

# Expert Opinion

1. Introduction
2. Gel-cap technology
3. Pharmacology and abuse liability
4. Clinical efficacy
5. Safety and tolerability
6. Expert opinion

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## PTI-821: sustained-release oxycodone using gel-cap technology

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PTI-821 is a long-acting formulation of oxycodone that is intended to deter abuse through its gel-cap technology. Produced by Pain Therapeutics in alliance with King Pharmaceuticals, PTI-821 is designed to provide strong pain relief with the intent of offering greater safety than is presently available from conventional controlled-release oxycodone products. This paper presents the available preliminary data on PTI-821 and discusses their potential clinical applications. The results of three pharmacokinetics studies and one Phase III, randomized, double-blind, clinical efficacy trial have been published in abstract form. PTI-821 has demonstrated a statistically significant difference from placebo ( $p < 0.05$ ) in the efficacy study's primary end point: percentage decrease in pain scores. A further large, clinical study is in progress.

**Keywords:** abuse, abuse deterrent, abuse resistant, addiction, chronic pain, diversion, extended-release, gel cap, opioids, oxycodone, sustained-release oxycodone

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### 1. Introduction

The problem of non-medical use, diversion and overdose involving prescription opioids to treat chronic pain has worsened in recent years [1]. Controlled-release (CR) oxycodone is one of many opioids that is linked to the growing national problem in the US. According to the Drug Abuse Warning Network (DAWN), oxycodone abuse resulted in 36,600 visits to US emergency rooms in 2004, 20,000 of which are known to stem from CR oxycodone formulations [2,3]. According to the 2004 National Survey on Drug Use and Health, 3.1 million Americans have used sustained-release oxycodone for non-medical purposes [4]. Unintentional overdose deaths from prescription drugs have increased dramatically in the past several years.

The pharmaceutical industry recognizes the problem and is developing new formulations to reduce the reward experienced by would-be abusers of opioids. Fentanyl patches represent one such attempt to prevent abuse and diversion, but would-be abusers have been able to find ways to extract the fentanyl from the patch. The development of CR formulations was itself an attempt to minimize abuse potential, but the formulations proved vulnerable to manipulation by 'dose dumping', which is the extraction of the abusable ingredient from a formulation so it can be used at a higher-than-intended concentration. The goal of abusers is to quickly release a full 12-h dose in an immediate spike. This can be accomplished in various ways, including crushing, grinding or dissolving in alcohol, water or other beverages. The product is then consumed orally, snorted or injected. Taking the opioid with alcohol can also increase the rate of absorption and induce a premature release of active ingredient from some formulations. The FDA has increased its scrutiny of formulations that appear to be alcohol sensitive.

Because of these dangers, research is evolving to develop formulations that are tamper resistant or that otherwise deter abuse, but still provide effective time-release analgesia to relieve chronic pain. PTI-821 is a product that is aimed at

Freeze and crush



**Figure 1. Sustained-release gel capsules impervious to alteration.** The viscous mass of oxycodone controlled-release does not fracture. The controlled-release matrix is preserved. Photo provided by Pain Therapeutics.

detering dose dumping by housing a long-acting oxycodone formula in a viscous gel base that is difficult to crush, break, freeze, heat or dissolve in a liquid. Based on its progress through clinical testing, this product is likely to be among the first new abuse-resistant opioid agonist formulations to enter the market.

Because the drug is still in development, data are preliminary. The results of four studies have been published in abstract form. Three of these detail laboratory tests that compare the pharmacokinetics of PTI-821 with CR oxycodone under different conditions. The fourth is a clinical, randomized trial of the analgesic efficacy. An additional large, clinical study is underway at present to document the efficacy and safety of PTI-821 for chronic pain.

## 2. Gel-cap technology

PTI-821 uses a patented CR technology based on a water-insoluble, high-viscosity component such as sucrose acetate isobutyrate (Figure 1). After administration by parenteral, oral, dermal or alternative route, the solvent dissolves, leaving a viscous, adhesive matrix of sucrose acetate isobutyrate, drug and any additives. As the gelatin capsule dissolves, the long-acting oxycodone mass is slowly released via the gastrointestinal tract. The gel-cap coating preserves long-acting properties, thus defeating attempts to extract the active ingredient.

