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Original Research Article

Abuse Potential Study of ALO-02 (Extended-Release Oxycodone Surrounding Sequestered Naltrexone) Compared with Immediate-Release Oxycodone Administered Orally to Nondependent Recreational Opioid Users

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Abstract

Objective. To evaluate the abuse potential of ALO-02, an abuse-deterrent formulation comprising pellets of extended-release oxycodone hydrochloride surrounding sequestered naltrexone hydrochloride.

Design. Randomized, double-blind, placebo-/active-controlled, 6-way crossover study, with naloxone challenge, drug discrimination, and treatment phases.

Subjects. Nondependent, recreational opioid users.

Methods. Oral administration of crushed and intact ALO-02, crushed immediate-release (IR)

**The author's name was misspelled in this article's original publication and has now been corrected.

oxycodone, and placebo. Primary endpoints were Drug Liking and High measured on visual analog scales and reported as maximum effect (E_{max}) and area-under-the-effect-curve from 0 to 2 hours (AUE_{0-2h}). Other pharmacodynamic, pharmacokinetic and safety assessments were included.

Results. Drug Liking and High (E_{max}) for crushed oxycodone IR 40 mg were significantly higher compared with placebo, confirming study validity ($P < 0.0001$). Drug Liking and High (E_{max}, AUE_{0-2h}) for crushed ALO-02 (40 mg/4.8 mg and 60 mg/7.2 mg) were significantly lower compared to corresponding doses of crushed oxycodone IR (40 and 60 mg; $P < 0.0001$). Likewise, Drug Liking and High (E_{max} and AUE_{0-2h}) for intact ALO-02 60 mg/7.2 mg were significantly lower compared with crushed oxycodone IR 60 mg ($P < 0.0001$). Secondary pharmacodynamic endpoints and plasma concentrations of oxycodone and naltrexone were consistent with these results. Fewer participants experienced adverse events (AEs) after ALO-02 (crushed or intact: 71.1–91.9%) compared with crushed oxycodone IR (100%). Most common AEs following crushed ALO-02 and oxycodone IR were euphoric mood, pruritus, somnolence, and dizziness.

Conclusions. The results suggest that ALO-02 (crushed or intact) has lower abuse potential than crushed oxycodone IR when administered orally in nondependent, recreational opioid users.

Key Words. Opioids; Abuse Potential; ALO-02; Abuse Deterrent; Oxycodone

Introduction

Though opioids have therapeutic value in treating pain, medical misuse and non-medical abuse of prescription opioids is also prevalent [1]. According to a recent Centers for Disease Control and Prevention report, opioid deaths have quadrupled in the United States from 1999 to 2011 [2]. There were about 488,000 visits to emergency departments relating to misuse and abuse of opioid analgesics in 2011, which represents an increase of 183% from 2004 [3]. The economic burden of prescription opioid abuse or dependence to employers between 2006 and 2012 was estimated at $10,627 in per-patient incremental annual healthcare costs and $1,244 in annual work-loss costs [4].

A pharmacological strategy to address this opioid abuse problem is the development of abuse-deterrent formulations (ADF) of opioid analgesics, an approach endorsed by the United States Food and Drug Administration (FDA) [5,6]. ADFs can be designed by including physical or chemical barriers that deter abuse by tampering or extraction, or with aversive properties, or as a pro-drug that is inactive until transformed in the gastrointestinal tract, or a more abuse-resistant delivery mechanism such as a subcutaneous implant. An agonist/antagonist combination is another possible ADF design strategy, where the antagonist is released upon tampering, and has shown promise in reducing the abuse potential of a drug [7].

After the introduction of an abuse-deterrent form of oxycodone that is difficult to crush, there was an approximately 49% reduction in opioid abuse in past-30-day abuse among patients at specific substance abuse treatment centers [8]. Prevalence of oxycodone abuse was significantly reduced for both oral and non-oral routes of abuse [8]. Data from Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System show that exposures due to therapeutic error declined 24% after the introduction of this abuse-deterrent formulation of oxycodone [9]. Rates of diversion of oxycodone also fell 53% after this formulation was available [9].

ALO-02 is an agonist/antagonist formulation that consists of capsules filled with pellets that contain extended-release (ER) oxycodone hydrochloride that surround sequestered naltrexone HCl (12% of the milligram amount of oxycodone HCl), which is released only upon manipulation of the pellets (e.g., by crushing or chewing or extraction with solvents). Naltrexone is a high affinity μ opioid receptor antagonist that can dampen the euphoria associated with opioid abuse [10,11]. The ratio of naltrexone to oxycodone in this formulation was based on dose-ranging human abuse potential studies on the optimal ratio that would deter abuse (on file, Pfizer). A phase III clinical study of intact ALO-02 showed that pain scores of patients with chronic low back pain improved significantly after receiving ALO-02 compared with placebo [12].

