minutes. Less oxycodone was extracted from *manipulated* REMOXY ER than *intact* OxyContin ER by all the manipulation methods except for method RM8 plus Stress B.

Solvent S5 was the worst case solvent among Solvents S1 – S5 to extract oxycodone from manipulated REMOXY ER. Less than 50% of the dose was extracted from manipulated REMOXY ER within 20 minutes. Greater than 80% of the dose was extracted from manipulated OxyContin ER within 5 minutes (Figure 6).

Figure 6 Oral Abuse: Percent Oxycodone Extracted in Solvent S5



M# refers to Manipulation Method number

Oxycodone extraction increased when manipulated drugs were tested at Temperatures D, E and F. Under this condition, the rate of drug extraction from REMOXY ER was slower than manipulated OxyContin ER and IR oxycodone in Solvents S1 – S5. In these studies, REMOXY ER is equally or more resistant to extraction compared to OxyContin ER.

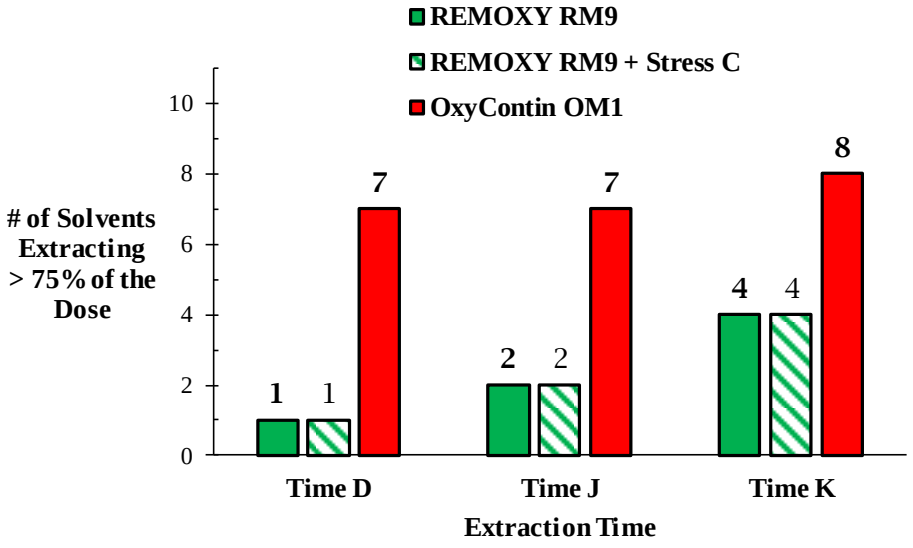
3.1.4 Extraction in Solvents S6 – S16

Summary

- Lab studies with Solvents S6 – S16 evaluate the likelihood of obtaining an isolate of high purity. Additional processing, equipment, time and expertise are required to separate oxycodone (and the excipients) from Solvent S6 – S16 into an abusable format.
- Within 2 hours, REMOXY ER was defeated in 4 of 11 of these solvents.
- Within 2 hours, OxyContin ER was defeated in 8 of 11 of these solvents.
- Most methods of abuse under evaluation did not defeat REMOXY ER's abuse-deterrent properties in Solvents S6 – S16.
- REMOXY ER has meaningful abuse-deterrent properties compared to OxyContin ER.
- Based on study results, REMOXY ER is expected to be less attractive to abusers and meaningfully reduce abuse using Volume D with Solvents S6 – S16.

Over 75% of the oxycodone dose was extracted from REMOXY ER in 4 of 11 solvents within 2 hours. Greater than 75% of the oxycodone dose was extracted from OxyContin ER in 8 of 11 solvents within 2 hours (Figure 7).

Figure 7 Number of Solvents S6 – S16 Capable of Extracting Greater Than 75% of the Dose (Volume D, Temperature B)



M# refers to the Manipulation Method number

3.1.5 Simulated Intravenous Abuse

Summary

- REMOXY ER could not be directly injected using typical needle sizes, due to its high viscosity formulation.
- OxyContin ER is quickly defeated into an abusable form for intravenous abuse.
- Methods used to inject OxyContin ER did not work for REMOXY ER.
- In all solvents and experimental conditions, oxycodone was extracted more rapidly from manipulated OxyContin ER than manipulated REMOXY ER.
- Oxycodone extracted from manipulated REMOXY ER was less than manipulated Xtampza ER in Solvent S20, and similar in Solvents S19 and S21**.**
- REMOXY ER has meaningful abuse-deterrent properties against intravenous abuse compared to OxyContin ER and Xtampza ER.
- Based on study results, REMOXY ER is expected to be less attractive to abusers and to meaningfully reduce intravenous abuse.

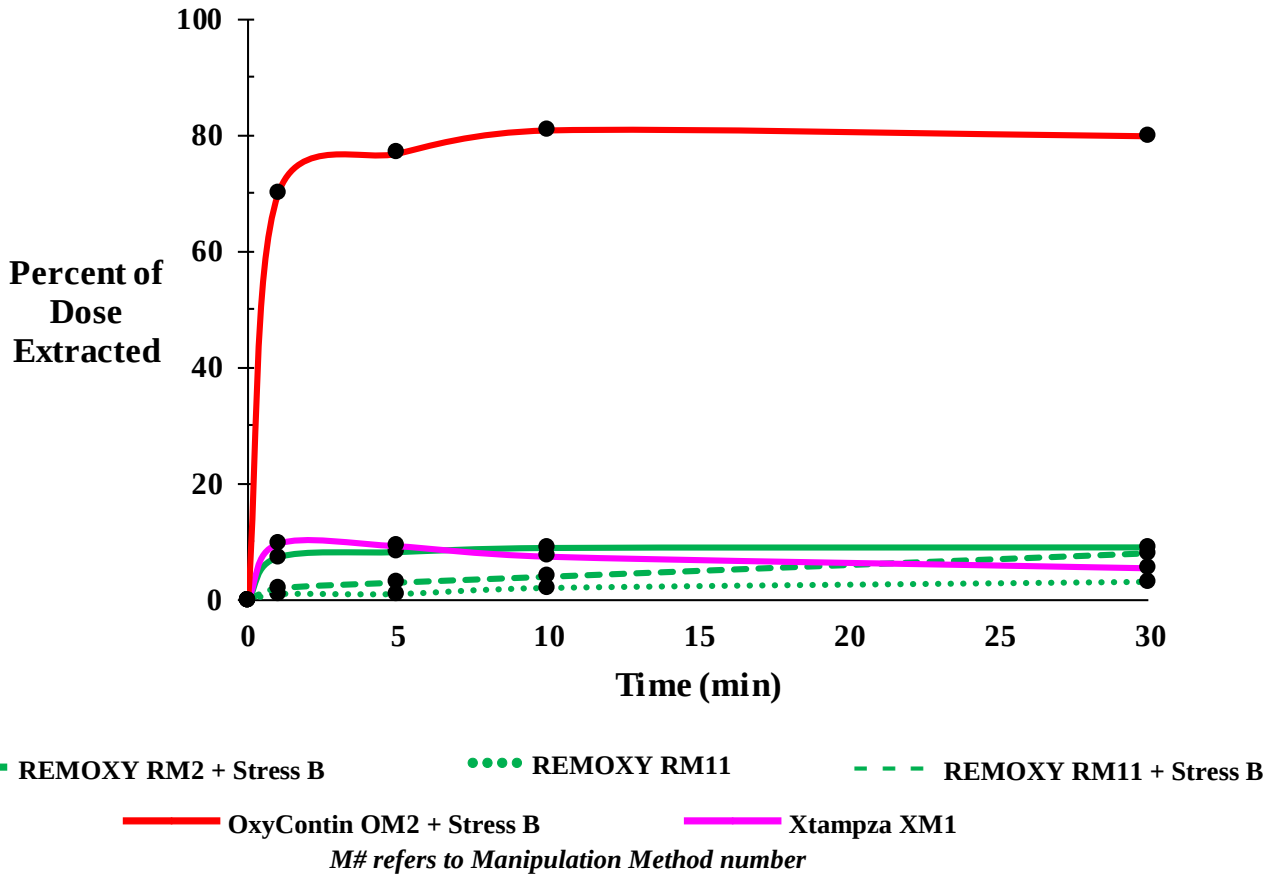
3.1.5.1 Solvent Extraction in Volumes A, B and C

REMOXY ER was manipulated using 2 different methods and Stress B and C, followed by extracted into Volumes A, B and C of solvents S19 – S24 at Temperature B through Temperature F. Extractions in Volume A were limited due to low recoverable extract. Extractable oxycodone was similar in Volume B and Volume C.

Extracted oxycodone was minimal from manipulated REMOXY ER. Stress B had little to no effect on oxycodone extraction from REMOXY ER.

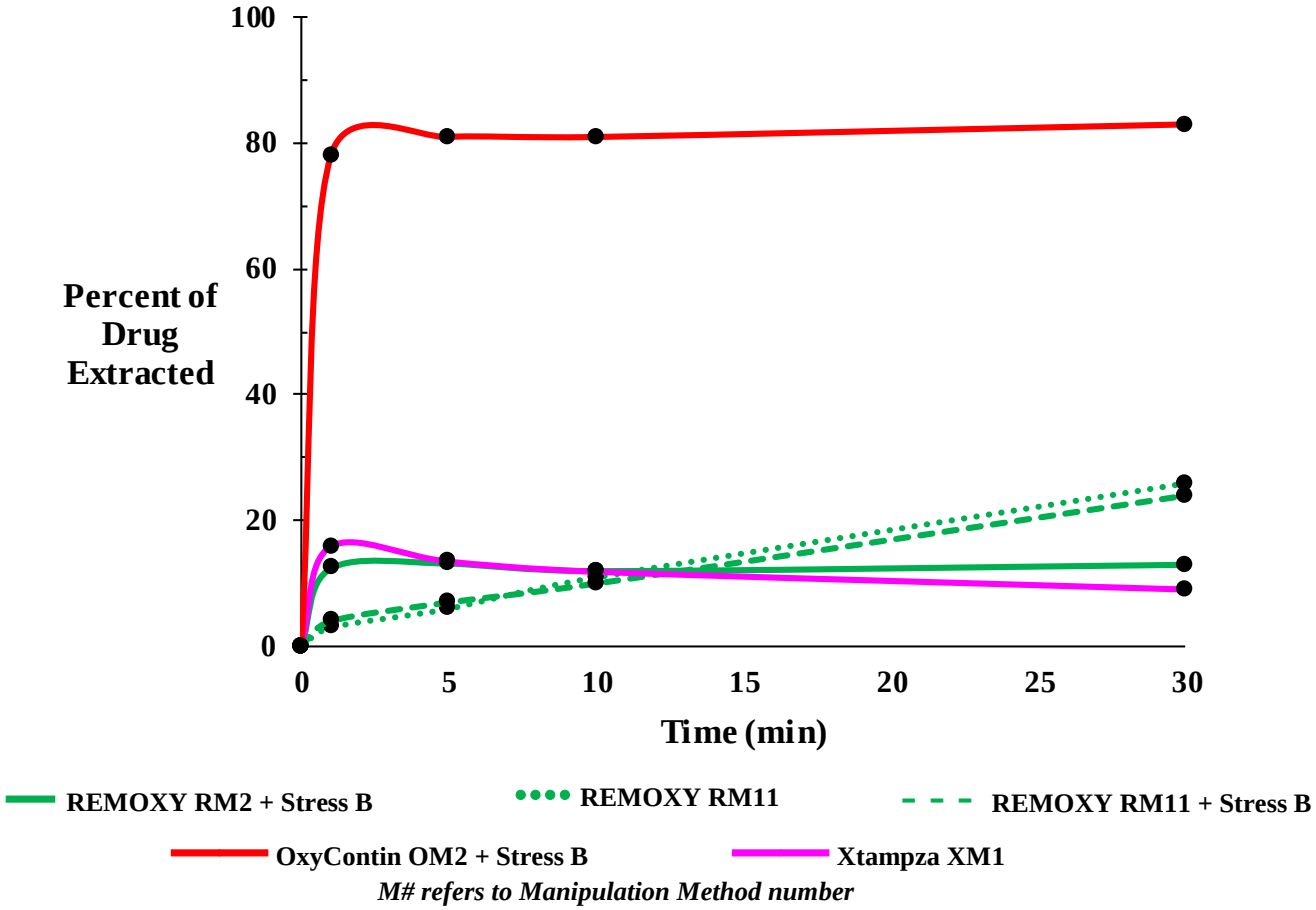
In Solvent S19, less than 10% of the oxycodone dose was extracted from manipulated REMOXY ER and Xtampza ER after 30 minutes, compared to >70% for OxyContin ER within 5 minutes (Figure 8).