## 3. Pharmacology and abuse liability

In two studies, early formulations of PTI-821 were compared with conventional oxycodone formulations under different conditions. The drugs were tested in unaltered form following single and multiple doses, then manipulated using the most

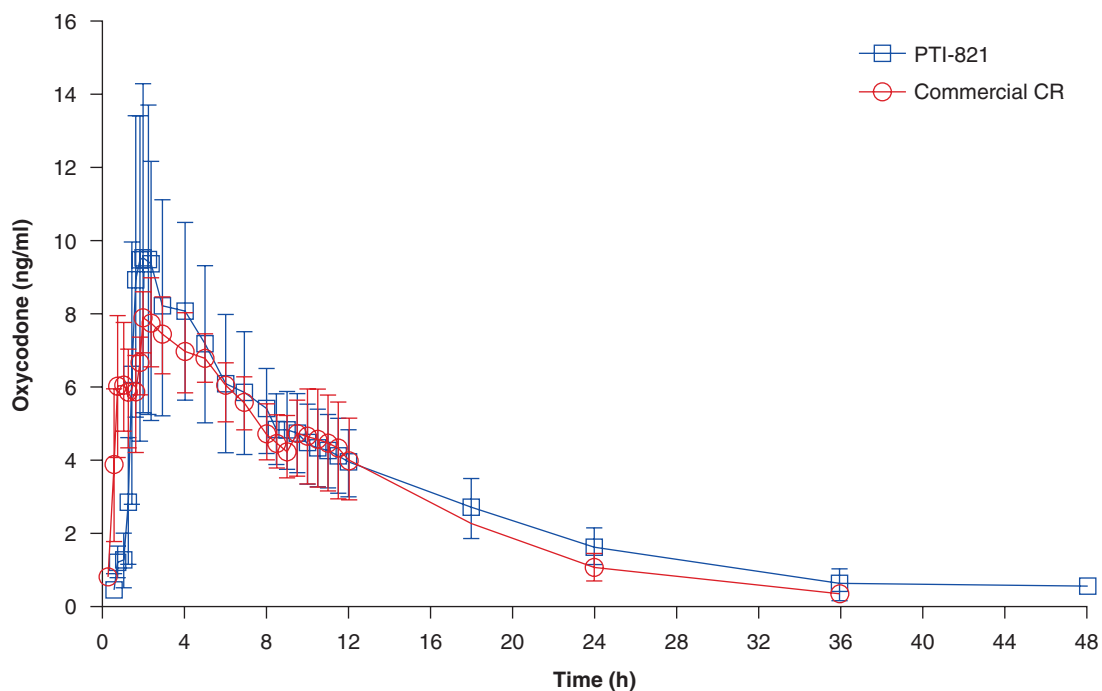
common methods of abuse. The data demonstrate that PTI-821 maintains its time-release mechanism under attempts to crush or to extract the drug in alcohol or water.

Cross-over testing was used to compare the pharmacokinetics of different formulations of PTI-821 with CR oxycodone tablets and an oxycodone immediate-release (IR) formula. There were 2 groups of 5 healthy male volunteers who were randomly assigned a 10-mg dose of one of the following 3 treatment arms: PTI-821, IR oxycodone or CR oxycodone [5]. The three formulations were ingested in separate sessions by: swallowing them whole with water (as intended); crushing and dissolving in water; or crushing and dissolving in alcohol. The investigators then measured and recorded subjects' plasma oxycodone levels.

When swallowed whole as intended, certain formulations of PTI-821 and the CR formulation produced similar plasma oxycodone levels in fed subjects (Figure 2). However, absorption of oxycodone from PTI-821 was significantly less than that of the commercial CR formulation in fasted subjects (Figure 3). When crushed and diluted with alcohol or water, the CR formulation produced plasma oxycodone levels similar to the IR formulation. In fact, the mean maximum serum concentration ( $C_{max}$ ) values of the crushed CR formulation in water (21.8 ng/ml) and in alcohol (21.0 ng/ml) were slightly higher than the mean  $C_{max}$  value of the commercial IR formulation (18.9 ng/ml; Figure 4). In contrast, PTI-821 produced a significantly lower mean oxycodone  $C_{max}$  value than the IR formulation after crushing and diluting in both water (6.2 ng/ml;  $p < 0.001$ ) and alcohol (7.7 ng/ml;  $p < 0.001$ ; Figure 5).