This human abuse liability study was performed to assess whether the strategy of using sequestered naltrexone would reduce the attractiveness of an ER formulation of oxycodone among recreational users when crushed and taken orally. The primary objective of this study was to determine the relative abuse potential of intact ALO-02 (60 mg/7.2 mg [oxycodone HCl/naltrexone HCl]) and crushed ALO-02 (40 mg/4.8 mg and 60 mg/7.2 mg) compared with crushed oxycodone HCl immediate-release (IR) tablets (40 and 60 mg) and placebo administered orally to nondependent, recreational opioid users. Secondary objectives were the evaluation of the pharmacokinetic profile of oxycodone, naltrexone and metabolites following oral administration of ALO-02 (crushed and intact) and oxycodone HCl IR crushed, as well as a comparison of the safety of ALO-02 (crushed and intact) with oxycodone HCl IR crushed and placebo in nondependent, recreational opioid users.

Methods

This was a randomized, double-blind, double-dummy, placebo-controlled, 6-way crossover study (ClinicalTrials.gov identifier: NCT01746901) conducted under the Guidelines for Good Clinical Practice and the Declaration of Helsinki

[13,14]. Written informed consent was obtained from all participants before the start of the study.

Study Population

Healthy, nondependent (based on the Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision criteria [15]), recreational opioid users between the ages of 18 and 55 years with a body mass index between 17.5 kg/m^2 and 30.5 kg/m^2 (total body weight $\geq$ 50 kg) were eligible for inclusion in the study. A recreational opioid user was defined as a user of opioids for nontherapeutic purposes (i.e., psychoactive effects) on at least 10 occasions within the previous year and at least once in the 8 weeks before the screening visit. Exclusion criteria included diagnosis of substance and/or alcohol dependence (excluding nicotine) or treatment for substance- and/or alcohol-related disorders (excluding nicotine); positive urine drug screen (excluding tetrahydrocannabinol) or alcohol breath test at screening or upon admission to study center during drug discrimination and treatment phases; any condition where an opioid is contraindicated; evidence or history of clinically significant disease; history of unresolved sleep apnea in the last 5 years; other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation.

Study Design

This study consisted of screening, naloxone challenge, drug discrimination, treatment, and end-of-study phases. The screening phase consisted of a standard medical evaluation to determine eligibility. During the naloxone challenge phase, eligible participants received intravenous naloxone (0.2 mg, followed by an additional 0.6 mg if no signs of withdrawal were observed within the first 30 seconds) and withdrawal was assessed using the Clinical Opiate Withdrawal Scale (COWS) [16,17]. Participants with a score of <5 on the COWS were eligible for the drug discrimination phase.

During the drug discrimination phase, participants were assessed for their ability to distinguish between orally administered crushed oxycodone HCl IR 40 mg and placebo (one treatment per day over two consecutive days, assigned in random order and in a double-blind fashion under fasted conditions). Ability to distinguish between oxycodone IR and placebo was defined as $\geq$ 15-point peak increase on the Drug Liking and Take Drug Again visual analog scales (VAS), and $\geq$ 30-point peak increase on the High VAS within 2 hours [18]. A peak score of $\geq$ 65 was required on Drug Liking within 2 hours and Take Drug Again at 5 hours postdose in response to oxycodone IR. Participants also had to display an acceptable placebo response, defined as a VAS response 0–10 points for High or 40–60 points for Drug Liking and Take Drug Again. Participants were also selected based on their ability to tolerate study treatment within the first 4 hours postdose, i.e., no vomiting. Those successfully completing the drug discrimination phase were randomized into the treatment phase.

The randomized, double-dummy, 6-way crossover treatment phase consisted of six treatment periods, separated by a minimum 5-day washout between consecutive treatments. Participants were randomized to receive the following six treatments in one of six treatment sequences: Treatment A, Placebo; Treatment B, ALO-02 60 mg/7.2 mg intact; Treatment C, ALO-02 60 mg/7.2 mg crushed; Treatment D, Oxycodone HCl IR 60 mg crushed; Treatment E, ALO-02 40 mg/4.8 mg crushed; Treatment F, Oxycodone HCl IR 40 mg crushed.

Doses selected represent a moderate to high range of oxycodone doses that have previously been safely administered orally to recreational opioid users and were known to produce significant subjective effects on measures for assessment of abuse potential [19–22]. A dose strength lower than 60 mg (i.e., 40 mg) was included in this study to assess abuse deterrence at lower doses. Fasted participants were instructed to swallow intact study medication whole, not to open the capsules, and not to chew medication prior to swallowing. All crushed doses administered during the treatment phase were administered orally as a solution (containing either active drug or placebo) in a dark, opaque bottle to maintain the integrity of the blinding. ALO-02 capsule contents, oxycodone IR tablets, and matched placebo pellets were crushed manually (using a standardized procedure with a mortar and pestle for 2 minutes) and mixed in an artificially sweetened, noncarbonated, flavored, room temperature solution. Following administration, treatment compliance was measured by examining the oral cavity, hands, and dosing containers of each participant. Appropriate rinsing procedures were followed to ensure the participant ingested the entire volume of solution.