Figure 8 IV Abuse: Percent of Oxycodone Dose Extracted from Solvent S19 at Temperature B and Volume C



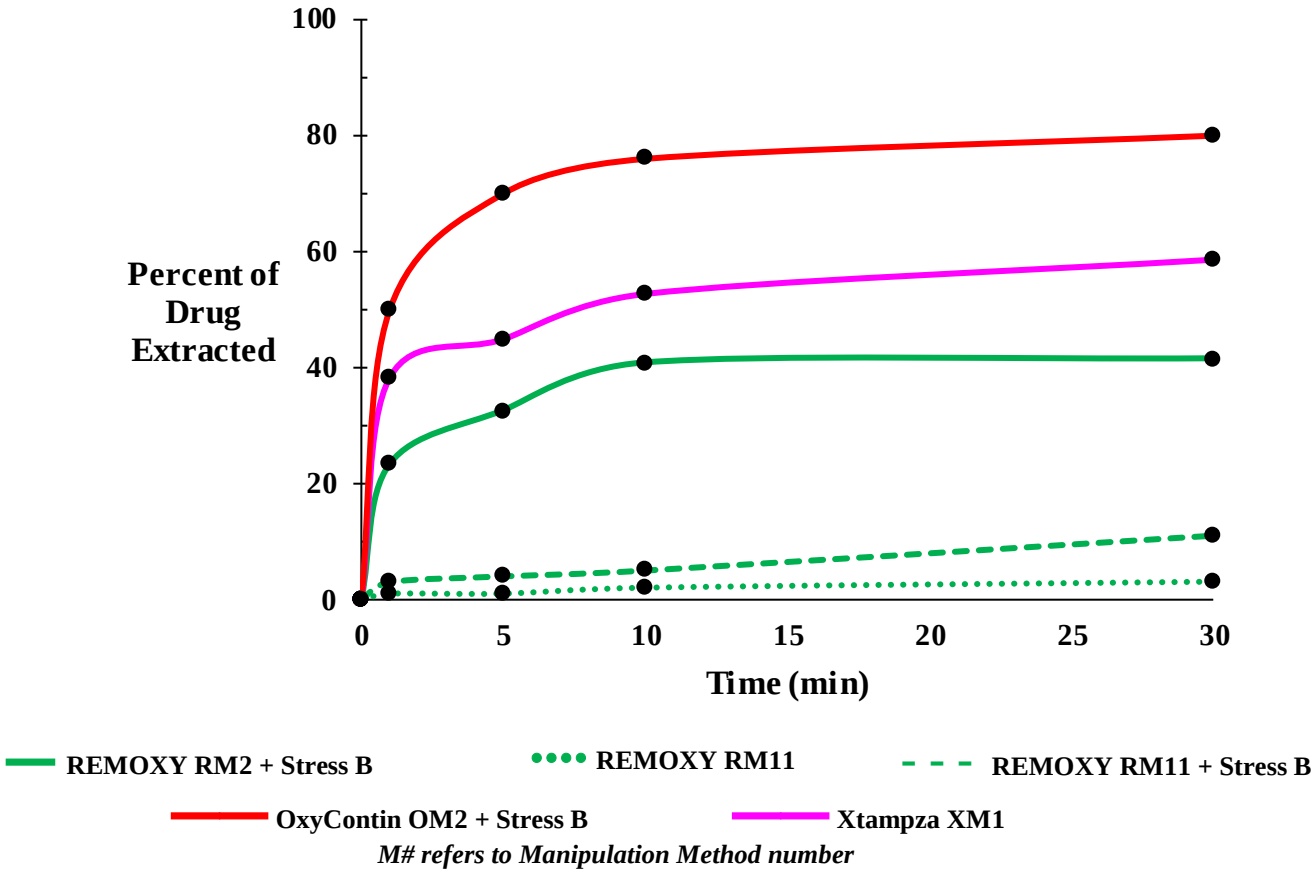
Studies were conducted on the manipulated products in Solvent S19 at Temperature F. At this condition, <30% of the oxycodone dose was extracted from REMOXY ER and Xtampza ER in 30 minutes, compared to >80% for OxyContin ER in 5 minutes (Figure 9).

Figure 9 **IV Abuse: Percent of Oxycodone Dose Extracted from Solvent S19 at Temperature F and Volume C**



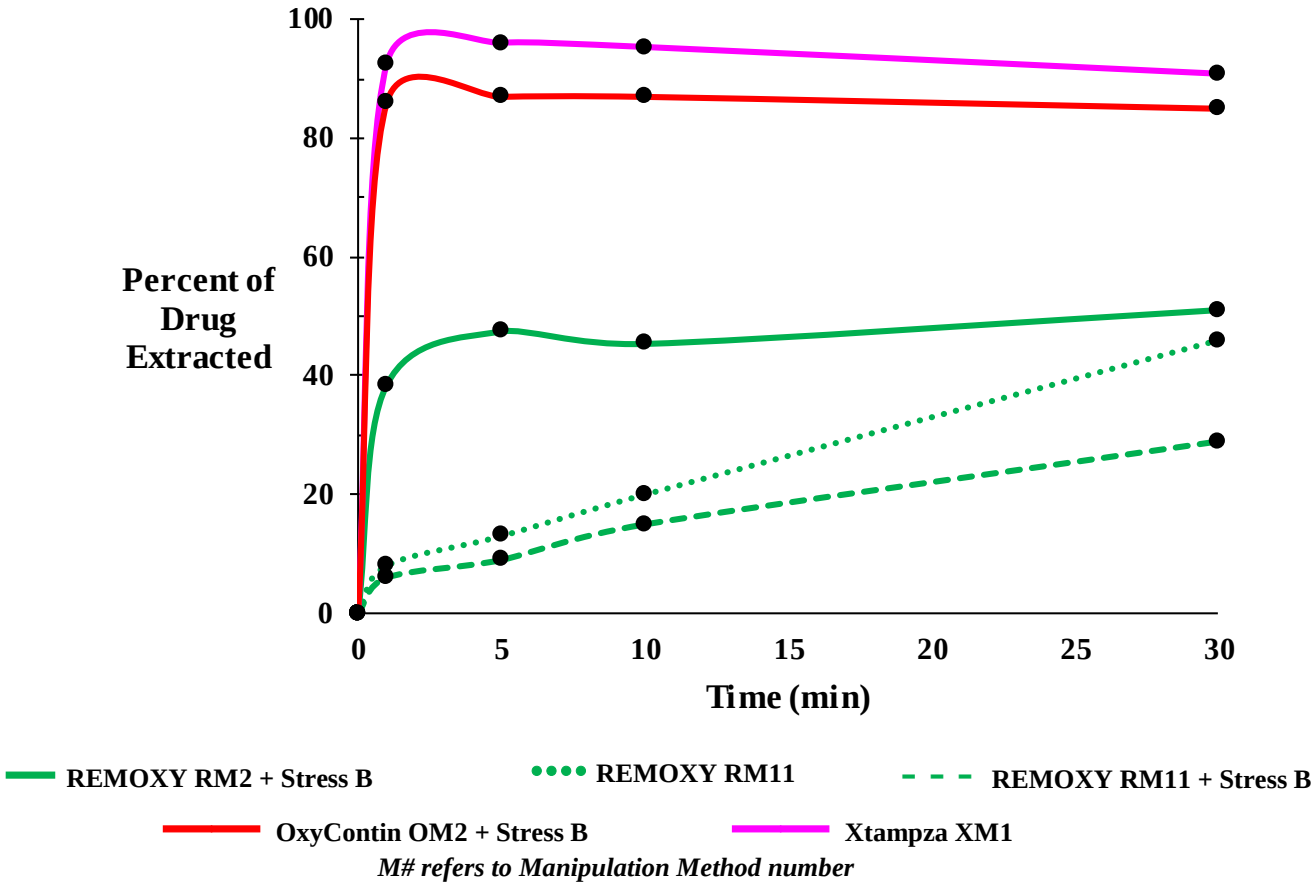
Solvent S20 extracted oxycodone from all three manipulated products. Solvent 20 extracted 41% of the oxycodone dose from REMOXY ER within 30 minutes using method RM2 and Stress B, and <15% using methods RM11, and RM11 and Stress B. Solvent 20 extracted 80% of the dose from manipulated OxyContin ER and 59% from manipulated Xtampza ER within 30 minutes (Figure 10).

Figure 10 IV Abuse: Percent of Oxycodone Dose Extracted from Solvent 20 at Temperature B and Volume C



Solvent S20 at Temperature F extracted oxycodone from manipulated REMOXY ER, OxyContin ER and Xtampza ER (Figure 11). For REMOXY ER, Solvent 20 at Temperature F extracted 51%, 46% and 29% of the dose using methods RM2 and Stress B, RM11, and RM11 and Stress B, respectively, all within 30 minutes. For OxyContin ER, Solvent 20 at Temperature F extracted 85% of the dose using method OM2 in under 5 minutes. For Xtampza ER, Solvent 20 at Temperature F extracted 91% of the dose using method XM1 in under 5 minutes.

Figure 11 IV Abuse: Percent of Oxycodone Dose Extracted from Solvent 20 at Temperature F and Volume C



Oxycodone was extracted more rapidly from OxyContin ER than REMOXY ER under all experimental conditions (Table 3).

Table 3 IV Abuse: Percent of Oxycodone Extracted from Manipulated Drug in Volume C of Solvent (Values >60%)

Temperature	Time	Solvent	REMOXY ER			Xtampza ER	OxyContin ER
			RM2 + Stress B	RM11	RM11 + Stress B	XM1	OM2 + Stress B
B	5 Minutes	S19	8	1	3	9	**77**
		S20	33	1	4	45	**70**
		S21	8	3	3	11	**80**
		S22	—	8	13	—	**71**
		S23	—	1	4	—	**71**
	30 Minutes	S19	9	3	8	6	**80**
		S20	41	3	11	59	**80**
		S21	11	9	11	8	**77**
		S22	—	24	31	—	**81**
		S23	—	3	8	—	**72**
D or F	5 Minutes	S19	13	6	7	13	**81**
		S20	48	13	9	**96**	**87**
		S21	8	3	3	11	**80**
		S22	—	14	16	—	**74**
		S23	—	14	11	—	**83**
	30 Minutes	S19	13	26	24	9	**83**
		S20	51	46	29	**91**	**85**
		S21	13	10	14	9	**82**
		S22	—	57	53	—	**83**
		S23	—	42	33	—	**83**

M# refers to the Manipulation Method number

3.1.5.2 Syringeability and Injectability Evaluations of REMOXY ER

REMOXY ER was evaluated to determine whether its formulation mass could be directly drawn into a syringe and injected for purposes of abuse.

Syringeability refers to the ability of a drug to pass easily through a hypodermic needle on transfer from a vial prior to an injection. Injectability refers to the performance of the formulation during actual injection.

Studies were conducted manually and using specialized instrumentation (dynamic glide force). Syringes with Luer-Lok™ fittings were used with hypodermic needle sizes A through D, at Temperature B and C.

In these evaluations, the sticky, high-viscosity properties of REMOXY ER offered a high level of practical and logistical challenges to syringe loading and direct injection. REMOXY ER could not be delivered through needles A through D at either Temperature B or at Temperature C.

The studies demonstrate REMOXY ER has practical and logistical challenges to syringe loading and direct injection. These properties are expected to meaningfully deter abuse by injection.

3.1.6 Simulated Smoking Abuse

Summary

- Vaporization studies demonstrate REMOXY ER is impractical to abuse by smoking.
- Minimal oxycodone is recovered from smoking REMOXY ER.
- REMOXY ER liberates an irritating vapor when smoked.
- The REMOXY formulation decomposes at high temperatures, resulting in carbonization of the formulation but limited, if any, liberation of oxycodone vapors.
- The amount of oxycodone vaporized was higher, and the rate of release was significantly faster, with OxyContin ER than REMOXY ER under all experimental conditions.
- REMOXY ER has meaningful abuse-deterrent properties compared to OxyContin ER, and data from Xtampza ER.
- Based on study results, REMOXY ER is expected to be less attractive to abusers and meaningfully reduce smoking abuse.

Simulated smoking studies were performed at constant heat at Temperature I. Vapors were continuously collected for Time G. These conditions represent a worst-case scenario: in practice, smokers do not and cannot inhale continuously for Time G. OxyContin ER was tested as a comparator drug using a manipulation method described on the internet.

Less oxycodone was recovered from REMOXY ER compared to OxyContin ER. REMOXY ER was manipulated using three techniques (RM2, RM12 and RM12 plus Stress B). No oxycodone was detected from manipulation methods RM1 and RM12 plus Stress B after Time D. Less than 3% of the oxycodone dose was recovered from REMOXY ER with method RM2. Approximately 9% of the oxycodone dose was recovered from manipulated OxyContin ER within Time D (Table 4).

Xtampza ER was not used as a comparator in these studies; however, according to published data, Xtampza ER releases 34% of its oxycodone dose within Time D, and 51% at a higher temperature (Collegium Pharmaceutical Inc., 2015).

At Temperatures G to I, REMOXY ER releases vapors that irritate the respiratory tract and eyes. The REMOXY ER formulation decomposed at Temperature I, resulting in carbonization of the formulation with limited liberation of oxycodone vapors.

Table 4 Simulated Smoking: Volatilization of Oxycodone from Manipulated REMOXY ER and Manipulated OxyContin ER

	Average % of Dose Recovered (n=3)			
	REMOXY ER			OxyContin ER
Time (min)	RM2	RM12	RM12 + Stress B	OM4
C	0.65	—	—	5.3
D	2.9	< LOD	< LOD	8.8
E	—	—	—	9.5
F	3.8	< LOD	< LOD	10.7
G	9.0	< LOQ	< LOQ	—

M# refers to the Manipulation Method number

The evaluations demonstrate REMOXY ER is unlikely to be abused by smoking. These properties are expected to meaningfully deter abuse by smoking.