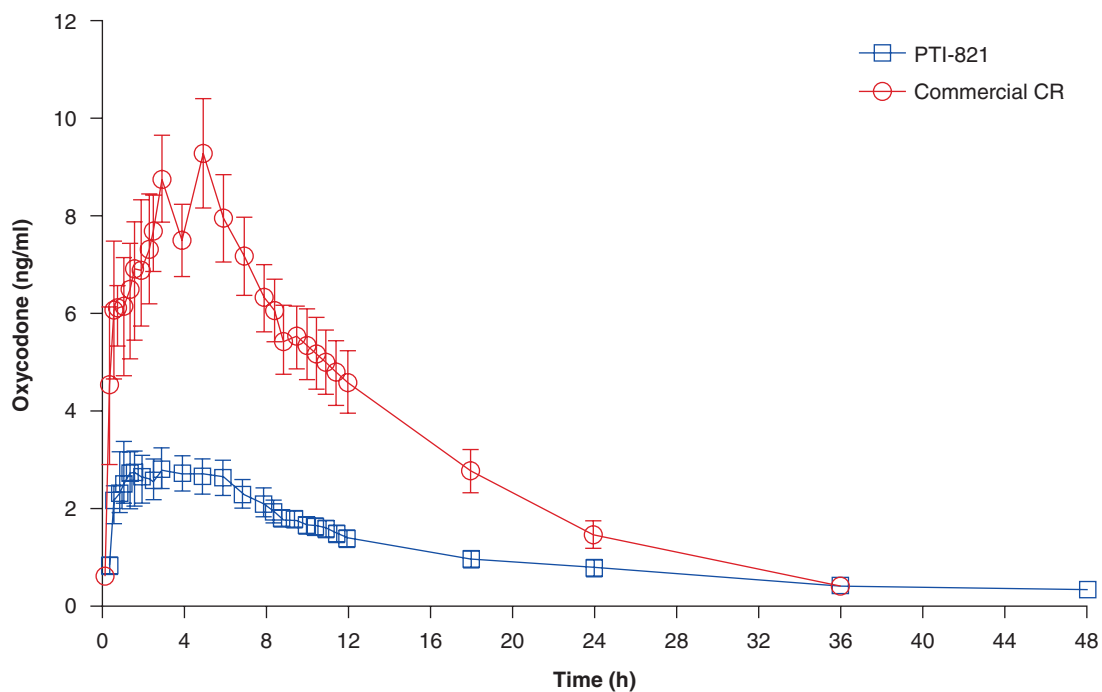
The AUC values for each of the crushed formulations and the IR formulation were also reported. The crushed and water-diluted CR formulation produced a slightly higher AUC than the IR formulation, whereas crushing and diluting PTI-821 with water resulted in significantly lower AUC values than those of the commercial IR formulation ( $p = 0.03$  at 45 min;  $p = 0.003$  at 1 h;  $p < 0.001$  at 2 h). The alcohol challenge produced similar results. The IR and crushed-and-diluted CR formulation produced similar oxycodone AUC values in tests performed with fasting subjects. Crushing PTI-821 in alcohol produced significantly lower AUC values than the IR formulation ( $p = 0.01$  at 45 min;  $p = 0.001$  at 1 h;  $p < 0.001$  at 2 h). The plasma level of oxycodone produced by PTI-821 after crushing and mixing with alcohol was only slightly higher than when it was taken as intended.

A separate study was conducted to determine the effects of partial (rather than complete) destruction of oxycodone formulations by chewing or dissolving in alcohol [6]. There were 2 groups of 5 subjects who were randomly assigned to receive either certain formulations of PTI-821 or the CR oxycodone formulation by: swallowing it whole with water; chewing it for 5 min followed by drinking of water; or probing/stirring in 28.35 g of 40-proof alcohol (20% alcohol content) for 10 min and drinking the mixture. Neither challenge fully compromised the commercial CR



