

# The Abuse Potential of Remoxy®, an Extended-Release Formulation of Oxycodone, Compared With Immediate- and Extended-Release Oxycodone

Beatrice Setnik, PhD,<sup>1</sup> Carl L. Roland, PharmD,<sup>1</sup> Jody M. Cleveland, MS,<sup>1</sup> Lynn Webster<sup>2</sup>

<sup>1</sup>Pfizer Inc, Cary, NC; <sup>2</sup>Lifetree Clinical Research and Pain Clinic, Salt Lake City, UT

## Introduction

- The abuse of prescription opioids has increased during recent decades.
  - Nearly 12 million persons (4.8%) in the United States  $\geq 12$  years of age reported non-medical use of prescription pain relievers in the past year.<sup>1</sup>
- Extended-release (ER) opioid formulations have been developed to allow slow release of drug to manage chronic pain.<sup>2</sup>
- Current ER formulations are a frequent target of drug abusers because of the ease of tampering to release the full opioid dose.<sup>3</sup>
  - Tampering methods include chewing, crushing and snorting, and dissolving and injecting.<sup>4</sup>
- Remoxy® (King Pharmaceuticals Inc, Bristol, TN, which was acquired by Pfizer Inc in March 2011) is a water-insoluble, highly viscous, oral formulation of ER oxycodone currently in development for the treatment of moderate to severe chronic pain.
- Limited oxycodone release has been demonstrated following manipulation, including crushing and extraction in alcohol and water<sup>5</sup>; however, the true impact that the Remoxy formulation may have on reducing misuse and abuse associated with tampering cannot be established until it is evaluated in the community at large.
- Abuse potential studies provide an opportunity to predict the likelihood of abuse by recreational users before larger populations are exposed to a drug.<sup>6,7</sup>

## Objectives

- To determine the abuse potential of orally administered Remoxy (whole and chewed) under fed conditions relative to oxycodone immediate release (IR, crushed) and oxycodone ER (whole and crushed) under fasted conditions and matching placebo

## Methods

### Study Design

- This was a phase I, randomized, double-blind, triple-dummy, placebo- and active-controlled, 6-way crossover study consisting of 3 phases: Naloxone Challenge Phase (Treatment Visit 2, Day 0), Drug Discrimination Phase (Treatment Visit 2, Days 1-2), and Abuse Potential Phase (Treatment Visits 2-5, Days 3-24; **Figure 1**).
- In the Abuse Potential Phase, patients were randomly assigned in a 3:1 ratio to Treatment Group X or Y (**Table 1**).
- Treatment Group X was considered the primary analysis group because treatments were administered under the fed/fasted states producing the highest bioavailability for Remoxy (fed state) and oxycodone (fasted state).
- Treatment Group Y was considered an exploratory analysis (to ensure the double-blind scheme of the study) that included Remoxy in the fasted state and oxycodone ER and IR in the fed state.
- Subjects in each group were randomized to 1 of 6 treatment sequences and received (in a double-blind fashion) single doses of Remoxy (whole and chewed), oxycodone IR (crushed), oxycodone ER (whole and crushed), and placebo (**Table 1**).
- Serial pharmacodynamic (PD) and safety measures were assessed pre-dose and up to 24 hours post-dose following each administration.
- Each treatment dose was separated by a washout period of  $\geq 92$  hours.
- The study was conducted in accordance with Good Clinical Practice requirements as described in the International Conference on Harmonisation guidelines, the protocol was reviewed and approved by the local institutional review board, and all subjects provided written informed consent.