3.2 Oral Abuse Potential Study

Summary

- **An oral abuse potential study was conducted to support the development of REMOXY ER.**

- **There were four co-primary endpoints in this study. REMOXY ER met two of the four co-primary endpoints with statistical significance ($p<0.0001$) but did not meet the other two co-primary endpoints.**

- **REMOXY ER did not "dose dump" when chewed vigorously for up to 5 minutes by recreational opioid abusers.**

- **The Sponsor is not seeking a label claim for oral abuse at this time.**

- **Oral Study Results: Pharmacokinetics (PK) Parameters**
  - PK assessments at early time points (0-2 hours, post-dose) were statistically significant in favor of REMOXY ER vs oxycodone IR, suggesting a deterrent effect against a quick euphoric high.
  - The Maximum Concentration (C_{max}) of *chewed* REMOXY ER is similar to the reported C_{max} of *intact* Xtampza ER.
  - The Time to C_{max} (T_{max}) was longer for chewed REMOXY ER (2.2 hours) versus oxycodone IR crushed (1.2 hours).

3.2.1 Oral Abuse Potential (Study B4501016)

This single-center, randomized, double-blind, triple-dummy, placebo and active controlled, single-dose, 4-way crossover study assessed the abuse potential of intact and chewed REMOXY ER compared to oxycodone IR tablets and placebo in non-dependent, recreational opioid users.

The primary objective was to compare the relative abuse potential of chewed REMOXY ER versus crushed oxycodone IR. The study protocol was reviewed in advance by FDA, and their comments were incorporated into the final version of the protocol.

The study included a Screening visit, a Qualification Phase, a Drug Discrimination Phase, a Treatment Phase, and a Follow-up visit.

During the Qualification Phase, subjects underwent a Naloxone Challenge to ensure they were not dependent on opioids. A Drug Discrimination Phase was used to ensure subjects could differentiate between the effects of oxycodone IR 20 mg, 40 mg, and placebo.

During the Treatment Phase, subjects were randomized to 1 of 4 treatment sequences (Table 5).

Table 5 Oral Study (B4501016) Treatment Sequence

Sequence	Treatment
1	REMOXY ER intact
2	REMOXY ER chewed
3	Oxycodone IR crushed in solution
4	Placebo

There were 46 evaluable subjects.

3.2.1.1 Oral Study Results - Pharmacokinetics (PK)

Maximum oxycodone levels (C_{max}) in plasma and the time to C_{max} (i.e., T_{max}) were both obtained directly from concentration-time data.

Chewed REMOXY ER showed no evidence of dose dumping. PK assessments at early time points (0-2 hours, post-dose) were statistically significant in favor of REMOXY ER vs oxycodone IR, suggesting deterrence against a quick euphoric high. (see Figure 12, Table 6 and Table 7).

Figure 12 Oxycodone Concentrations Following Oral Administration (0-2 Hours)

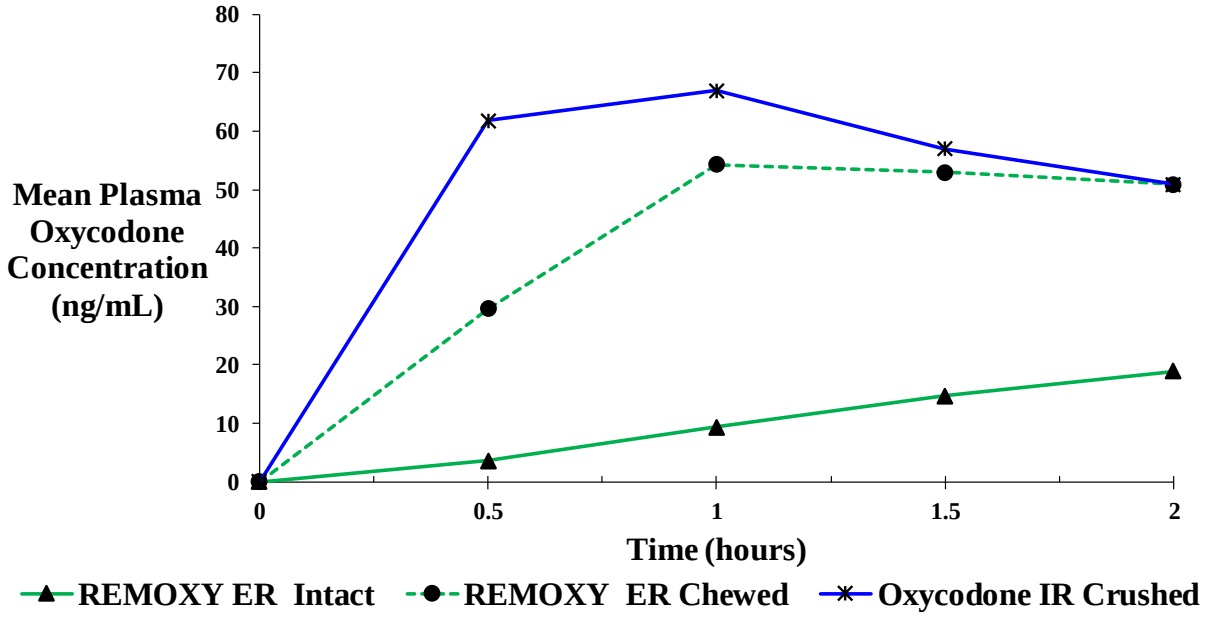


Table 6 AUCs for REMOXY ER Chewed vs Oxycodone IR

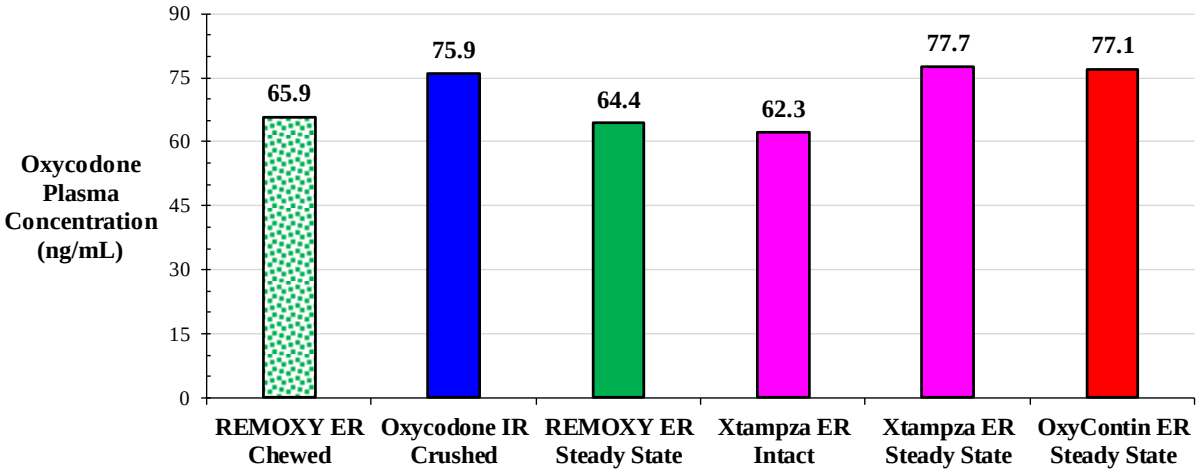
Parameter (ng.h/mL)	REMOXY ER Chewed	Oxycodone IR	p Values
$AUC_{0-0.5}$	1.73	2.65	$p < 0.0001$
AUC_{0-1}	3.21	3.80	$p < 0.0001$
$AUC_{0-1.5}$	3.93	4.31	$p < 0.0001$
AUC_{0-2}	4.33	4.61	$p < 0.0001$

Oxycodone PK parameters across independent studies are shown in Table 7 and Figure 13.

Table 7 Oxycodone PK Parameters Across Independent Studies

	REMOXY ER Chewed[3] Single Dose	**Oxycodone IR** Crushed[4] Single Dose	**REMOXY ER** Intact[5] Multi-Dose Steady State	**Xtampza ER** Intact[6] Single Dose	**Xtampza ER**[7] Multi-Dose Steady State	**OxyContin ER**[8] Multi-Dose Steady State
C_{max} (ng/mL), mean ± SD	65.9 ± 13.8	75.9 ± 19.5	64.4 ± 26.3	62.3 ± 13	77.7 ± 23.6	77.1 ± 17.8
T_{max} (hr), median (range)	2.2 (0.7 – 5.2)	1.2 (0.6 – 5.2)	4.5 (2.5 – 10.0)	4.0 (1.5 – 6)	3.5 (1.0–5.5)	4.5 (1.0–6.5)

Figure 13 Oxycodone C_{max} Across Independent Studies



[3] Source: Study PTI-B4501016
[4] Source: Study PTI-B4501016
[5] Source: Study PTI-821-CX
[6] Source: Study #17 (Collegium Pharmaceutical Inc., 2015)
[7] Source: Study #18 (Collegium Pharmaceutical Inc., 2015)
[8] Source: Study #18 (Collegium Pharmaceutical Inc., 2015)

3.2.1.2 Oral Study Results - Pharmacodynamics (PD)

This study's co-primary primary endpoints consisted of 4 pharmacodynamic parameters:

- Drug Liking $AUE_{0\text{-}2h}$ (Area Under the Effect for two hours post-dose);
- Drug High $AUE_{0\text{-}2h}$;
- Drug Liking, Peak Effect ($E_{max,}$); and
- Drug High, Peak Effect (E_{max})

Chewed REMOXY ER met the co-primary endpoints of Drug Liking AUE_{0-2h} and Drug High AUE_{0-2h} ($p < 0.0001$). REMOXY ER chewed did not meet the co-primary endpoints of Drug Liking E_{max} and Drug High E_{max}.

Results for Drug Liking VAS and Drug High VAS at the early timepoints (0 - 1.5 hours post dose) demonstrated a statistical difference in favor of REMOXY ER chewed relative to oxycodone IR (Figure 14 and Figure 15).

Figure 14 Drug Liking VAS Following Oral Administration

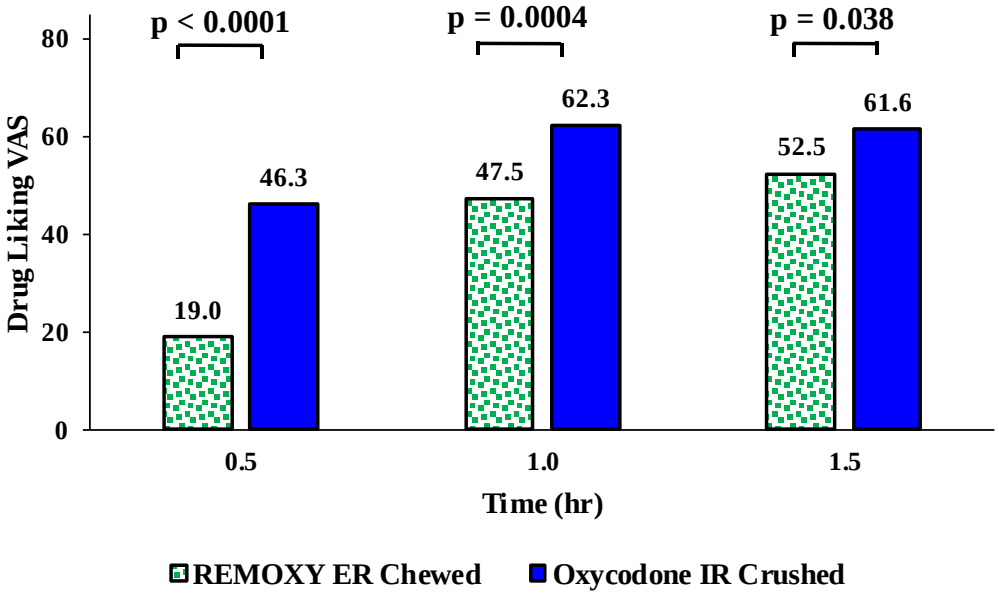
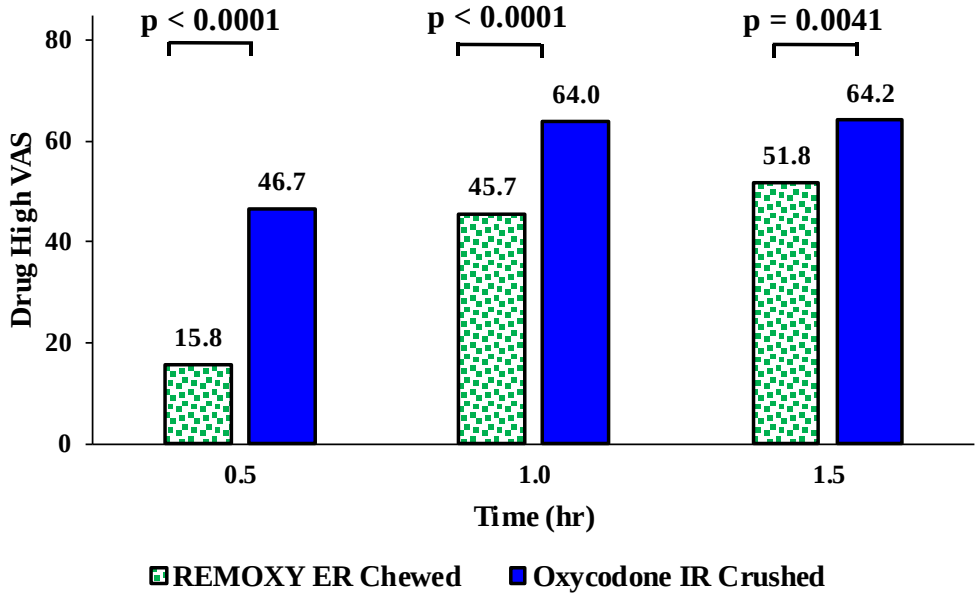


Figure 15 Drug High VAS Following Oral Administration



3.2.1.3 Conclusion

In this oral abuse potential study, REMOXY ER met two of four co-primary endpoints with statistical significance ($p < 0.0001$) but did not meet the other two co-primary endpoints. REMOXY ER showed no evidence of dose dumping. Results demonstrate that REMOXY ER has abuse-deterrent properties at the early time points (0 - 2 hours, post-dose), when abusers seek a quick euphoric high.