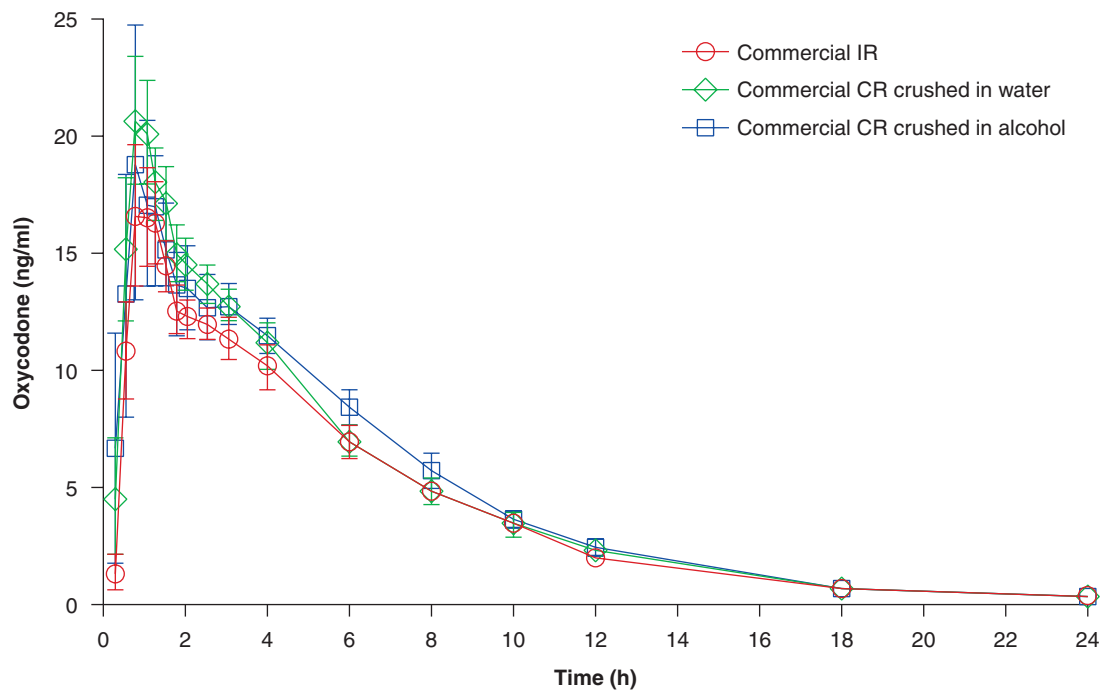
**Figure 2. Plasma oxycodone levels in fed subjects.**

Source: FRIEDMANN N, DE KATER AW, BUTERA PG, WEBSTER LR, RATCLIFFE S, VAN RADERS PA, LANGFORD LM: Remoxy™: a novel drug candidate, deters oxycodone abuse in humans. 21st annual meeting of the American Academy of Pain Medicine, Palm Springs, California, USA (23 – 27 February 2005).



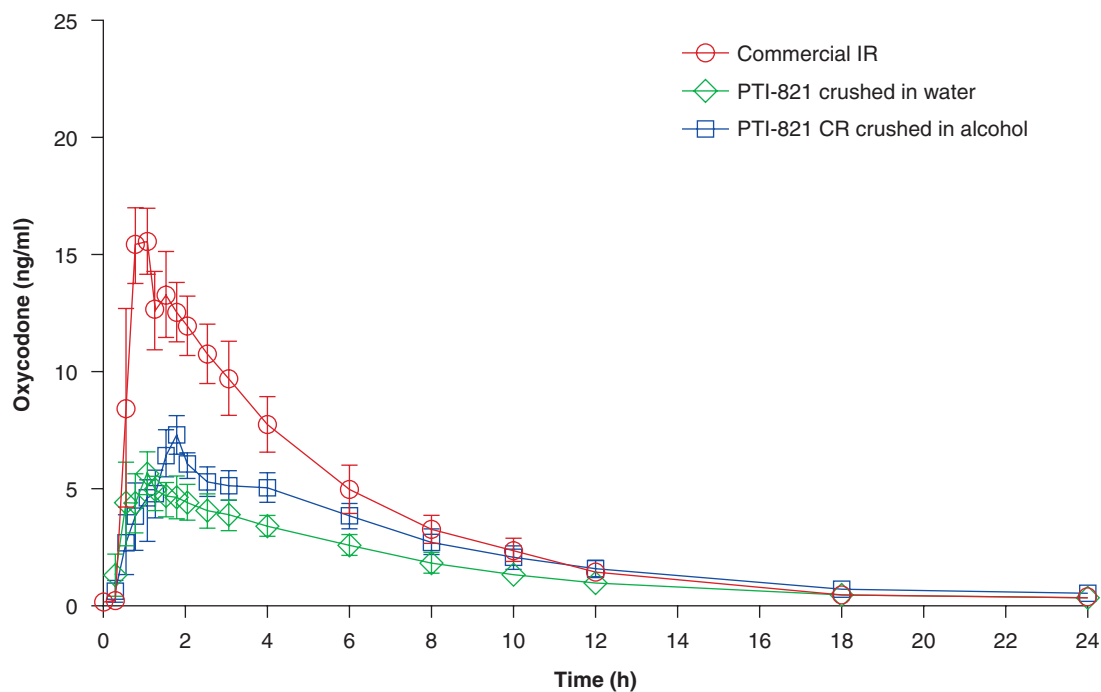
**Figure 3. Plasma oxycodone levels in fasted subjects.**

Source: FRIEDMANN N, DE KATER AW, BUTERA PG, WEBSTER LR, RATCLIFFE S, VAN RADERS PA, LANGFORD LM: Remoxy™: a novel drug candidate, deters oxycodone abuse in humans. 21st annual meeting of the American Academy of Pain Medicine, Palm Springs, California, USA (23 – 27 February 2005).