Figure 1. Study design

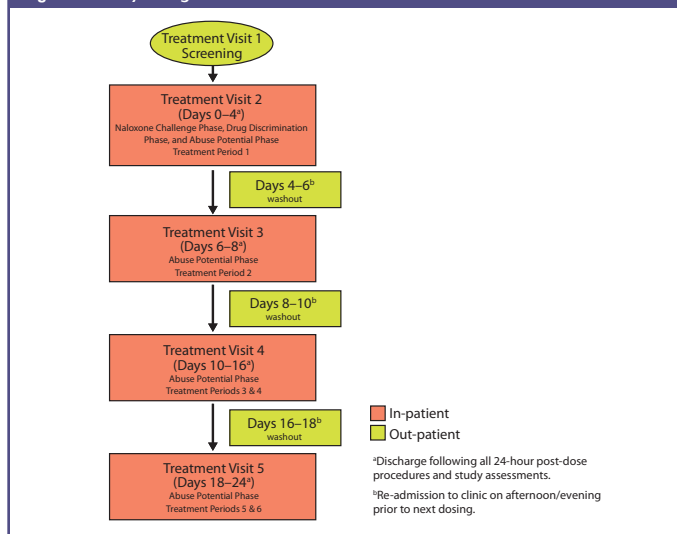


Table 1. Description of treatment groups X and Y

Treatment	Treatment Group X	Treatment Group Y
Treatment A: Placebo	Fed	Fasted
Treatment B: Remoxy 40 mg (whole)	Fed	Fasted
Treatment C: Remoxy 40 mg (chewed)	Fed	Fasted
Treatment D: Oxycodone HCl ER 40 mg (whole)	Fasted	Fed
Treatment E: Oxycodone HCl ER 40 mg (crushed)	Fasted	Fed
Treatment F: Oxycodone HCl IR 40 mg (crushed)	Fasted	Fed

### Key Inclusion/Exclusion Criteria

- Male and female nondependent recreational opioid users aged 18-50 years (inclusive) with a body mass index of 18-33 kg/m<sup>2</sup>
- Opioid use to achieve a "high" on  $\geq 5$  occasions in the 12 months before screening and  $\geq 1$  occasion in the 90 days before screening, but not physically dependent on opioids
- Preference for opioids (among users of multiple drugs)
- Urine drug screens and alcohol breath tests were conducted at each clinic admission to confirm compliance with study restrictions.

### Study Drugs and Dosing

- In the Abuse Potential Phase, treatments were administered in a triple-dummy fashion and each treatment consisted of:
  - Swallowing 2 intact capsules (Remoxy, oxycodone ER, or placebo)
  - Chewing 1 capsule (Remoxy or placebo)
  - Ingesting 150 mL of solution (oxycodone ER, oxycodone IR, or placebo)
- Fasted treatments were administered following an overnight fast of  $\geq 8$  h.
- Fed treatments were administered 30 to 60 minutes following a standard breakfast (8 oz of orange juice, 2 fried eggs, and 2 slices of toast with butter and preserves).
- A period of 10 minutes was allotted for chewing of capsules (Remoxy or placebo).

### Outcomes and Assessments

- The primary endpoint was the unipolar 100-mm visual analog scale (VAS; 0=none, 100=extremely) for Drug Liking assessed by the following principal PD parameters: maximum effect ( $E_{max}$ ), time to maximum effect ( $TE_{max}$ ), area under the effect curve for 0-1 h ( $AUE_{0-1h}$ ), and 0-2 h ( $AUE_{0-2h}$ ).

- Secondary endpoints were High, Good Drug Effects, and the Cole/Addiction Research Center Inventory Morphine Benzodrine Group Scale (Cole/ARCI MBG) scale assessed by similar PD parameters as the primary endpoint.
- Exploratory endpoints included chewing duration and taste/texture pleasantness assessments using a bipolar 100-mm VAS (0=extremely unpleasant, 100=extremely pleasant, 50=neutral).
- Safety assessments included adverse events (AEs), vital signs, clinical laboratory tests, oxygen saturation, and end tidal CO<sub>2</sub>.

### Statistical Analyses

- The primary population used for PD analyses was the completer population, which included all randomly assigned patients who received all 6 treatments and contributed post-dose data for each treatment period in the Abuse Potential Phase.
- Multiple comparison adjustments for all pairwise treatment comparisons for the primary endpoint used the Benjamini-Hochberg method.<sup>8</sup>
- PD parameters were analyzed using a linear mixed model with fixed effects for sequence, period, and treatment and a random effect for subject nested in sequence to test the hypothesis that there is no difference in abuse potential between Remoxy (whole/chewed, fed) and each of the active comparators separately.