Participants who received at least one dose of study drug in the treatment phase were requested to return for a final safety assessment that took place during the end-of-study phase.

Pharmacodynamic Assessments

Pharmacodynamic assessments were conducted predose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 14, 24, and 36 hours postdose. VAS for Drug Liking, Take Drug Again, and other measures specific to a drug effect (VAS for any, bad, good effects) were not conducted at pre-dose. Primary endpoints to assess abuse potential were VAS for Drug Liking and VAS for High presented electronically. Drug Liking was assessed postdose using a bipolar 0–100 point scale, with 50 as neutral, that asked "*At this moment, my liking for this drug is*" with the participant moving the slider to indicate "Strong disliking," "Neither like nor dislike," or "Strong liking." High was assessed by asking the participant to rate the statement "*I am feeling high*" using a unipolar 1–100 point scale anchored by "Not at all" and

"Extremely." The secondary endpoints of Overall Drug Liking and Take Drug Again, assessed at 12, 24, and 36 hours postdose, were also presented electronically. For the Overall Drug Liking VAS, the participant was asked to rate the statement, "*Overall, my liking for this drug is"* on a bipolar scale from "Strong disliking" to "Neither like nor dislike" to "Strong liking." Similarly, for the Take Drug Again VAS, participants rated the statement *"I would take this drug again"* from "Definitely not" to "Neutral" to "Definitely so." Additional secondary endpoints were VAS for Any Drug Effects, Bad Drug Effects, Good Drug Effects, Feel Sick, Nausea, Sleepy, and Dizzy presented on a unipolar 0–100 point scale (0 "definitely not"–100 "definitely so"). Pupillometry assessments were made using standardized conditions following each dose during the drug discrimination and treatment phases to evaluate oxycodone HCl exposure. The same eye for each participant was used for all measurements during the study. Principal parameters of interest for all pharmacodynamic endpoints included the maximum (peak) effect (E_{max}) and area under the effect curve from time 0 to 2 hours ($AUE_{0\text{-}2h}$).

Pharmacokinetic Assessments

To determine oxycodone (following treatment with ALO-02 and oxycodone IR) and naltrexone (ALO-02 only) plasma concentrations, blood samples were collected at pre-dose and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 14, 24, and 36 hours postdose for all treatments. Samples were analyzed using standard procedures [23]. Pharmacokinetic endpoints included maximum plasma drug concentration (C_{max}); time to C_{max} (T_{max}); terminal half-life ($t_{1/2}$); and area under the plasma concentration-time curves from time 0 to 2 hours postdose ($AUC_{0\text{-}2h}$), from time 0 to the last quantifiable concentration (AUC_{last}), and from time 0 extrapolated to infinity (AUC_{inf}), for plasma oxycodone, noroxycodone, oxymorphone, naltrexone, and 6-β-naltrexol.

Safety Assessments

Safety endpoints were treatment-emergent adverse events, vital signs (blood pressure, heart rate, and respiratory rate), oxygen saturation of hemoglobin, and end-tidal carbon dioxide.

Statistical Analyses

The sample size was determined so that 30 completed participants would provide at least 90% power at the 1-sided significance level of 0.025 to detect treatment differences of 15 points in E_{max} for Drug Liking, assuming a standard deviation (SD) of 20 points. This sample size would also provide at least 80% power at the 1-sided significance level of 0.025 to detect treatment differences of at least 12 points in E_{max} for Drug Liking.

The primary analysis population was the completer population, which included all randomized participants who completed all six periods of the treatment phase and contributed to the postdose pharmacodynamic data from each period. The safety population included all participants who received at least one dose of the study drug, beginning with the naloxone challenge. The pharmacokinetic population included all treated participants with at least one concentration in the treatment phase.

Study validity was confirmed by comparison of mean E_{max} for Drug Liking, High, and Take Drug Again between crushed oxycodone IR 40 mg and placebo administered during the treatment phase. Data were analyzed using a mixed-effect model with treatment, period, and sequence as fixed effects, and participant nested within sequence as random effect. Analyses of endpoints with baseline (predose) measurements included the baseline measurement as a covariate in the model. To control for type I errors arising from multiple comparisons, Benjamini-Hochberg procedure was used across primary treatment comparisons of the principal parameters of the two primary endpoints [24].