**Figure 4. Plasma oxycodone levels after crushing commercial CR formulation.**

Source: FRIEDMANN N, DE KATER AW, BUTERA PG, WEBSTER LR, RATCLIFFE S, LANGFORD RM: Remoxy™, a novel drug candidate deters oxycodone abuse in humans. *3rd International Congress World Institute of Pain*, Barcelona, Spain (21 – 25 September 2004) (Abstract).  
CR: Controlled release.



**Figure 5. Plasma oxycodone levels after crushing PTI-821.**

Source: FRIEDMANN N, DE KATER AW, BUTERA PG, WEBSTER LR, RATCLIFFE S, LANGFORD RM: Remoxy™, a novel drug candidate deters oxycodone abuse in humans. *3rd International Congress World Institute of Pain*, Barcelona, Spain (21 – 25 September 2004) (Abstract).

formulation; however, PTI-821 produced significantly lower oxycodone plasma AUC values after chewing at all time points between 30 min and 2 h ( $p = 0.06$  at 15 min;  $p = 0.04$  at 30 min;  $p = 0.03$  at 45 min;  $p = 0.01$  at 1 and 2 h; **Figure 6**). The alcohol dilution challenge produced significantly lower AUC values for PTI-821 at 1 and 2 h ( $p = 0.06$  at 15 min;  $p = 0.09$  at 30 min;  $p = 0.07$  at 45 min;  $p = 0.03$  at 1 h;  $p = 0.006$  at 2 h; **Figure 7**).

Another study [7] was conducted to assess the differences between the pharmacokinetics of certain formulations of PTI-821 with CR oxycodone after single (with or without food) and multiple doses. In the single-dose segment of the study, 3 groups of 5 healthy male volunteers received 9 mg of either PTI-821 or CR formulation after fasting overnight. Later, three subjects who first received PTI-821 when fasted received PTI-821 after a high-fat breakfast. The bio-availability of PTI-821 compared with CR oxycodone was 41% without food and 102% with food. Investigators concluded that increased peristalsis may be responsible for the increased absorption of PTI-821 with food. Published data indicate no significant effect from food on the commercial CR formulation [8].

The multi-dose segment of the study was conducted in a double-blind, placebo-controlled, parallel group of five healthy male volunteers. The first dose (PTI-821 10 mg b.i.d.) was administered 30 min after starting breakfast and the second dose immediately after the evening meal. The 5-day study indicated that steady state was achieved by day 3 with a twice-daily, repeat dose of PTI-821 (oxycodone 10 mg). The half-life of PTI-821 is longer than the half-life of 3.5 – 4 h that was reported for IR oxycodone formulations. Plasma concentration declined more slowly with PTI-821 than with the CR formulation. Plasma levels remained at ~ 20% and 16% of  $C_{max}$  at 24 and 36 h, respectively. The CR formulation of oxycodone was not quantifiable in 4 out of 5 subjects after 36 h.

#### 4. Clinical efficacy

Only one published study addresses effective analgesia of PTI-821, but oxycodone, which is the active ingredient in PTI-821, has been shown in numerous publications to be an effective analgesic. The randomized, double-blind study consisted of 209 patients with moderate-to-severe osteoarthritis pain enrolled in multiple sites [9]. Patients with pain intensity  $\geq 5$  on a scale of 0 – 10 received either PTI-821 or placebo. Patients were initiated on 10 mg b.i.d. for 1 week, then titrated to 20 mg b.i.d. for 4 weeks. Demographics and baseline pain intensity (7.1) were similar in both groups.