3.3 Nasal Administration – Category 2 and 3 Studies

Summary

- A comprehensive Category 2 (PK) and Category 3 (human abuse potential) evaluation of the nasal abuse-deterrent properties of REMOXY ER was conducted.

- Category 2 (PK) nasal data
  - PK data indicate a significant reduction in abuse liability for REMOXY ER, manipulated and intact, relative to ground oxycodone IR and ground OxyContin ER.

- Category 3 (human abuse potential) nasal data
  - The primary endpoint of Drug Liking E_{max} was significantly different in favor of manipulated ($p = 0.0079$) and intact ($p = 0.0073$) REMOXY ER compared to ground oxycodone.
  - Take Drug Again at 12 and 24 hours was significantly different ($p < 0.0001$) in favor of manipulated and intact REMOXY ER compared to ground oxycodone.
  - Other secondary endpoints were significantly different in favor of manipulated and intact REMOXY ER compared to ground oxycodone.
  - Results overall strongly support nasal abuse resistance of REMOXY ER relative to ground oxycodone

- REMOXY ER has meaningful nasal abuse-deterrent properties compared to OxyContin ER.
- Based on study results, REMOXY ER is expected to be less attractive to abusers and meaningfully reduce nasal abuse.

3.3.1 Nasal Abuse Potential of REMOXY ER (Study PTI-821-C08)

A randomized, double-blind, placebo and active-controlled, 4-way crossover study was conducted to assess the nasal abuse potential of REMOXY ER relative to crushed oxycodone IR and placebo in non-dependent, recreational opioid users.

The study included a Screening visit, a Qualification Phase, a Drug Discrimination Phase, a Treatment Phase, and a Follow-up visit. During the Qualification Phase, subjects underwent a Naloxone Challenge to ensure that they were not dependent on opioids. A Drug Discrimination Phase was used to ensure subjects could differentiate between the effects of 40 mg crushed oxycodone IR and matching placebo delivered intranasally.

During the Treatment Phase, subjects were randomized to 1 of 4 treatment sequences (Table 8).

For each of the 4 treatment periods, a double-dummy design was used. Subjects self-administered an intranasal treatment into *each* nostril. One treatment was a viscous liquid and the other was a powder.

Table 8 Nasal Study Treatment Sequence

Sequence	Nostril 1	Nostril 2
1	Manipulated REMOXY ER	Placebo Powder
2	Intact REMOXY ER	Placebo Powder
3	Crushed Oxycodone IR	Placebo Gel
4	Placebo Gel	Placebo Powder

For the crushed oxycodone IR and matching placebo powder, subjects were directed to insufflate the full dose from a glass vial using an applicator. Subjects were directed to self-administer a full dose REMOXY ER or matching placebo gel mass using an applicator that was selected based on a survey of recreational nasal abusers.

The first twenty subjects who completed the blinded 4-way crossover portion of the study also participated in an additional treatment arm in which they intranasally self-administered ground

OxyContin ER 40 mg. OxyContin ER was ground using method OM2. Administration of ground OxyContin ER was unblinded.

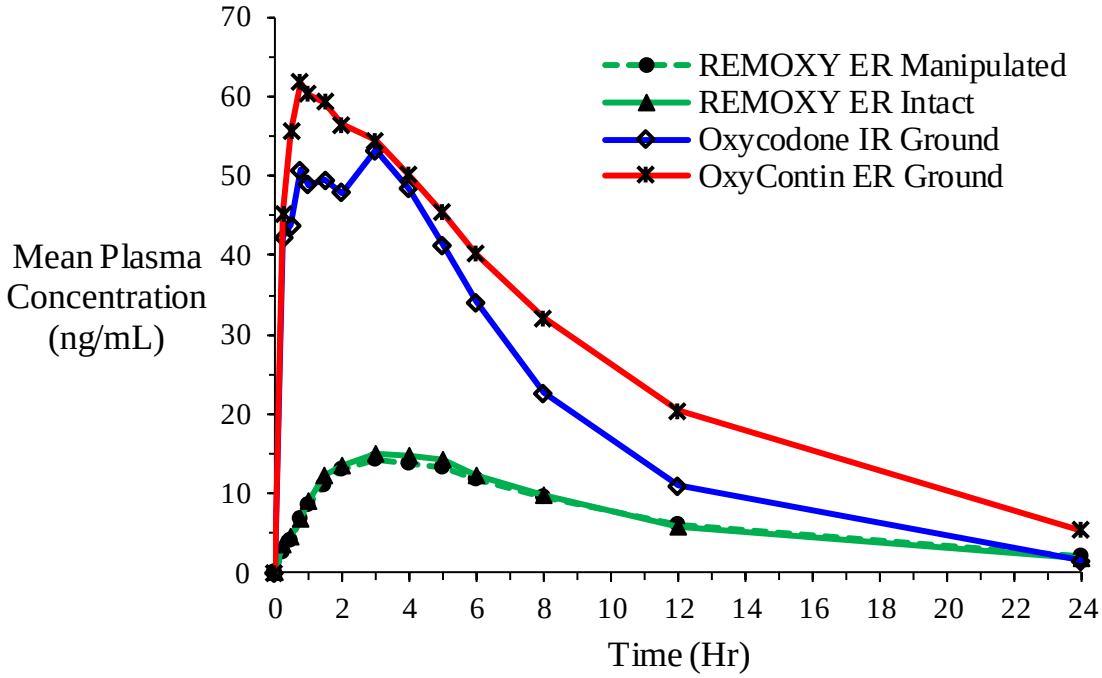
Thirty-eight subjects entered the Treatment Phase and received at least 1 dose of study drug, comprising the safety population. Of these, 36 subjects (94.7%) completed the Treatment Phase of the study and were defined as the completer population.

Category 2 (pharmacokinetic) and Category 3 (human abuse potential) data were both collected in the study. The protocol and statistical analysis plan were both reviewed by FDA and their comments incorporated into the final versions.

3.3.1.1 Category 2 (PK) Assessments and Results

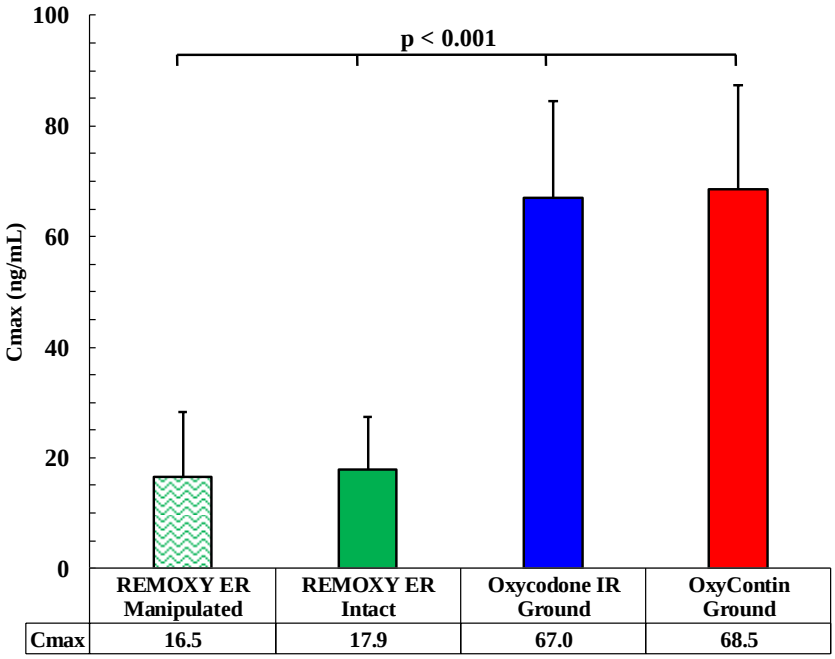
Category 2 assessments included oxycodone exposure after intranasal drug administration. Both intact and manipulated REMOXY ER demonstrated an extended-release profile and lower bioavailability than crushed oxycodone IR and ground OxyContin ER. The oxycodone plasma concentration-time profile for this study is shown in Figure 16.

Figure 16 Oxycodone Concentrations Following Nasal Administration



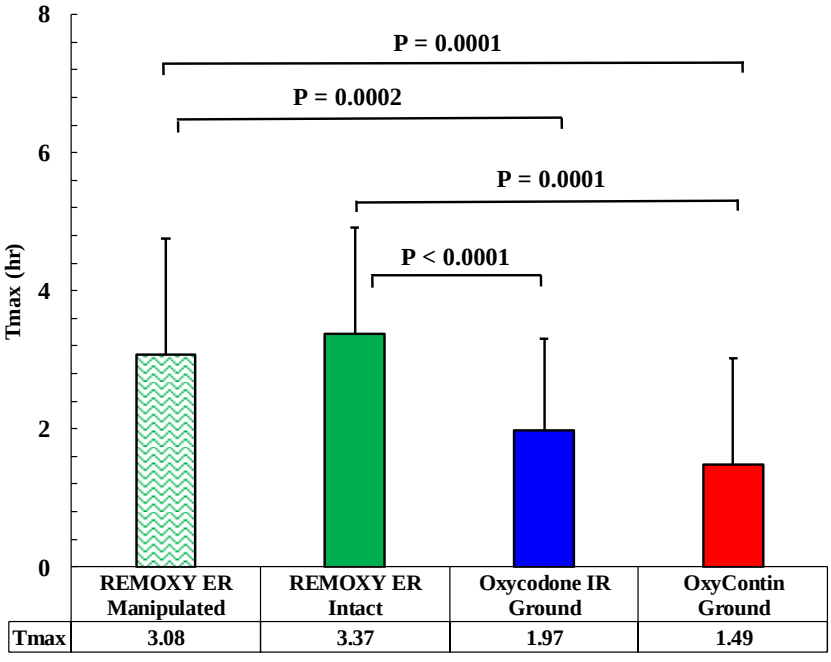
Intranasal peak exposure to oxycodone (C_{max}) was significantly lower ($p < 0.001$) for manipulated ant intact REMOXY ER than crushed oxycodone IR and ground OxyContin ER, regardless of whether REMOXY ER was manipulated or intact (Figure 17).

Figure 17 C_{max} Following Nasal Administration



REMOXY ER, manipulated and intact, both demonstrated a longer T_{max} ($p \leq 0.0002$) compared to ground oxycodone IR and ground OxyContin ER (Figure 18). A longer T_{max} (time to C_{max}) is generally associated with abuse deterrence, since abusers desire the fastest possible euphoric high.

Figure 18 T_{max} Following Nasal Administration



3.3.1.2 Nasal Category 3 (Human Abuse Potential) Pharmacodynamic Assessments

Drug Liking maximum effect (E_{max}) was the primary endpoint for this study and was assessed using a 0-100 bipolar visual analog scale (VAS). A score of 0 is a strong negative response; a score of 50 is a neutral response; and a score of 100 is a strong positive response. Take Drug Again was measured using the same VAS scale and assessed whether a subject would take the drug again if given the opportunity. Subject pupil diameter was measured at set timepoints throughout the study. A drug effects questionnaire measured Drug High, Any Drug Effects, Good Drug Effects, Bad Drug Effects, sick, nausea, sleepy, and dizzy.

Drug Liking E_{max} for REMOXY ER, both manipulated and intact, was significantly lower than for crushed oxycodone IR ($p < 0.001$, Figure 19). Mean Drug Liking over time is provided in Figure 20.