## Results

### Patient Disposition and Baseline Characteristics

- 65 patients enrolled and 45 patients continued to the Abuse Potential Phase (**Figure 2**).
- 34 patients were randomized to Treatment Group X and 11 patients were randomized to Treatment Group Y.
- The completer population consisted of 32 patients in Treatment Group X and 11 patients in Treatment Group Y, the majority of whom were white (94% in Group X and 91% in Group Y) and male (78% in Group X and 82% in Group Y); the mean age in Group X was 25.2 years (range, 18-38 y) and 24.3 years (range, 21-28 y) in Group Y (**Table 2**).

Figure 2. Patient disposition

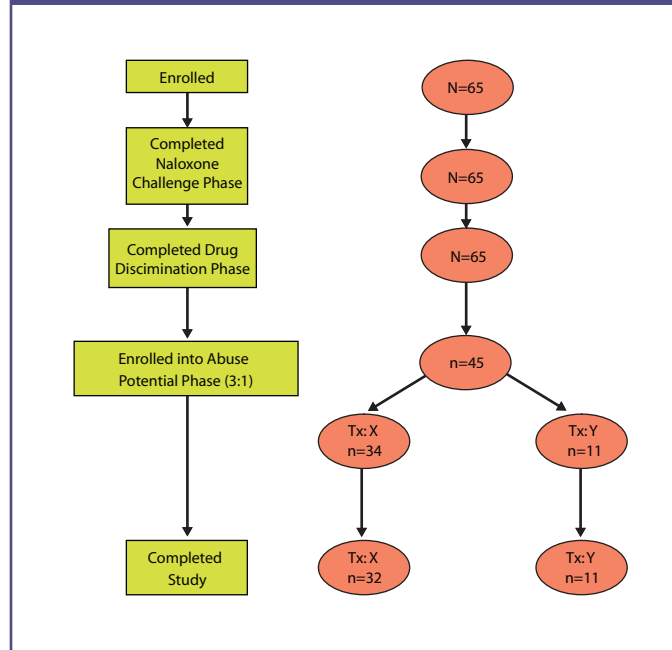


Table 2. Patient Demographics (Completer Population)

Demographic	Treatment Group X (n=32)	Treatment Group Y (n=11)
Age (years)		
Mean (SD)	25.2 (4.65)	24.3 (2.83)
Median	24.5	23.0
Range	18, 38	21, 28
Gender, n (%)		
Men	25 (78)	9 (82)
Women	7 (22)	2 (18)
Ethnicity, n (%)		
Not Hispanic or Latino	30 (94)	10 (91)
Hispanic or Latino	2 (6)	1 (9)
Race, n (%)		
White	30 (94)	10 (91)
Native Hawaiian or Pacific Islander	1 (3)	0
Asian	1 (3)	1 (9)
Weight (lb)		
Mean (SD)	167.2 (35.03)	164.0 (27.32)
Median	167.5	165.0
Range	117.0, 251.0	120.5, 207.0
Height (in)		
Mean (SD)	70.0 (3.67)	69.5 (2.04)
Median	70.0	70.0
Range	62.5, 77.0	66.5, 72.0
Body Mass Index (kg/m <sup>2</sup> )		
Mean (SD)	23.8 (3.47)	23.8 (3.38)
Median	22.8	23.5
Range	18.9, 32.7	18.1, 28.9