PTI-821 produced a significant percentage decrease in pain intensity scores compared with placebo, meeting the study's primary end point ( $p = 0.043$ ; **Figure 8**). The AUC for the change in pain intensity for baseline was significantly greater for PTI-821 than for placebo ( $p = 0.013$ ). PTI-821 also

performed better on secondary measures compared with placebo. PTI-821 patients reported better function and quality of life using the Short-Form 12 Question Health Survey (SF-12) and Western Ontario and MacMaster Universities (WOMAC) Osteoarthritis Index subscales and total score. WOMAC score:  $p = 0.045$ ; pain subscale,  $p = 0.015$ ; stiffness subscale,  $p = 0.040$ . SF-12 physical function scale:  $p < 0.001$ . Furthermore, in patient assessment of quality of analgesia, 60.9% of patients taking PTI-821 and 38.4% of patients taking placebo rated the overall quality of analgesia as excellent, very good or good.

A further double-blind, placebo-controlled, multicenter clinical study is in progress and is expected to report on 400 patients with moderate-to-severe chronic pain. The primary end point is a reduction in pain scores compared with baseline. Patients will be randomized for 12 weeks to either PTI-821 10 – 80 mg/day or placebo.

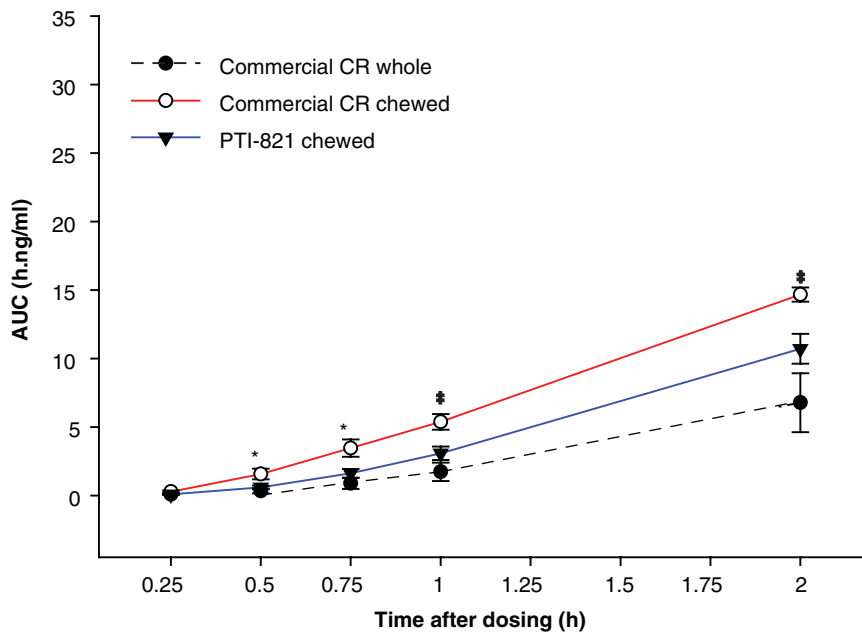
#### 5. Safety and tolerability

Oxycodone has been studied extensively and shown to be safe and well tolerated when taken as directed. The available safety and efficacy data for PTI-821 show it to be well tolerated in chronic pain patients. In the clinical efficacy study conducted by Gilderman *et al.*, no serious drug-related safety issues were noted and PTI-821-related adverse events were judged to be typical of opioid-related side effects, including nausea/vomiting, dizziness, pruritis, drowsiness and constipation [9]. Drop-out rates were higher in the PTI-821 arm ( $n = 37$ ) compared with the placebo arm ( $n = 25$ ).

#### 6. Expert opinion

PTI-821 represents a first wave of new products that are now in development aimed at reducing the risk of abuse, diversion and overdose associated with opioids. PTI-821 has the potential to deter the dangers of 'dose dumping'; namely, accessing an entire 12-h dose of CR medication at 1 time. The viscous gel-cap base of PTI-821 cannot be injected and its CR mechanism resists crushing and dissolution in alcohol or water. Alcohol-induced effects are a new focus of regulatory attention.