Results

Participant Disposition, Demographics, and Baseline Characteristics

Of the 81 participants screened, 75 were treated in the naloxone challenge phase (safety population, n = 75). Three participants discontinued due to adverse events (AEs; n = 2) and not meeting entrance criteria (n = 1). Seventy-two participants entered the drug discrimination phase, and 31 participants were discontinued prior to completion of this phase. Reasons for discontinuation were AEs (n = 6), not meeting entrance criteria (n = 19), and protocol violations (n = 6). Forty-one participants completed the drug discrimination phase and were randomized to the treatment phase. During the treatment phase, there were nine discontinuations: five due to positive urine drug screens, two due to AEs, one withdrew consent, and one was lost to follow up. In addition, there was a protocol deviation due to site failure to administer study drug correctly during the treatment phase; the correct solution dose of crushed oxycodone IR 60 mg was administered, but the solid placebo dose was not administered. Data from this participant were included in the pharmacodynamic analysis since the analysis was performed on the data as randomized.

The completer population analyzed for pharmacodynamic parameters included 32 participants who completed all periods of the treatment phase and contributed postdose pharmacodynamic data from each period. The majority of the completer population was white (78%), and had a mean (SD) age of 37.8 (9.3) years, with mean (SD) body weight and body mass index of 78.1 (9.4) kg and 25.6 (2.3) kg/m^2, respectively. Alcohol (87.5% of completer population) and cannabinoids (81.3%) were commonly used recreationally in the 12 months prior to the study. The most common

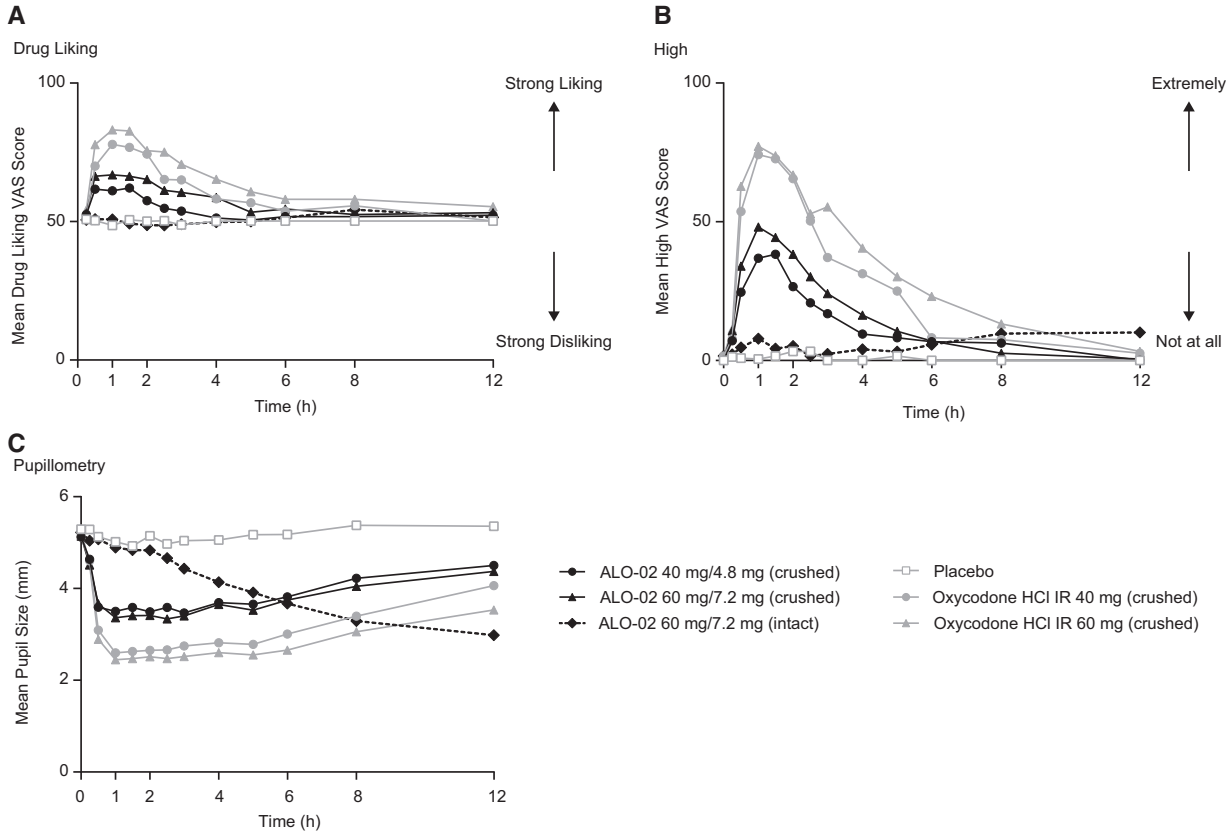

Figure 1 Pharmacodynamic measures over time (completer population).

opioids used recreationally during the previous 12 months reported were oxycodone (50%), OxyContin® (31.3%), and Percocet® (18.8%).