### Pharmacodynamic Analyses

- Mean Drug Liking was statistically significantly lower for Remoxy 40 mg (whole, fed) and Remoxy 40 mg (chewed, fed) compared with oxycodone IR 40 mg (crushed, fasted) and oxycodone ER 40 mg (crushed, fasted) for  $AUE_{0-1h}$ ,  $AUE_{0-2h}$ , and  $E_{max}$  ( $P \leq 0.0461$ ; **Table 3**).
- The time to peak ( $TE_{max}$ ) Drug Liking was significantly delayed for Remoxy (whole and chewed) compared with oxycodone IR (crushed) and oxycodone ER (crushed);  $P \leq 0.0193$ ; **Table 3**).
- Mean Drug Liking for Remoxy 40 mg (whole, fed) was significantly lower than oxycodone ER 40 mg (whole, fasted) for both  $AUE_{0-2h}$  and  $E_{max}$  ( $P \leq 0.0374$ ; **Table 3**).
- Mean Drug Liking for Remoxy 40 mg (chewed, fed) was significantly higher than oxycodone ER (whole, fasted) for  $AUE_{0-1h}$  and  $AUE_{0-2h}$  ( $P \leq 0.0275$ ; **Table 3**).
- Mean VAS scores for Drug Liking, High, Good Drug Effects, and Cole/ARCI demonstrate the consistency of effect across positive subjective endpoints from time 0 (dosing) through 8 hours post-dose (**Figures 3A-D**).
- The mean chewing time for Remoxy was 0.8 minutes, with a maximum reported chewing time of 1.5 minutes.
- The majority of patients reported the taste (mean VAS score = 17.7) and texture (mean VAS score = 21.6) of Remoxy as unpleasant (**Figure 4**).
- Results from the completers in Treatment Group Y (n=11) were similar to those seen for the completers in Treatment Group X (n=32).
- The AEs associated with Remoxy and oxycodone IR and ER were typical of those that occur with any opioid-containing drug, and no serious AEs, deaths, or discontinuations due to AEs occurred.
- There were no clinically important changes from baseline in vital signs or laboratory values.
- Mean end tidal CO<sub>2</sub> demonstrated an opioid treatment effect in the active treatment groups relative to the placebo group; however, mean SpO<sub>2</sub> and end tidal CO<sub>2</sub> remained within normal ranges.

Table 3. LS Mean Difference in Visual Analog Scale Scores for Drug Liking in Treatment Group X (Completer Population)

PD Parameter	Remoxy 40 mg (Whole, Fed) Versus				Remoxy 40 mg (Chewed, Fed) Versus			
	Placebo (Fed) (n=32)	Oxycodone IR 40 mg (Crushed, Fasted) (n=32)	Oxycodone ER 40 mg (Crushed, Fasted) (n=32)	Oxycodone ER 40 mg (Whole, Fasted) (n=32)	Placebo (Fed) (n=32)	Oxycodone IR 40 mg (Crushed, Fasted) (n=32)	Oxycodone ER 40 mg (Crushed, Fasted) (n=32)	Oxycodone ER 40 mg (Whole, Fasted) (n=32)
$AUE_{0-1h}$ (h*mm)								
LS mean difference <sup>a</sup>	4.1	-32.2	-28.8	-2.8	13.7	-22.6	-19.1	6.9
95% CI <sup>a</sup>	(-1.8, 10.0)	(-38.1, -26.3)	(-34.7, -22.9)	(-8.6, 3.1)	(7.9, 19.6)	(-28.5, -16.7)	(-25.0, -13.3)	(1.0, 12.8)
Adjusted P value <sup>b</sup>	0.1879	<0.0001	<0.0001	0.3718	<0.0001	<0.0001	<0.0001	0.0275
$AUE_{0-2h}$ (h*mm)								
LS mean difference <sup>a</sup>	12.8	-71.6	-65.9	-21.2	49.8	-34.6	-28.9	15.8
95% CI <sup>a</sup>	(1.2, 24.5)	(-83.2, -60.0)	(-77.6, -54.3)	(-32.8, -9.6)	(38.2, 61.5)	(-46.3, -23.0)	(-40.6, -17.3)	(4.2, 27.5)
Adjusted P value <sup>b</sup>	0.0372	<0.0001	<0.0001	0.0007	<0.0001	<0.0001	<0.0001	0.0109
$E_{max}$ (mm)								
LS mean difference <sup>a</sup>	30.7	-26.4	-21.6	-8.9	43.7	-13.4	-8.6	4.1
95% CI <sup>a</sup>	(22.5, 38.8)	(-34.6, -18.3)	(-29.8, -13.4)	(-17.1, -0.8)	(35.6, 51.8)	(-21.5, -5.2)	(-16.7, -0.4)	(-4.0, 12.3)
Adjusted P value <sup>b</sup>	<0.0001	<0.0001	<0.0001	0.0374	<0.0001	0.0022	0.0461	0.3423
$TE_{max}$ (h)								
LS mean difference <sup>a</sup>	3.4	2.2	2.0	0.9	2.6	1.4	1.2	0.1
95% CI <sup>a</sup>	(2.4, 4.4)	(1.2, 3.1)	(1.1, 3.0)	(-0.1, 1.8)	(1.6, 3.5)	(0.4, 2.3)	(0.2, 2.2)	(-0.9, 1.0)
Adjusted P value <sup>b</sup>	<0.0001	<0.0001	<0.0001	0.0836	<0.0001	0.0089	0.0193	0.9033