Figure 19 Drug Liking E_{max} Following Nasal Administration

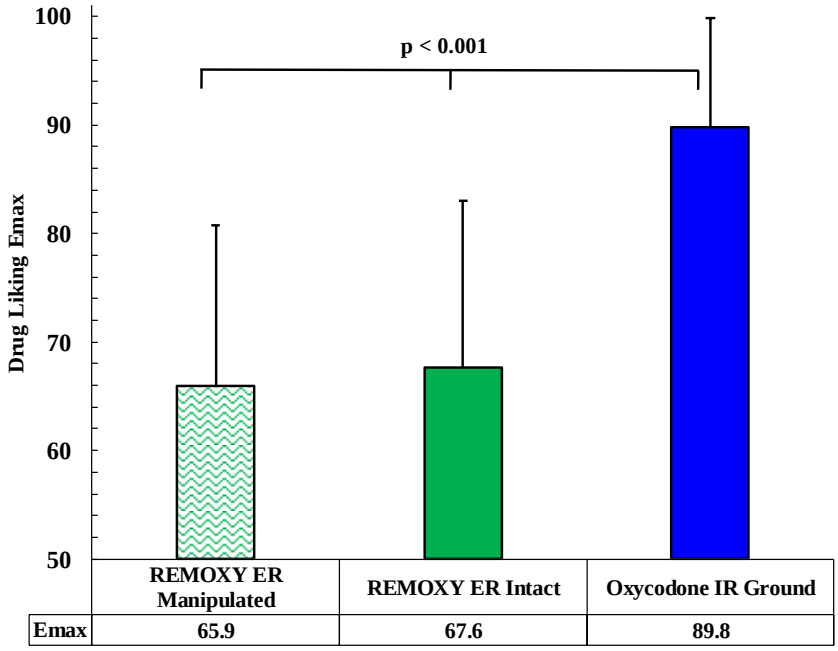
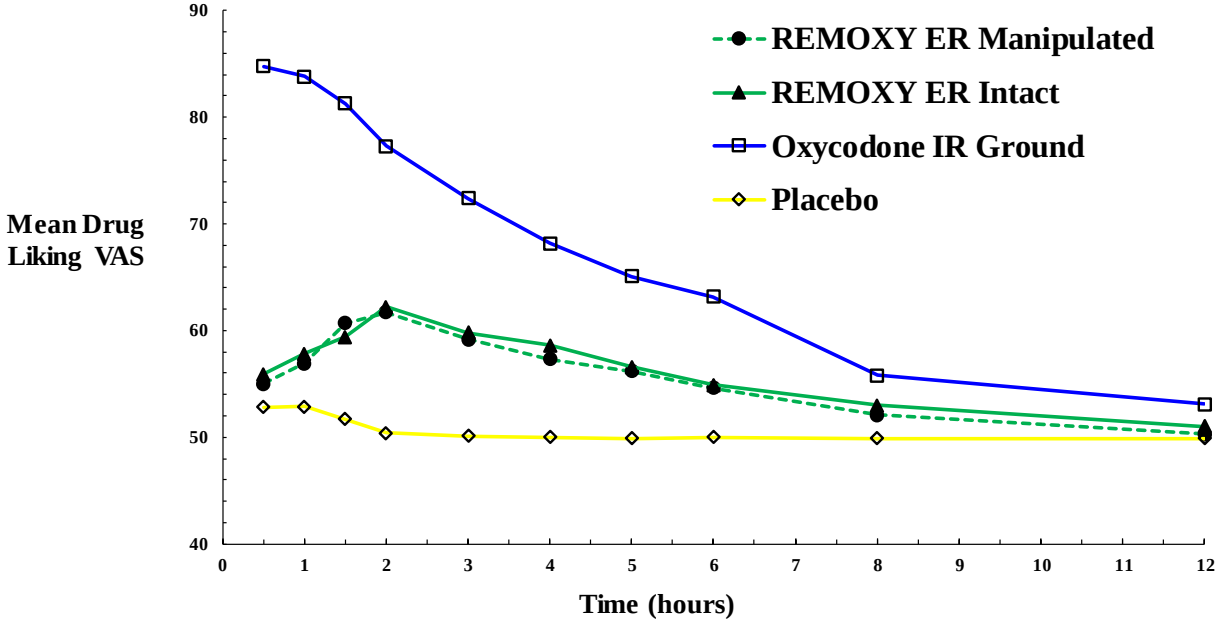
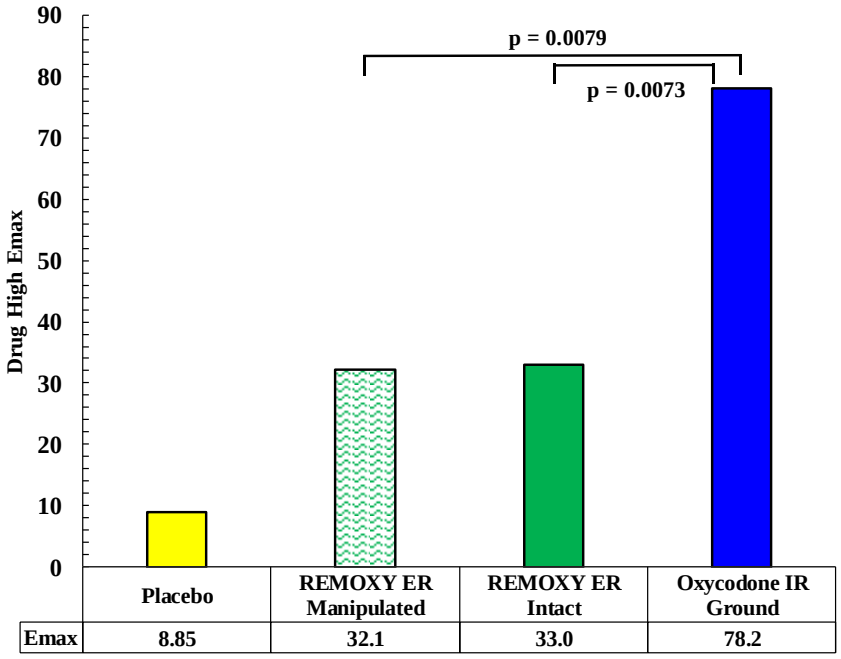


Figure 20 Mean Drug Liking Following Nasal Administration



Drug High E_{max} for manipulated and intact REMOXY ER were significantly lower than crushed oxycodone IR by more than 45% (p = 0.0079) and 40% (p = 0.0073), respectively (Figure 21).

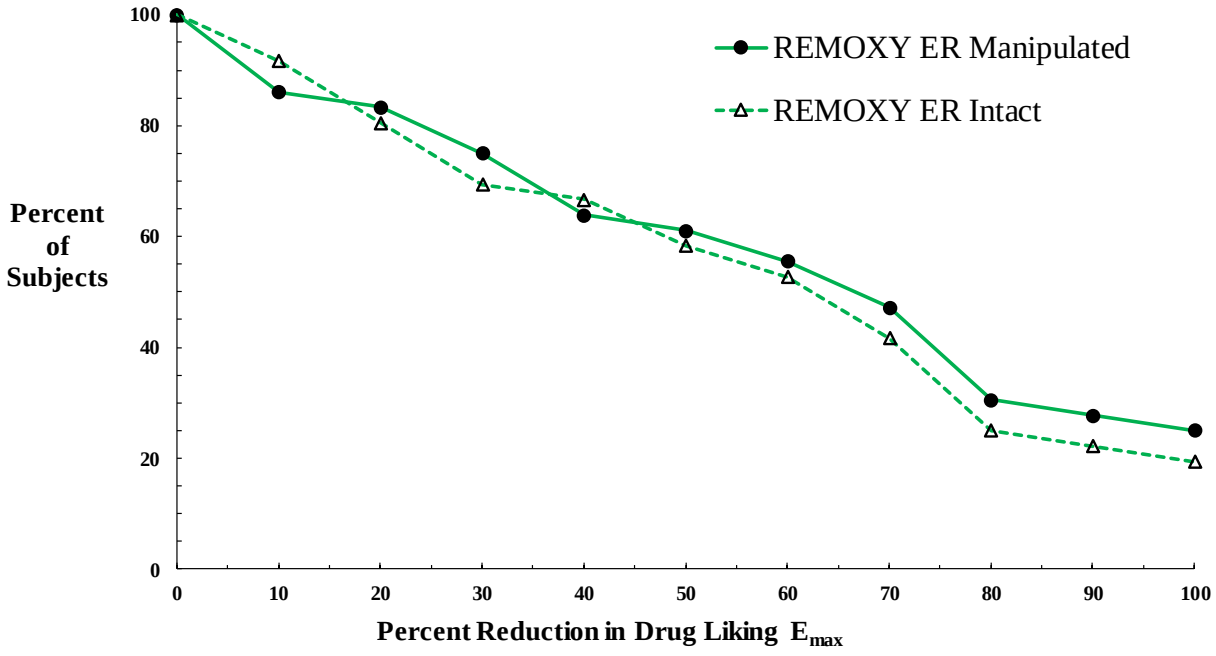
Figure 21 Drug High E_{max} Following Nasal Administration



The primary PD analysis is supported by all AUE parameters. Ground oxycodone IR was significantly more liked than manipulated or intact REMOXY ER at all time points (P<0.0001).

All subjects demonstrated lower Drug Liking E_{max} from manipulated and intact REMOXY ER compared to crushed oxycodone IR (Figure 22).

Figure 22 Responder Analysis: Percent Reduction in Drug Liking E_{max} Following Nasal Administration



Lower abuse potential for REMOXY ER (both manipulated and intact) relative to crushed IR oxycodone was corroborated by results for secondary assessments. Drug Effects Questionnaire, Overall Drug Liking, Take Drug Again Assessment and pupillometry each showed significantly lower E_{max} values for REMOXY ER (both manipulated and intact) relative to crushed IR oxycodone (Table 9).

Table 9 Secondary Parameters of Abuse Potential Following Nasal Administration

Parameter	REMOXY ER Manipulated vs oxycodone IR		REMOXY ER Intact vs oxycodone IR	
	LS Mean Difference (Test-Reference)	Two-sided P-value	LS Mean Difference (Test-Reference)	Two-sided P-value
Overall Drug Liking				
12 hour	-21.71	<.0001	-17.09	<.0001
24 hour	-21.05	<.0001	-17.19	<.0001
Take Drug Again Assessment				
12 hour	-28.39	<.0001	-24.04	<.0001
24 hour	-28.69	<.0001	-22.80	<.0001
Drug Effects Questionnaire				
Dizziness	-7.21	0.0011	-8.11	0.0002
High	-46.11	<.0001	-45.23	<.0001
Nauseous	-9.71	0.0007	-9.57	0.0009
Feeling Sick	-9.25	0.0004	-10.56	<.0001
Sleepiness	-19.18	0.0002	-24.53	<.0001
Any Drug Effects	-45.32	<.0001	-44.35	<.0001
Bad Drug Effects	-7.32	0.0104	-8.32	0.0037
Good Drug Effects	-45.56	<.0001	-44.92	<.0001
Pupil Constriction	-1.57	<.0001	-1.39	<.0001

Take Drug Again VAS scores at 12 hours and 24 hours are shown in Figure 23 and Figure 24.

Figure 23 Take Drug Again 12 Hour Assessment Following Nasal Administration

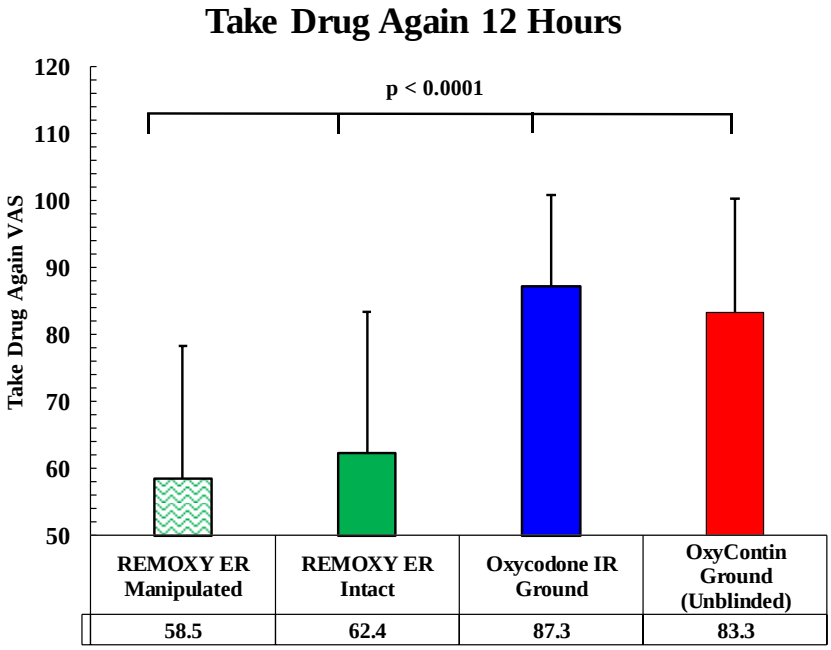
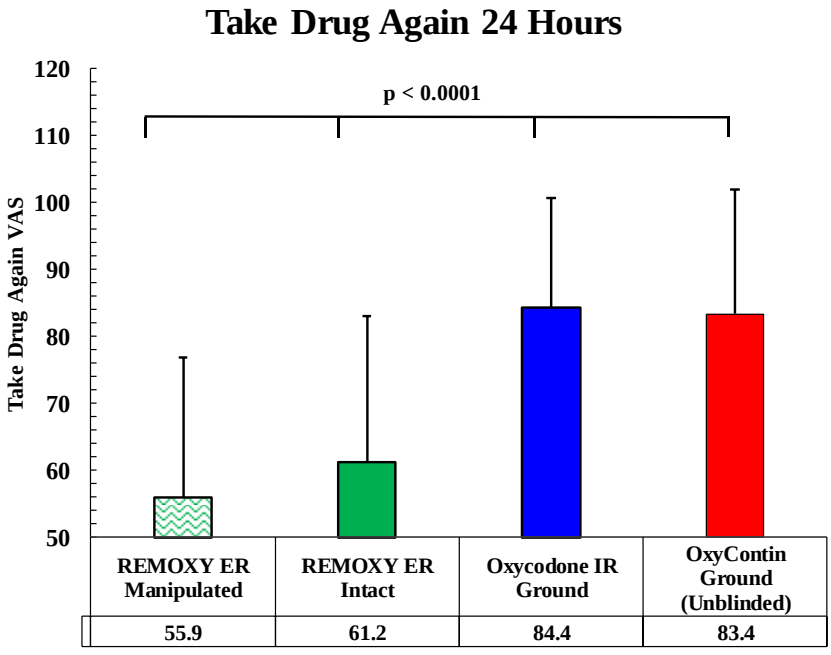


Figure 24 Take Drug Again 24 Hour Assessment Following Nasal Administration



In this study, nasal administration of REMOXY ER was more difficult, unpleasant, and irritating to the nostrils than IR oxycodone. Mean Ease of Snorting/Application scores were lower

(indicating more difficulty) for REMOXY ER gel than the powder treatments. Likewise, mean Pleasantness of Snorting/Application scores were lower (indicating unpleasant) for REMOXY ER gel than the powder treatments. Overall, noxious nasal effects were most pronounced for REMOXY ER gel than the powder treatments and were highest at the earliest time points (i.e., 5 and 15 minutes).