Pharmacodynamic Endpoints (Primary and Secondary)

Time course profiles for mean Drug Liking (at the moment) and High VAS scores and mean pupil diameter for the completer population are summarized in Figure 1. In general, Drug Liking and High VAS scores were greater for crushed oxycodone IR doses compared with crushed and intact ALO-02 and placebo (Figure 1A and 1B). Mean peak effects for crushed treatments generally occurred within 1–2 hours postdose. In contrast, the time course profiles of intact ALO-02 60 mg/7.2 mg were relatively flat with scores remaining low over time, although small, incremental increases in High VAS scores were observed at 8–12 hours postdose. Likewise, for pupillometry, both doses of crushed oxycodone IR resulted in greater decreases in pupil diameter compared with the corresponding crushed ALO-02 doses, and all crushed treatments tended to show peak effects within 1 hour postdose. Intact ALO-02 60 mg/7.2 mg was initially associated with minimal miosis, but the effect gradually increased over time (Figure 1C).

For the primary endpoints, Drug Liking and High (E_{max}) least squares mean VAS scores for crushed oxycodone IR 40 mg were significantly higher than placebo ($P < 0.0001$; Table 1), confirming study validity (the requirement of a significantly higher score for Take Drug Again was also observed; Table 2). Drug Liking and High (E_{max} and $AUE_{0\text{-}2h}$) least squares mean VAS scores for all ALO-02 doses (crushed and intact) were significantly lower than dose-matched oxycodone IR ($P < 0.0001$; Table 1) and significantly higher than placebo in most cases ($P < 0.05$). Intact ALO-02 60 mg/7.2 mg was associated with significantly lower Drug Liking and High (E_{max} and $AUE_{0\text{-}2h}$) compared with all treatments, including crushed ALO-02, except placebo ($P < 0.001$).

When ALO-02 treatment was compared with an equivalent dose of oxycodone IR, the overall mean percentage reduction for Drug Liking E_{max} was 39% for the crushed ALO-02 40 mg/4.8 mg group, 38% for crushed ALO-02 60 mg/7.2 mg, and 80% for intact ALO-02 60 mg/7.2 mg. The majority of participants receiving crushed ALO-02 40 mg/4.8 mg (72%), crushed ALO-02 60 mg/7.2 mg (75%), and intact ALO-02 60 mg/7.2 mg (91%), experienced a reduction in Drug Liking E_{max} relative to their respective dose of crushed oxycodone IR (Figure 2A). Results were similar for High E_{max}, with an overall mean percentage reduction of 42% with crushed

Table 1 Summary of primary endpoints: least squares mean VAS scores (95% CI; completer population, n = 32)

Endpoint	Placebo	ALO-02 40 mg/4.8 mg (crushed)	ALO-02 60 mg/7.2 mg (intact)	ALO-02 60 mg/7.2 mg (crushed)	Oxycodone IR 40 mg (crushed)	Oxycodone IR 60 mg (crushed)
Drug liking						
E_{max}	51.6 (46.0, 57.2)	70.2*,† (64.6, 75.7)	59.3*,‡ (53.7, 64.9)	74.5*,† (68.9, 80.1)	85.5* (79.9, 91.1)	89.8* (84.2, 95.4)
AUE_{0-2h}	100.1 (91.4, 108.9)	118.4*,† (109.6, 127.1)	100.1‡ (91.4, 108.9)	127.3*,† (118.5, 136.0)	141.3* (132.5, 150.1)	149.5* (140.7, 158.3)
High						
E_{max}	10.2 (−0.7, 21.1)	46.5*,† (35.6, 57.4)	22.5*,‡ (11.6, 33.4)	52.8*,† (41.9, 63.7)	78.6* (67.7, 89.5)	85.7* (74.8, 96.6)
AUE_{0-2h}	2.8 (−12.2, 17.8)	55.4*,† (40.4, 70.4)	9.7‡ (−5.3, 24.7)	71.6*,† (56.6, 86.6)	112.1* (97.1, 127.1)	117.7* (102.7, 132.7)

AUE_{0-2h} = area under the effect curve from time 0 to 2 hours; CI = confidence interval; E_{max} = maximum (peak) effect; IR = immediate release; VAS = visual analog scale.
*$P \leq 0.05$, drug vs placebo group.
†$P \leq 0.0001$, dose-matched crushed ALO-02 vs crushed oxycodone IR.
‡$P \leq 0.0001$, dose-matched intact ALO-02 vs crushed oxycodone IR.