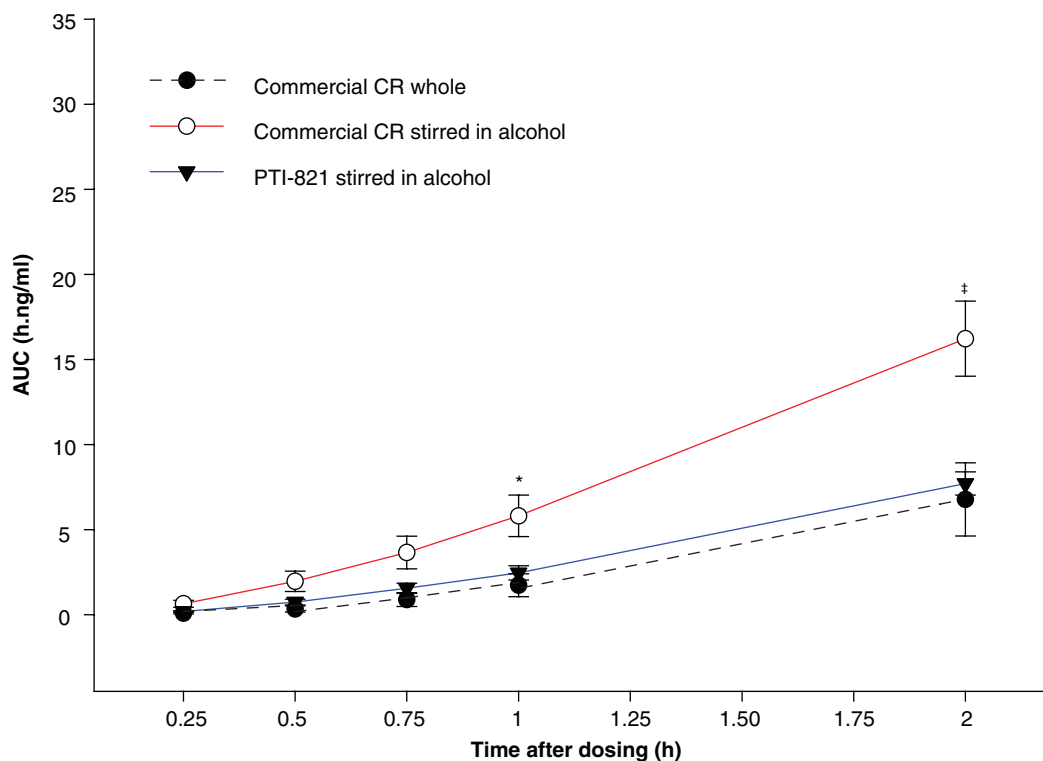
Pharmacokinetics testing revealed that crushing and diluting PTI-821 with alcohol or water produced significantly lower oxycodone plasma levels than those resulting from both IR and crushed CR formulations. These tests were performed with fasting subjects because investigators were concerned that the alcohol might otherwise cause nausea or vomiting. The stable pharmacokinetic parameters that were demonstrated in tests of single and multiple doses indicate that PTI-821 will present a predictable, manageable dosing regimen. Tests of analgesic efficacy indicate that twice-daily dosing with PTI-821 is superior to placebo at providing effective analgesia and functional improvement for patients with chronic osteoarthritis pain.



**Figure 6. AUC comparisons of oxycodone formulations both chewed and whole.**

Source: FRIEDMANN N, DE KATER AW, BUTERA PG, WEBSTER LR, RATCLIFFE S, LANGFORD RM: Remoxy™, a novel drug candidate deters oxycodone abuse in humans. *3rd International Congress World Institute of Pain*, Barcelona, Spain (21 – 25 September 2004) (Abstract).

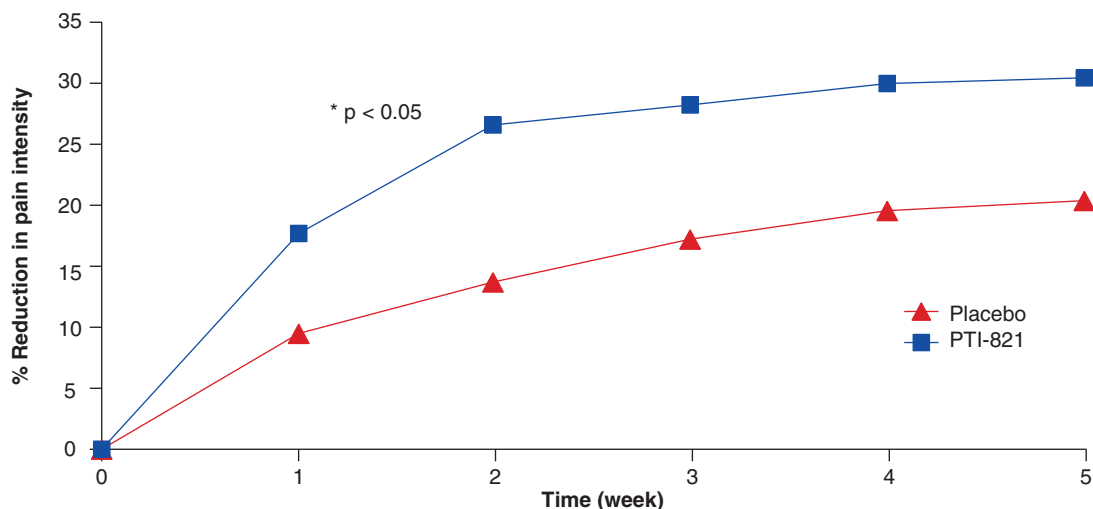
\* $p \leq 0.05$ . † $p \leq 0.01$ .