3.3.1.3 Conclusion

Category 2 (PK) and Category 3 (human abuse potential) results demonstrate REMOXY ER has abuse-deterrent properties against nasal administration. Crushed oxycodone IR was significantly more liked by recreational abusers than manipulated or intact REMOXY ER at all time points ($p < 0.0001$).

These properties are expected to meaningfully deter abuse by the nasal route.

4 CLINICAL EVALUATIONS

4.1 Clinical Pharmacology

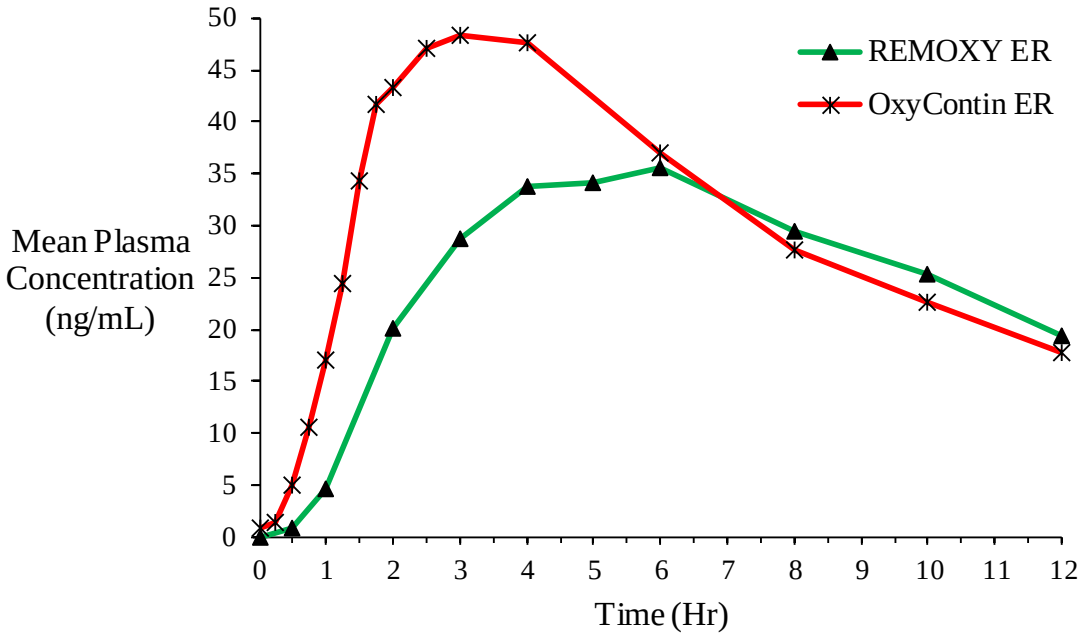
Summary

- Clinical Pharmacology
  - REMOXY ER twice-daily dosing was established by single-dose and steady-state PK studies.
  - Dose-proportionality was established between the 5 mg, 20 mg and 40 mg dosage strengths of REMOXY ER.
  - REMOXY ER does not dose dump when co-administered with 40% alcohol.

4.1.1 Single-Dose Pharmacokinetics (Study B4501035)

A Phase I clinical pharmacology study evaluating single-dose PK effects with REMOXY ER (Study B4501035) and OxyContin ER (PTI-821-CF) is described below. Concentration-time profiles are provided in Figure 25.

Figure 25 Single-Dose PK of REMOXY ER 40 mg and OxyContin ER 40 mg



Results demonstrate a significant difference between the pharmacokinetics of REMOXY ER and OxyContin ER.

4.1.2 Steady-State Study of 40 mg REMOXY ER (Study PTI-821-CX)

PTI-821-CX was a single-center multidose pharmacokinetic study of 40 mg REMOXY ER administered twice-daily (BID). The study enrolled 36 subjects, with 33 subjects completing and included in the PK analysis. Subjects were administered REMOXY ER 40 mg BID for 4 days and one 40 mg dose on Day 5 (9 doses per subject). Each subject was administered an oral dose of naltrexone HCl the evening prior to the first REMOXY ER dose, 30 minutes prior to each dose, and 12 hours after the morning dose of naltrexone HCl given on the final REMOXY ER dosing day.

REMOXY ER achieved a steady-state by Study Day 2 and demonstrated a PK profile consistent with BID performance. Steady-state pharmacokinetic parameters for REMOXY ER 40 mg and publicly reported values for commercial comparators (Collegium Pharmaceutical Inc., 2015) are summarized in Table 10. The REMOXY ER 40 mg plasma concentration-time profile at steady state (Day 5) is shown in Figure 26.

REMOXY ER has a different steady state pharmacokinetic profile than OxyContin ER and Xtampza ER. At steady state, REMOXY ER has a lower C_{max} and significantly less peak to trough fluctuation than OxyContin ER and Xtampza ER.

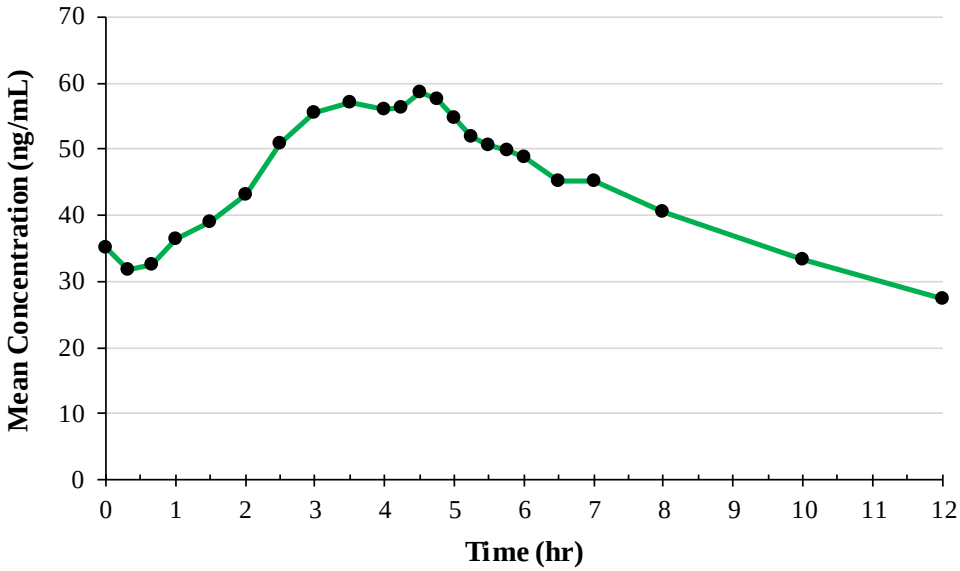
Table 10 Steady-State PK Parameters for REMOXY ER 40 mg and Commercial Comparators

	PTI-821-CX	Collegium Study CP-OXYDET-18 [9]	
PK Parameter	REMOXY ER 40 mg	Xtampza ER 40 mg	OxyContin ER 40 mg
C_{max} (ng/mL), mean ± SD	64.4 ± 26.3	77.7 ± 23.6	77.1 ± 17.8
T_{max} (hr), mean ± SD	4.3 ± 1.5	3.5 * (1.0 - 5.5)	4.5 * (1.0 - 6.5)
C_{min} (ng/mL), mean ± SD	25.6 ± 7.1	21.3 ± 7.1	21.2 ± 6.4
AUC_{tau} (hr*ng/mL), mean ± SD	510.2 ± 156	511 ± 116	532 ± 118
% PTF (12-hour dosing interval) **	87.9 ± 33.3	134 ± 35.8	127 ± 18.9

* T_{max} values are reported as median (range)

** % PTF = Percentage of peak-trough fluctuation within dosing interval

Figure 26 Mean Steady-State Oxycodone Plasma Concentration-Time Profile of REMOXY ER 40 mg (PTI-821-CX at Day 5)

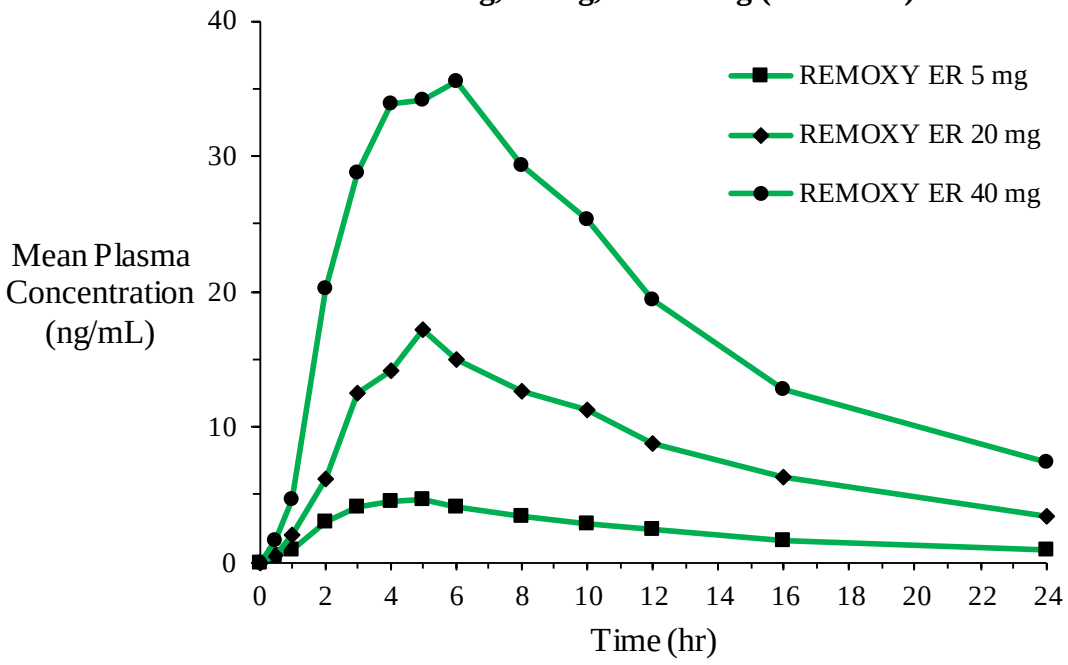


[9] Source: Study #18 (Collegium Pharmaceutical Inc., 2015)

4.1.3 Dose Proportionality (Study B4501035)

The results of a Phase I clinical pharmacology study evaluating dose proportionality of REMOXY ER is described here. Study B4501035 was an open-label, randomized, single-dose, three-way crossover study to evaluate the dose proportionality of 5 mg, 20 mg and 40 mg of REMOXY ER. Dose proportionality was established, indicating linear pharmacokinetics among dosage strengths from 5 mg to 40 mg (Figure 27).

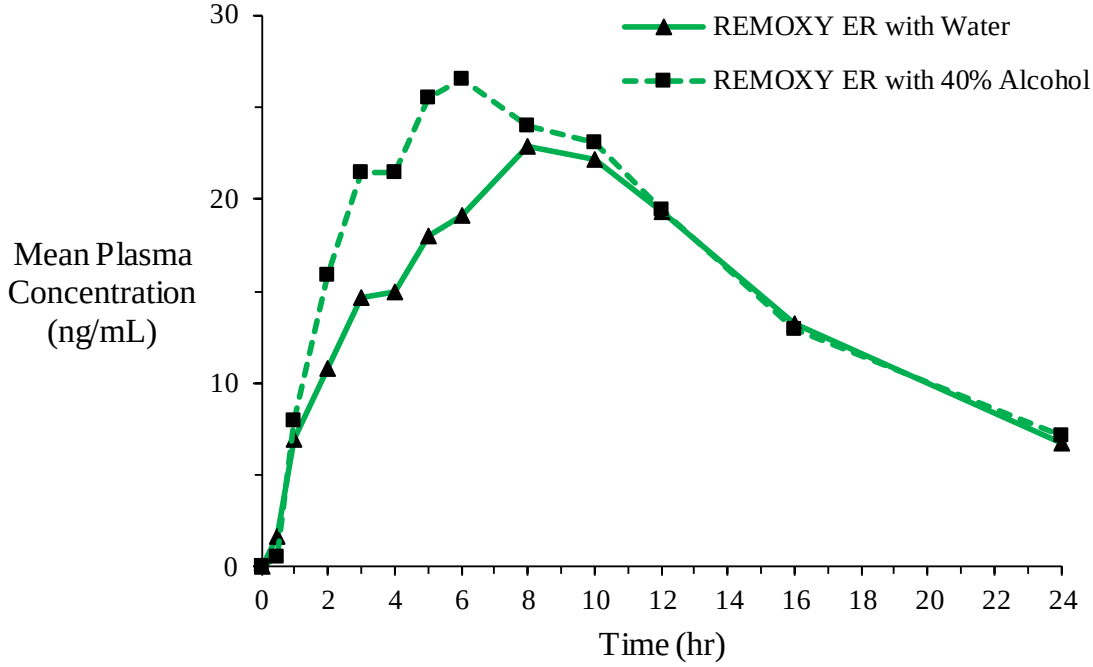
Figure 27 Mean Oxycodone Plasma Concentration-Time Profiles Following Single Oral Doses of REMOXY ER 5 mg, 20 mg, and 40 mg (B4501035)



4.1.4 Effect of Alcohol (Study B4501037)

Study B4501037 was an open-label, single-dose, randomized, 2-period crossover study in 17 healthy volunteers with the primary objective of estimating the effects of consuming 240 mL of 40% ethanol (equivalent to a bottle of wine) in 15 minutes on the bioavailability of oxycodone from 40 mg doses of REMOXY ER under fasted conditions. Results demonstrate a small effect of 40% ethanol on the rate and extent of absorption of oxycodone from REMOXY ER without any indication of dose dumping or loss of the formulation's extended-release characteristics. (Figure 28).