ALO-02 40 mg/4.8 mg, 34% with crushed ALO-02 60 mg/7.2 mg, and 78% with intact ALO-02 60 mg/7.2 mg. Compared with their respective dose of oxycodone IR, 78% of participants in the crushed ALO-02 40 mg/4.8 mg group, 78% in the crushed ALO-02 60 mg/7.2 mg group, and 97% in the intact ALO-02 60 mg/7.2 mg group experienced a reduction in High E_{max} (Figure 2B).

All secondary VAS measures were generally lower for crushed or intact ALO-02 when compared with corresponding doses of crushed oxycodone IR (Table 2). Global subjective effects measured by the Overall Drug Liking and Take Drug Again VAS support the results of the primary endpoints. For both these scales, placebo and ALO-02 (both intact and crushed) showed significantly lower E_{max} scores compared with corresponding doses of crushed oxycodone IR ($P < 0.001$), with the exception of crushed ALO-02 60 mg/7.2 mg versus crushed oxycodone IR 60 mg. The VAS results for Good Drug Effects and Any Effects were similar, with all ALO-02 groups showing significantly lower E_{max} scores relative to respective doses of oxycodone IR ($P < 0.0001$). For negative effects (Bad Drug Effects, Nausea, and Feel Sick VAS), most comparisons resulted in significantly higher E_{max} scores for crushed oxycodone IR (40 mg and 60 mg) compared with placebo, and crushed ALO-02 60 mg/7.2 mg was significantly lower than crushed oxycodone IR 60 mg ($P < 0.05$).

Pharmacokinetic Profile

Oxycodone plasma concentration-time curves are shown in Figure 3A and illustrate similar profiles following administration of crushed ALO-02 compared with crushed oxycodone IR, at both dose levels. Overall, maximum oxycodone plasma absorption (C_{max}) and total exposure (AUC_{inf}) were similar between crushed ALO-02 doses and their comparator oxycodone IR doses (Table 3). For the 1.5-fold dose increment from 40 to 60 mg, C_{max} and AUC_{inf} increased in a dose proportional manner by 1.34- and 1.47-fold, respectively, for oxycodone IR and by 1.46- and 1.45-fold, respectively, for crushed ALO-02. The median T_{max} and mean $t_{1/2}$ values ranged from 0.6–1.0 hours and 4.2–4.4 hours, respectively, and appeared to be unrelated to dose or drug treatment. Total oxycodone exposure following intact ALO-02 60 mg/7.2 mg was similar to that of the crushed treatments based on AUC_{inf}; however, consistent with the ER formulation of ALO-02, C_{max} as well as the partial AUC_{0-2h} for intact ALO-02 60 mg/7.2 mg were lower than those observed for crushed ALO-02 and oxycodone IR. T_{max} was delayed to 12 hours and $t_{1/2}$ was prolonged to 9.3 hours.

Oxycodone metabolites also followed a similar pattern. After crushed ALO-02 or oxycodone IR, noroxycodone median T_{max} ranged from 0.6–1.1 hours and oxymorphone had a median T_{max} of 0.6 hours. Following administration of intact ALO-02, noroxycodone and oxymorphone T_{max} were observed at 14 hours. Noroxycodone and oxymorphone overall systemic exposure based on AUC_{inf} for all active treatments were similar.

Naltrexone plasma concentrations were below the limit of detection in all samples collected following intact ALO-02 (Table 3). Naltrexone plasma concentration-time curves for the crushed ALO-02 groups are shown in Figure 3B.

Table 2 Summary of secondary endpoints: least squares mean VAS scores (95% CI; completer population, n = 32)