<sup>a</sup>AUE=area under the effect curve;  $E_{max}$ =maximum effect; ER=extended release; IR=immediate release; LS=least squares;  $TE_{max}$ =time to maximum effect; VAS=visual analog scale; LS means, 95% CI, and unadjusted P values were from a linear mixed model with fixed effects for sequence, period, and treatment, and a random effect for patients nested in sequence. <sup>b</sup>P values for the primary endpoint only were based on the Benjamini-Hochberg adjustment for multiplicity.

Figure 3. Mean visual analog scale scores for (A) Drug Liking, (B) High, (C) Good Drug Effects, and (D) Cole/ARCI MBG Scale in Treatment Group X (Completer Population)

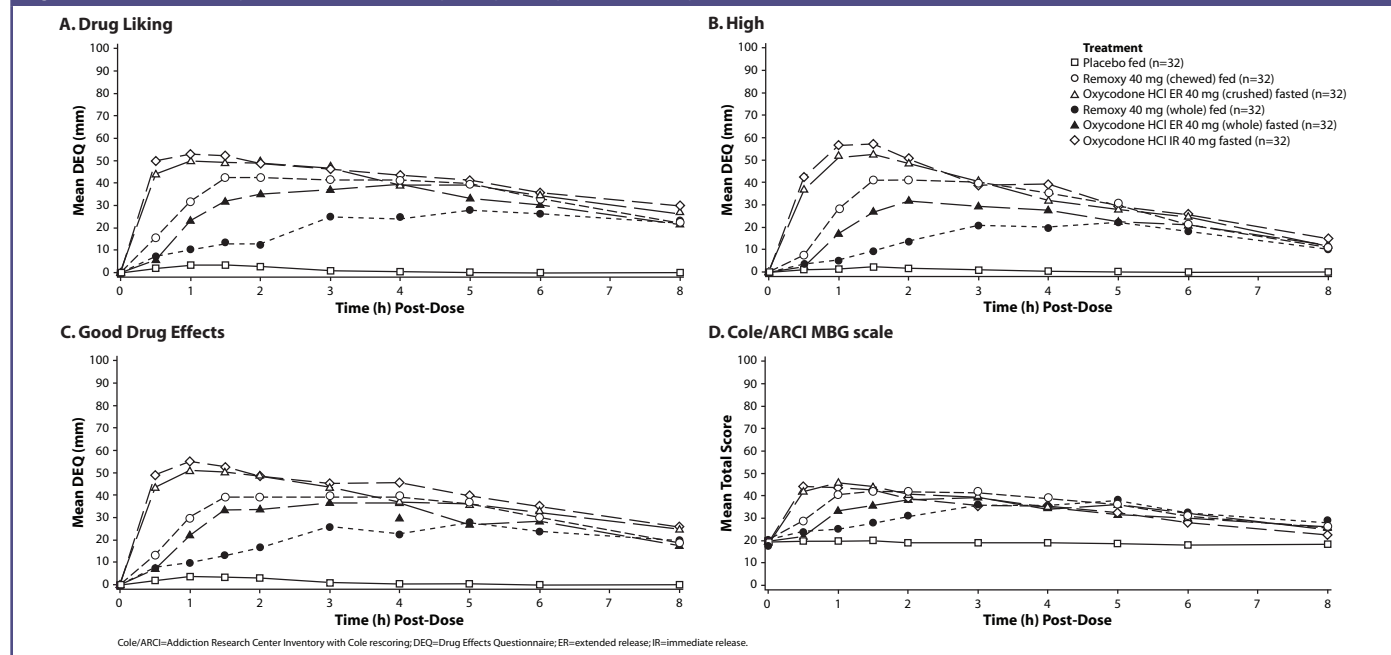
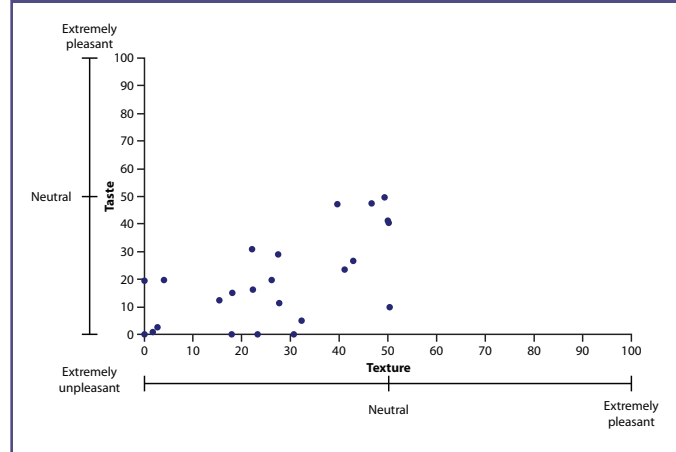