Figure 28 Mean Oxycodone Plasma Concentration-Time Profiles Following Single Oral Doses of REMOXY ER 40 mg with Water and Alcohol (B4501037)



Administration of REMOXY ER 40 mg capsules with 40% ethanol increased AUC_{inf} and C_{max} by approximately 13% and 19%, respectively, and decreased T_{max} from 8 hours to 6 hours, compared to administration with water (Table 11).

Table 11 Oxycodone PK Parameters Following Single Oral Doses of REMOXY ER 40 mg with Water and Alcohol (B4501037)

	REMOXY ER with Water	REMOXY ER with 40% Ethanol
T_{max} (hr), median (range)	8.0 (2.0 - 12.0)	6.00 (2.0 - 12.0)
C_{max} (ng/mL), mean ± SD	25.4 ± 8.7	30.2± 15.7
AUC_{inf} (ng hr/mL), mean ± SD	398 ± 128	445 ± 190

PK parameters are geometric mean (%CV), except for T_{max} = median (range)

4.2 Clinical Efficacy

Summary

- A 12-week, double-blind, placebo-controlled randomized, Phase III Study, (PTI-821-CO) evaluated the analgesic efficacy of REMOXY ER. This study was granted a Special Protocol Assessment (SPA) by the FDA, which is a regulatory process in which concurrence is reached around the adequacy and acceptability of specific, critical elements of overall protocol design, to ensure that the study supports the regulatory requirements for approval.

- Study PTI-821-CO demonstrates that REMOXY ER provides persistent analgesia.

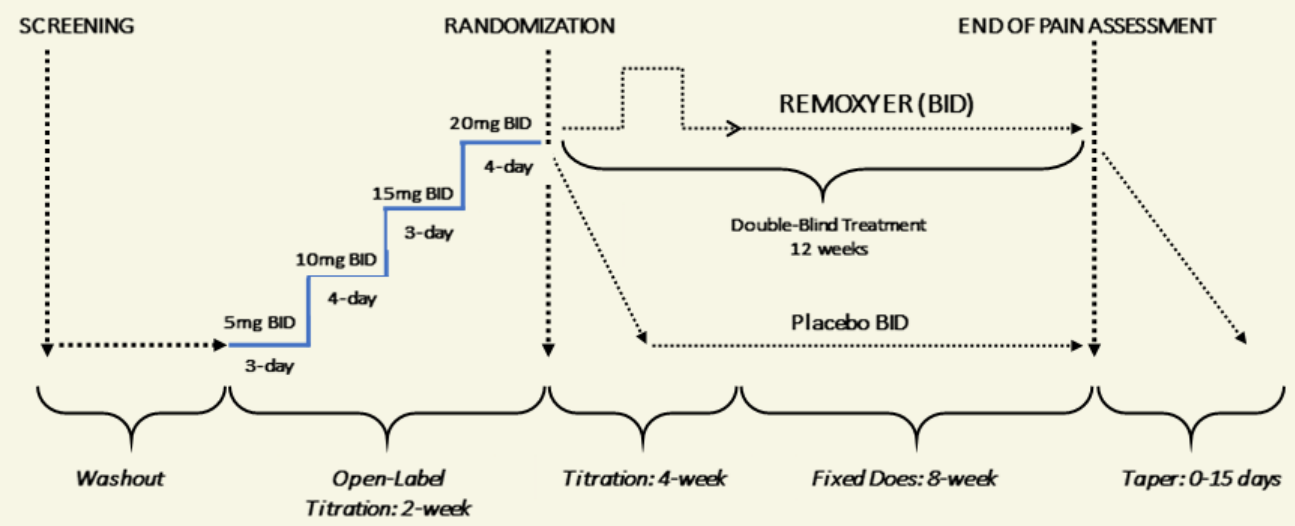
- Study PTI-821-CO met its primary endpoint, demonstrating a statistically significant improvement in pain reduction scores for REMOXY ER versus placebo ($p = 0.007$). All secondary endpoints related to pain were statistically significant.

- Safety and efficacy of REMOXY ER was never questioned in prior regulatory reviews.

4.2.1 Efficacy Study Design (PTI-821-CO)

Study PTI-821-CO was a 12-week, multi-center, randomized, double-blind, placebo-controlled Phase III study conducted in the US. The primary objective was to determine the analgesic efficacy of twice-daily REMOXY ER compared to placebo in adult subjects with moderate-to-severe chronic pain due to osteoarthritis of the hip or knee. A total of 412 patients were randomized to the double-blind portion of the study. The study design is shown in Figure 29.

Figure 29 Schematic Presentation of PTI-821-CO Study Design



Efficacy Study PTI-821-CO consisted of four study periods: washout, open-label titration, double-blind treatment and taper.

Washout. Subjects who met the study eligibility entry criteria stopped taking all pain medication other than acetaminophen during a 4 to 10-day washout period. Subjects used a daily diary to record their overall pain intensity (PI) score, which was measured on an 11-point numerical rating scale where 0 was no pain and 10 was worst pain. If the mean value of the diary PI score over the last two days of the washout period (baseline PI score) was ≥ 5, diary compliance was ≥ 75%, and the subject continued to meet all study entry criteria, subjects entered an open-label titration period.

Open-label Titration. Prior to entry in the open-label titration period, subjects underwent baseline quality of life assessments using the Short Form 12 Question Health Survey (SF-12) and the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index. Subjects were then dose-escalated from REMOXY ER 5 mg to 20 mg twice-daily (BID) during a two-week, open-label period. At the end of a two-week, open-label period, subjects who were able to tolerate REMOXY ER 20 mg BID, and whose diary compliance was ≥ 75%, were randomized and enrolled in the 12-week double-blind, placebo-controlled treatment period.

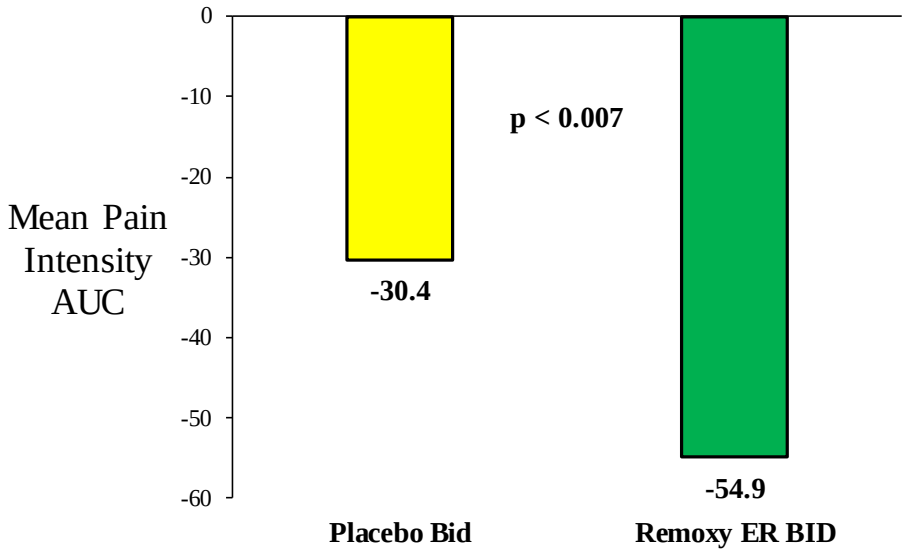
Double-blind Treatment. During the first 4 weeks following the start of the 12-week double-blind treatment period, subjects were permitted to titrate up or down to analgesic effect. The dose at the end of Week 4 was fixed for the remaining eight weeks. Subjects in the placebo group were blindly titrated down from their open-label REMOXY ER dose over the first two weeks of the double-blind treatment period to prevent the emergence of opioid withdrawal symptoms. Subjects returned to the clinic at the end of each week for the first four weeks and then every two weeks for the remainder of the double-blind fixed-dose treatment period. Subjects were required to record their overall PI score before bedtime each day. Once per week, subjects were prompted to record scores for Quality of Analgesia and Global Assessment of Study Medication.

Taper. At the end of the 12-week double-blind treatment period, subjects were gradually tapered off of study medication in a blinded fashion over a period of 0 to 15 days, depending on the final fixed dose and time on study drug, to prevent the emergence of opioid withdrawal symptoms.

4.2.2 Primary Efficacy Results for PTI-821-CO

The primary efficacy endpoint was Area Under the Curve (AUC) for the change in Pain Intensity (PI) scores from pre-randomization to the end of Week 12 during the double-blind treatment period. Results demonstrated a statistically significant difference in favor of REMOXY ER versus the placebo (p = 0.007, Figure 30).

Figure 30 Primary Efficacy Results for PTI-821-CO



This indicates that subjects on REMOXY ER experienced a significantly greater improvement in their pain compared to subjects in the placebo group.

4.2.3 Supportive Efficacy Variables for PTI-821-CO

Supportive efficacy variables included average PI scores by week; Quality of Analgesia by week; Global Assessment of Study Medication by week; Quality of Life Measures (SF-12 Subscale Scores; WOMAC Subscale and Total Scores); and AUC for the change in PI score from baseline.

Quality of Analgesia. Quality of Analgesia was rated significantly better with REMOXY ER than placebo ($p = 0.004$ at week 12) at all weeks after double-blind Week 1.

Global Assessment of Study Medication. REMOXY ER was rated significantly better than placebo ($p = 0.007$ at week 12) in Global Assessment of Study Medication at all weeks after double-blind Week 1.

SF-12 Subscale Scores. At the end of Week-12/early termination visit, a statistically significant ($p = 0.003$) greater improvement in Physical Component Summary (PCS) scores from pre-randomization was observed for subjects receiving REMOXY ER compared to subjects receiving placebo.

WOMAC Osteoarthritis Index. At the end of the 12-week period, a significantly greater improvement in the WOMAC pain sub-scale was observed for the REMOXY ER group ($p = 0.023$) compared to the placebo group.

4.2.4 Phase III Efficacy Conclusions (Study PTI-821-CO)

Efficacy Study PTI-821-CO was designed and conducted under a SPA from the FDA. The primary efficacy endpoint was met with statistical significance ($p = 0.007$). In addition, statistically significant differences in favor of REMOXY ER were observed for all secondary endpoints related

to pain when compared to placebo. Results of this Efficacy Study demonstrate that REMOXY ER provides persistent analgesia.

4.3 Clinical Safety

Summary

- Clinical data demonstrate that REMOXY ER administered in doses from 5 mg to 80 mg twice-daily (BID) for up to 12 months has an overall safety and tolerability profile consistent with other marketed oxycodone ER formulations.
- The clinical safety database for REMOXY ER includes 2,429 unique subjects exposed to REMOXY ER, with 469 subjects receiving REMOXY ER for at least 6 months and 381 subjects receiving REMOXY ER for one year.
- Importantly, no new or unexpected treatment-emergent adverse events were observed.

4.3.1 Exposure to REMOXY ER

Over 2,400 subjects were exposed to REMOXY ER in its development program. Of these, 469 subjects received REMOXY ER for at least 6 months and 381 subjects received REMOXY ER for 12 months.

4.3.2 Safety Results for Efficacy Study (PTI-821-CO)

Adverse events reported during this study are consistent with those typically associated with opioid therapy. Frequent events in the REMOXY ER group (N=205) were constipation, somnolence, nausea, and vomiting. Adverse events occurring from randomization though post-treatment follow-up are summarized in Table 12.

Table 12 Adverse Events Occurring in 5% or More of Patients

	Placebo N (%)	REMOXY ER N (%)
Gastrointestinal Disorders	39 (18.8)	84 (41.0)
Constipation	9 (4.3)	35 (17.1)
Diarrhea	12 (5.8)	9 (4.4)
Nausea	20 (9.7)	41 (20.0)
Vomiting	6 (2.9)	29 (14.1)
Nervous System Disorders	23 (11.1)	45 (22.0)
Dizziness	9 (4.3)	17 (8.3)
Headache	11 (5.3)	10 (4.9)
Somnolence	4 (1.9)	23 (11.2)

4.3.3 Long-Term Safety Study (PTI-821-CM)

The results of a long-term clinical safety study (PTI-821-CM) evaluating REMOXY ER is described here. Exposure in this study consisted of 469 patients for 6 months and 381 patients for one year. Most adverse events were mild or moderate in severity. The overall incidence of adverse events tended to decrease over time. No new events emerged as exposure to REMOXY ER increased to 12 months. Evaluations of clinical laboratory tests, vital signs, and ECGs revealed no clinically significant results, and no trends were noted as REMOXY ER doses and exposure increased.