Endpoint	Placebo	ALO-02 40 mg/4.8 mg (crushed)	ALO-02 60 mg/7.2 mg (intact)	ALO-02 60 mg/7.2 mg (crushed)	Oxycodone IR 40 mg (crushed)	Oxycodone IR 60 mg (crushed)
Take drug again						
E_{max}	46.1 (36.8, 55.5)	58.1*,† (48.8, 67.4)	48.7‡ (39.4, 58.0)	72.5* (63.2, 81.8)	83.7* (74.4, 93.0)	81.5* (72.2, 90.8)
Overall drug liking						
E_{max}	51.1 (43.6, 58.5)	64.4*,† (56.9, 71.8)	53.3‡ (45.9, 60.7)	74.3* (66.9, 81.7)	80.9* (73.5, 88.4)	81.8* (74.3, 89.2)
Good drug effects						
E_{max}	11.7 (0.4, 23.0)	48.1*,† (36.8, 59.4)	24.3‡ (13.0, 35.6)	54.7*,† (43.5, 66.0)	81.8* (70.5, 93.1)	84.5* (73.2, 95.8)
Bad drug effects						
E_{max}	5.7 (−5.2, 16.5)	16.5 (5.6, 27.3)	20.4* (9.6, 31.3)	16.7† (5.9, 27.6)	26.3* (15.4, 37.1)	31.5* (20.7, 42.4)
Any drug effects						
E_{max}	8.7 (−2.4, 19.8)	47.1*,† (36.0, 58.2)	27.5*,‡ (16.4, 38.6)	55.9*,† (44.8, 66.9)	82.2* (71.2, 93.3)	88.8* (77.7, 99.8)
Feel sick						
E_{max}	2.7 (−4.4, 9.9)	4.9 (−2.3, 12.1)	9.7 (2.5, 16.8)	1.9† (−5.2, 9.1)	9.0 (1.9, 16.2)	13.3* (6.1, 20.5)
Nausea						
E_{max}	6.0 (−3.6, 15.7)	11.4 (1.7, 21.0)	9.4‡ (−0.2, 19.0)	11.2† (1.6, 20.9)	17.6* (8.0, 27.3)	22.7* (13.0, 32.4)
Sleepy						
E_{max}	22.8 (10.8, 34.8)	55.7*,† (43.7, 67.7)	38.6*,‡ (26.6, 50.6)	58.9*,† (46.9, 70.9)	71.1* (59.1, 83.1)	77.4* (65.3, 89.4)
Dizzy						
E_{max}	3.3 (−7.7, 14.4)	22.9* (11.8, 33.9)	11.7‡ (0.7, 22.8)	19.1*,† (8.1, 30.1)	30.2* (19.2, 41.3)	40.0* (28.8, 51.1)

CI = confidence interval; E_{max} = maximum (peak) effect; IR = immediate release; VAS = visual analog scale.
*$P \leq 0.05$, drug vs placebo group.
†$P \leq 0.05$, dose-matched crushed ALO-02 vs crushed oxycodone IR.
‡$P \leq 0.05$, dose-matched intact ALO-02 vs crushed oxycodone IR.

Naltrexone mean C_{max} after administration of crushed ALO-02 40 mg/4.8 mg and crushed ALO-02 60 mg/7.2 mg were 1.1 ng/mL and 1.8 ng/mL, respectively (Table 3). For the 1.5-fold dose increment of naltrexone in ALO-02 (from 4.8 to 7.2 mg), the naltrexone C_{max} and AUC_{inf} values appeared to increase in a dose-proportional manner by 1.69- and 1.63-fold, respectively. For crushed ALO-02 40 mg/4.8 mg and crushed ALO-02 60 mg/7.2 mg, the median T_{max} and mean $t_{1/2}$ values were 0.6 hours and 5.4–5.6 hours, respectively, and appeared to be unrelated to the dose level. All other naltrexone plasma exposure parameters for the crushed treatments were similar (Table 3). Following administration of crushed ALO-02 40 mg/4.8 mg and crushed ALO-02 60 mg/7.2 mg, maximum plasma 6-β-naltrexol concentrations (C_{max}: 8.2 and 13.4 ng/mL, respectively) were observed within a median T_{max} of 0.6 hours (range: 0.2–2.6 hours).

Safety

The safety population included all participants who received one or more doses of study drug, beginning with the naloxone challenge. During the naloxone challenge phase, five (6.7%) participants experienced five AEs, of which two AEs (pruritus and hematoma) were considered treatment-related by the investigator. There were two discontinuations resulting from mild severity AEs: extrasystoles (attributed to an underlying condition) and second degree atrioventricular block.

During the drug discrimination phase, 70 (97.2%) participants experienced 203 AEs after treatment with crushed oxycodone IR 40 mg, of which 202 were considered to be treatment-related by the investigator. There were 14 (20.3%) participants who experienced 20 AEs after placebo treatment with 16 of these AEs