Figure 4. Visual Analog Scale scores for taste and texture of chewed Remoxy in Treatment Group X (Completer Population).



## Conclusions

- Remoxy may be associated with a reduced potential for abuse, including conditions in which Remoxy is manipulated through crushing, compared with oxycodone products with established abuse potential.
- There were no unexpected safety findings in this study.
- Ample time in the marketplace will be required to determine if Remoxy is associated with reduced misuse and abuse by tampering in the community.

## References

- Substance Abuse and Mental Health Services Administration. Results from the 2008 national survey on drug use and health: national findings. NSDUH Series H-36 Publication No. SMA 09-4434. Available at: <http://oas.samhsa.gov/2k8/2k8nsduh/2k8Results.pdf>. Accessed October 20, 2010.
- US General Accounting Office. Prescription drugs, OxyContin abuse and diversion, and efforts to address the problem. Available at: <http://www.gao.gov/new.items/d04110.pdf>. Accessed July 20, 2010.
- Martins SS, et al. Drug Alcohol Depend. 2009;99(1-3):58-67.
- Webster LR. Expert Opin Investig Drugs. 2007;16(3):359-366.
- Zamlot M, et al. J Appl Res. 2010;10(3):88-96.
- Griffiths RR, et al. Drug Alcohol Depend. 2003;70(3 suppl):S41-S54.
- Food and Drug Administration. Draft Guidance for Industry: Assessment of Abuse Potential of Drugs. Silver Springs, MD: US Department of Health and Human Services; 2010.
- Benjamini Y and Hochberg M. J R Statist Soc B. 1995;57(1):289-300.

**Disclosures and Acknowledgments**  
B. Setnik, C. L. Roland, and J. M. Cleveland are employees of King Pharmaceuticals, which was acquired by Pfizer Inc in March 2011. Medical writing support was provided by Complete Publication Solutions; this assistance was funded by King Pharmaceuticals, which was acquired by Pfizer Inc in March 2011.