The most commonly reported AEs during the study (occurring in ≥5% of subjects) were constipation, diarrhea, nausea, vomiting, fatigue, influenza, upper respiratory tract infection, dizziness, headache, somnolence, anxiety, depression, insomnia, hyperhidrosis, pruiritus, and hypertension. Most of these AEs were mild or moderate in severity and are commonly associated with opioid use.

Opioid and non-opioid related AEs occurring in ≥ 5% of subjects (N = 823) are shown in Table 13 and Table 14, respectively.

Table 13 Opioid Related Adverse Events in ≥5% of Subjects

	REMOXY ER N (%)
Number of Subjects reporting any AE	678 (82.4)
Constipation	257 (31.2)
Nausea	228 (27.7)
Somnolence	137 (16.6)
Vomiting	116 (14.1)
Dizziness	89 (10.8)
Pruritus	75 (9.1)

Table 14 Non-opioid Related Adverse Events in ≥5% of Subjects

	REMOXY ER N (%)
Number of Subjects reporting any AE	678 (82.4)
Headache	110 (13.4)
Insomnia	101 (12.3)
Diarrhea	97 (11.8)
Fatigue	56 (6.8)
Hypertension	54 (6.6)
Depression	51 (6.2)
Hyperhidrosis	48 (5.8)
Influenza	47 (5.7)
Anxiety	45 (5.5)
Upper Respiratory Tract Infection	43 (5.2)

REMOXY ER administered BID for up to 12 months did not have any clinically meaningful effects on vital signs, laboratory safety tests, physical examinations or ECGs.

Based on these results, long-term treatment with REMOXY ER at doses ranging from 5 mg to 80 mg BID was safe and well-tolerated.

4.3.4 Safety Conclusions

In summary, based on clinical results REMOXY ER is safe and well-tolerated. Most treatment-emergent adverse events reported by 2,429 subjects receiving at least one dose of REMOXY ER are commonly associated with ER opioid use. Most were mild or moderate in severity, the overall incidence of adverse events tended to decrease over time and no new events emerged as exposure to REMOXY ER increased to 12 months. Evaluations of clinical laboratory tests, vital signs, and ECGs revealed no clinically significant results.

5 BENEFIT / RISK ASSESSMENT

A variety of therapies are available to treat pain, including non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, antiepileptic drugs, antidepressants, and local and regional anesthetics. Opioids, such as extended-release (ER) formulations of oxycodone, are an alternative to treat long-term severe pain and have been approved by FDA for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

ER formulations of oxycodone have advantages over immediate-release (IR) formulations by providing less frequent dosing intervals and improved pain control. However, extended release formulations contain higher dosage levels of oxycodone and, thus, have an inherent risk of intentional/unintentional misuse, abuse, or diversion if the extended release mechanism can be easily disrupted by common methods of physical manipulation or chemical challenge. Administration following disruption of the time-release mechanism results in an immediate surge in oxycodone blood levels, providing abusers with an immediate, and dangerous, euphoric high. The intensity of the high is directly related to the rate of absorption and peak exposure of the opioids. The rapid release of a substantial amount of oxycodone can lead to overdose and death,

especially in individuals who are not opioid dependent. The euphoric high effect is reinforcing and can lead to dependence and addiction. Although advancements have been made in developing oxycodone formulations intended to deter abuse, oxycodone abuse continues to be a significant public health problem. Oral abuse is the most prevalent form of abuse, however alternative routes of abuse such as injection, inhalation (smoking) or nasal administration carry increased risks of disease, infection or death.

REMOXY ER is an extended-release, high viscosity, gel formulation of micronized oxycodone base filled into a capsule and has been specifically designed to manage long-term severe pain. The formulation resists common methods of physical or chemical challenge that could result in rapid release of oxycodone leading to abuse and addiction.

5.1 Benefits of REMOXY ER

The analgesic efficacy of oxycodone in the treatment of chronic pain is well established in the literature. The analgesic efficacy of REMOXY ER was confirmed in a pivotal, 12-week randomized, double-blind, placebo-controlled Phase III study, designed and conducted under a SPA from the FDA, in subjects with moderate to severe chronic pain due to osteoarthritis of the hip or knee. The study's primary efficacy endpoint was met with statistical significance ($p = 0.007$). In addition, statistically significant differences in favor of REMOXY ER were observed for all secondary endpoints related to pain when compared to placebo. Results of the Efficacy Study demonstrates that REMOXY ER provides persistent analgesia.

The long-term safety and efficacy of REMOXY ER is supported by the results from a long-term open-label study in subjects with moderate to severe chronic pain with up to 12 months treatment with REMOXY ER. The overall clinical safety database for REMOXY ER includes 2,429 unique individuals exposed to REMOXY ER. Importantly, no new or unexpected treatment-emergent adverse events were observed in the long-term clinical safety program with REMOXY ER.

Abuse and misuse of prescription opioids are a major public health concern. The two currently marketed ER oxycodone products in the US both employ solid formulation technologies that can

be manipulated into low-volume liquids for injection, ingestion or smoking. This converts the drug product into an immediate-release form ready for abuse, and may enable oral, nasal, smoking and IV abuse. Tampering with an ER formulation to enable abuse by non-oral routes is common (Vietri et al., 2014). Furthermore, evidence suggests that tampering and abuse by non-oral routes of administration is associated with more severe negative health consequences when overdosed and with greater healthcare utilization (Katz et al., 2011).

A significant benefit of REMOXY ER is that it has properties intended to deter common methods of abuse and prevent rapid release of oxycodone while maintaining the required release characteristics to provide around-the-clock analgesia.

Category 1 (lab) studies simulated a broad range of physicochemical manipulations associated with oral, injection, and inhalation/smoking routes of abuse. Results demonstrate that REMOXY ER has properties to deter abuse relative to OxyContin ER and Xtampza ER.

Results of Category 1 (lab) extraction studies also demonstrate that oxycodone extracted from *manipulated* REMOXY ER is often less than *intact* OxyContin. The quantity of oxycodone extracted with various solvents and manipulations show that OxyContin's extended-release features can be rapidly defeated and, under many simulated conditions of abuse, more closely resemble an IR formulation than an ER formulation.

Results of a combined Category 2 (PK) and Category 3 (human abuse potential) intranasal study demonstrate that both manipulated and intact REMOXY ER Drug Liking scores are significantly lower relative to crushed IR oxycodone. In this study, secondary endpoints of Overall Drug Liking, Take Drug Again, and elements of the Drug Effects Questionnaire were also statistically significant in favor of REMOXY ER for all comparisons. PK results demonstrated significantly lower values for REMOXY ER compared to both crushed oxycodone IR and ground OxyContin ER. These intranasal results support a lower nasal abuse liability for REMOXY ER compared to both crushed oxycodone IR and ground OxyContin ER.

In a Category 3 (human abuse potential) oral study, data from the early timepoints, including the co-primary endpoints of Drug Liking $AUE_{0\text{-}2h}$ and Drug High $AUE_{0\text{-}2h}$, as well as early measurements of pupil diameter, were statistically significant in favor of REMOXY ER compared to oxycodone IR. Consistent with the PD assessment, PK assessments showed statistically significant lower oxycodone levels for REMOXY ER at early timepoints (0-2 hours), when abusers desire a quick euphoric high. Published data also show that *chewed* REMOXY ER has a similar Cmax to *intact* Xtampza ER (Collegium Pharmaceutical Inc., 2015).

The totality of the data demonstrate that REMOXY ER's abuse-deterrent properties are expected to meaningfully deter abuse and, consistent with the FDA Guidance, are not expected to completely prevent abuse.

5.2 Risks of REMOXY ER

The risks of REMOXY ER can be characterized as the known risks of ER oxycodone. The adverse effect profile of REMOXY ER is consistent with that observed with other oxycodone drug products. Clinical management of oxycodone-related risks includes individualized treatment of patients using a progressive plan of pain management. Health care professionals should follow appropriate principles of pain management including careful assessment and ongoing monitoring. It is critical to adjust the dosing regimen for each patient individually, taking into consideration a patient's prior analgesic treatment experience. Chronic use of oxycodone may be associated with the development of tolerance, physical dependence and addiction. Tolerance is defined as the diminution in the effect of the drug on repeated administration. Physical dependence is defined as an altered physiological state brought about by repeated administration of a drug, which necessitates continued use of the drug to prevent the appearance of characteristic signs and symptoms (i.e., withdrawal). Addiction refers to craving and compulsive use of the drug (Yaksh & Wallace, 2015). The abrupt withdrawal of opioid treatment is known to precipitate withdrawal. The opioid withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis.

In summary, the adverse drug events reported in the REMOXY ER development program support a risk profile that is comparable to other ER oxycodone products.

5.3 Risk Evaluation and Mitigation Strategy (REMS)

REMOXY ER will be a Schedule II drug under the Controlled Substances Act. The drug product will have class labeling appropriate of an ER/LA opioid analgesic, as well as a Medication Guide for patients. REMOXY ER will also be subject to the ER/LA Opioid Analgesic REMS. The Sponsor is committed to conducting pharmacovigilance and surveillance activities to monitor for safety issues during post-authorization use, including abuse, misuse, addiction, and overdose. The goal of the ER/LA Opioid Analgesic REMS (U.S. Food and Drug Administration, 2018) is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics, while maintaining patient access to important pain medication. Adverse outcomes of concern include addiction, unintentional overdose, and death. Sponsors of ER/LA opioid analgesic medications collaborated with the FDA to develop and implement the REMS, which is focused on educating healthcare professionals through accredited Continuing Medical Education/Continuing Education (CE) to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics. The content of REMS-compliant CE activities is substantially based on the FDA Blueprint for Prescriber Education for ER and Long-acting Opioid Analgesic, which covers topics related to assessment and counseling of patients, initiation, dose modification, ongoing management and discontinuation of therapy, as well as general information about the class of ER/LA opioid analgesics and specific characteristics of medications within the class. The REMS also include annual distribution of "Dear Healthcare Provider" letters to new DEA-registered prescribers (Schedule II or III prescribers), a Patient Counseling Document, a website, and a call center. The REMS includes the preparation of annual assessment reports in order to monitor progress of the REMS and inform on any changes necessary to improve the program. The Sponsor currently has Observer Status within the industry REMS group and will participate as a full voting member upon approval of REMOXY ER.

In addition to surveillance of spontaneous reports of adverse events, the Sponsor will also employ a strategy of active surveillance for abuse, overdose, tampering and diversion of REMOXY ER

and other ER oxycodone by regular, periodic monitoring of data collected from multiple sources: patients entering a national network of methadone treatment and private substance abuse treatment centers; poison centers covering over 92% of the US population; multi-annual online surveys of nationally representative samples of college-age students; monitoring of electronic posts to social media such as web sites, online blogs, web forums and other internet sites; and a national network of drug diversion investigators representing municipal police departments, multi-jurisdictional drug task forces, county sheriffs' departments and other pharmaceutical boards and departments of health.

In summary, the Sponsor is committed to a program of risk mitigation, communication, and monitoring activities via the ER/LA opioid analgesics REMS and post-marketing pharmacovigilance and surveillance activities to monitor for safety issues during post-authorization use, including abuse, misuse, addiction, and overdose. In combining the abuse-deterrent properties of REMOXY ER with these programs, the Sponsor aims to positively impact this public health epidemic of abuse and misuse of prescription opioids.

5.4 Benefit / Risk Balance

REMOXY ER has demonstrated a favorable benefit/risk balance:

- The active pharmaceutical ingredient in REMOXY ER is marketed in the US. The analgesic efficacy of oxycodone in the treatment of chronic pain is well established.

- The nonclinical testing program affirms the safety of the excipients in the REMOXY ER formulation, as well as the safety of the complete final formulation itself.

- The safety profile of REMOXY ER is consistent with other ER oxycodone drugs. No new or unexpected treatment-emergent adverse events were observed in the long-term clinical safety program with REMOXY ER.

- The analgesic efficacy of REMOXY ER was confirmed in a pivotal 12-week randomized, double-blind, placebo-controlled study in subjects with moderate to severe chronic pain due to osteoarthritis of the hip or knee.

- If approved, REMOXY ER 5 mg would be the lowest ER titration starting dose for opioid-naive patients with a need to safely initiate opioid therapy.

- Category 1 (lab) studies demonstrate that REMOXY ER has meaningful abuse-deterrent properties compared to both marketed ER oxycodone drugs.

- A Category 2 (PK) study in recreational opioid abusers confirmed REMOXY ER's nasal abuse-deterrent properties relative to oxycodone IR and OxyContin ER.

- A Category 3 (human abuse potential) study in recreational opioid abusers confirmed REMOXY ER's nasal abuse-deterrent properties relative to oxycodone IR.

- Results from the totality of these studies indicate REMOXY ER can be expected to meaningfully deter abuse, and, consistent with FDA Guidance, is not expected to completely prevent abuse.

6 CONCLUSION

REMOXY ER has a favorable benefit/risk profile in the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. REMOXY ER has robust evidence to support labeling as an analgesic with properties that can be expected to meaningfully deter the injection, snorting and smoking routes of abuse.

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