**Figure 7. AUC comparisons of oxycodone formulations both probed and stirred in alcohol.**

Source: FRIEDMANN N, DE KATER AW, BUTERA PG, WEBSTER LR, RATCLIFFE S, LANGFORD RM: Remoxy™, a novel drug candidate deters oxycodone abuse in humans. *3rd International Congress World Institute of Pain*, Barcelona, Spain (21 – 25 September 2004) (Abstract).

\*  $p \leq 0.05$ . †  $p \leq 0.01$ .



**Figure 8. Percent reduction in pain intensity.**

Source: GILDERMAN L, BUTERA P, GILMORE D, MORAN L, FRIEDMANN N: Remoxy™: a new opioid drug with effective analgesia and abuse-resistance. *Program and abstracts of the 25th Annual Scientific Meeting of the American Pain Society*, San Antonio, Texas, USA (3 – 6 May 2006):755 (Poster).

This study does not represent the beginning of abuse-deterrent research. Sustained-release and constant-release oral and transdermal formulations were the first attempt to deter inappropriate use. Other approaches to abuse prevention that are under investigation include adding an opioid antagonist (such as naltrexone) to a therapeutic agonist agent. One type of formulation is designed to release the antagonist, which then reverses the agonist effect if the product is crushed, dissolved, mixed with alcohol or otherwise manipulated. Another antagonist/agonist formulation uses an ultra-low-dose opioid antagonist in combination with a sustained-release opioid agonist to slow the build-up of tolerance and physical dependence [10]. Although early test data show promise, it remains unclear whether an antagonist added to an opioid formulation can serve as an effective deterrent to abuse without blocking analgesia or precipitating withdrawal.

The gel-cap technology of PTI-821 seems to hold promise for being difficult to abuse. However, the technology underlying abuse deterrence does not mean the patient cannot abuse the formulation or become addicted. A patient could still abuse PTI-821 by taking too much, as with any other long-acting opioid. It is also possible that people determined to alter and abuse an opioid formulation may still find ways to do so, with oral and intranasal abuse being the most common routes. Internet sites devoted to the support of recreational drug use provide their readers with many examples of creative tampering, including how to extract an abusable portion of an active ingredient and how to alter formulations for alternate routes of administration. Such attempts to circumvent barriers to abuse can be expected to continue and any success experienced by would-be abusers reported. Even so, such extra steps or potentially sophisticated chemistry provide a significant hurdle for the typical abuser seeking a drug-induced euphoria.

Abuse-resistant testing must take into consideration:

- who is likely to abuse the formulation
- whether the product can be abused without manipulation
- potential methods of alteration
- the effects of multiple doses
- possible alternate routes of administration
- physical or chemical means of extracting the active ingredient
- methods of compromising extended-release formulations
- potential abuse in combination, particularly with alcohol

Questions to be answered include whether higher doses of PTI-821 will be needed to achieve the same analgesia and, if so, whether the benefit of gel-cap technology could be compromised by an increased dose requirement. If the analgesic efficacy of CR oxycodone and PTI-821 are proven to be comparable in future testing, then the abuse-resistant technology could be significantly beneficial to clinicians.

The terms 'abuse deterrence' and 'abuse resistance' are not generally considered as regulatory terms for the purpose of labeling. The FDA has ruled that these terms cannot be claimed on the label prior to the completion of long-term, epidemiologic studies. Instead, the label will detail the product's chemistry and properties, and a package insert may state that PTI-821 is a formulation from which it is difficult to extract oxycodone by crushing or mixing with water or alcohol.

The development of opioids that limit abuse has been met with only limited success in the past. If new products are to be promoted as presenting less risk for abuse, postmarketing studies must be put into place to substantiate the claims.

## Disclosure

LR Webster received an honorarium as a consultant at King Pharmaceutical.

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