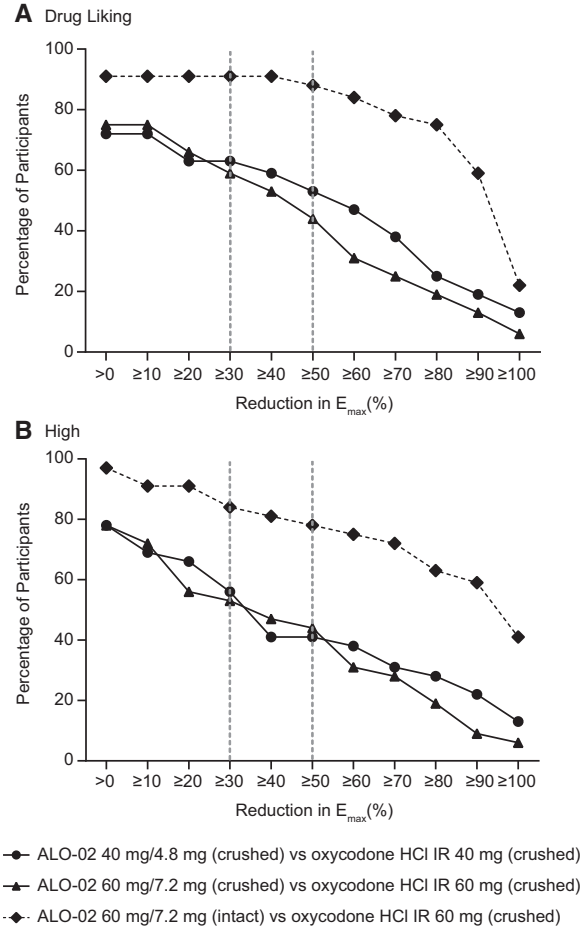

Figure 2 Percent reduction profile for E_{max} of drug liking and high VAS for ALO-02 v. Oxycodone HCl IR at same dose (completer population). Dashed vertical lines indicate $\geq$ 30% and $\geq$ 50% responder rates. E_{max} = maximum (peak) effect; IR = immediate release.

considered treatment-related by the investigator. The most common AEs after dosing with crushed oxycodone IR 40 mg were euphoric mood (76.4%), pruritus (48.6%), somnolence (29.2%), dry mouth (19.4%), nausea (18.1%), and dizziness (13.9%). Somnolence (5.8%), fatigue (4.3%), and dizziness (2.9%) were the most common AEs after placebo treatment. There were six discontinuations due to AEs, five of which were considered related to the study drug. Three participants discontinued due to vomiting, and three others discontinued, one participant each, due to T-wave inversion on electrocardiogram, sinus arrest, and syncope. All AEs, except syncope, were attributed to oxycodone IR 40 mg treatment. One participant experienced a sinus arrest during the drug discrimination phase after receiving crushed oxycodone IR 40 mg, which was considered a treatment-related serious AE (SAE). The SAE and all AEs during the drug discrimination phase were resolved.

During the treatment phase, fewer participants experienced AEs following intact ALO-02 60 mg/7.2 mg (71.1%), crushed ALO-02 40 mg/4.8 mg (80.6%), and crushed ALO-02 60 mg/7.2 mg (91.9%) compared with participants who received crushed oxycodone IR 40 (100%) or 60 mg (100%). There were 12 participants (32.4%) who reported experiencing an AE after placebo treatment. There were no deaths or SAEs during the treatment phase of this study. The majority of AEs across all the treatments were mild in severity and fewest after placebo treatment. Known opioid effects (euphoric mood, pruritus, dizziness) occurred in both the oxycodone IR and ALO-02 treatments; however, there were fewer occurrences in the crushed ALO-02 40 mg/4.8 mg, crushed ALO-02 60 mg/7.2 mg, and intact ALO-02 60 mg/7.2 mg treatments (Table 4). Two participants (2.7%) were discontinued from the study due to an AE: the first due to atrial flutter (169 hours after crushed oxycodone IR 40 mg treatment) and the second due to second degree atrioventricular block (9.2 hours after crushed ALO-02 40 mg/4.8 mg treatment). Each AE subsided within the same day of occurrence.

No clinically significant findings were reported for vital signs, laboratory parameters, pulse oximetry, or capnography. There was no evidence of respiratory depression with any of the treatments.

Discussion

The objective of this study was to compare the oral abuse potential of ALO-02, an ER oxycodone/naltrexone abuse-deterrent formulation, with oxycodone IR. The study was conducted according to the recommendations of the FDA on the assessment of abuse-deterrent opioid formulations [6]. Study validity was confirmed with crushed oxycodone IR 40 mg showing significantly higher E_{max} values for Drug Liking, High, and Take Drug Again compared with placebo. Intact and crushed ALO-02 were associated with significantly lower scores on the primary endpoint, Drug Liking and High VAS, compared with respective doses of the active comparator, oxycodone IR. With few exceptions, results on secondary pharmacodynamic endpoints supported these findings. Notably, global subjective measures, (i.e., Take Drug Again and Overall Drug Liking), which reflect the persistence of drug effects after the initial effects have subsided, were significantly lower after intact and crushed ALO-02 administration (with the exception of crushed ALO-02 60 mg/7.2mg) versus crushed oxycodone IR. Together, these data suggest that ALO-02, intact or crushed, may have less abuse potential than equivalent doses of crushed oxycodone IR when orally administered to nondependent, recreational opioid users.

Oxycodone plasma exposure for crushed ALO-02 followed a similar pattern to crushed oxycodone IR with maximal concentrations occurring within the first hour of dosing. Likewise, plasma concentrations of naltrexone following crushed ALO-02 were maximal within the first

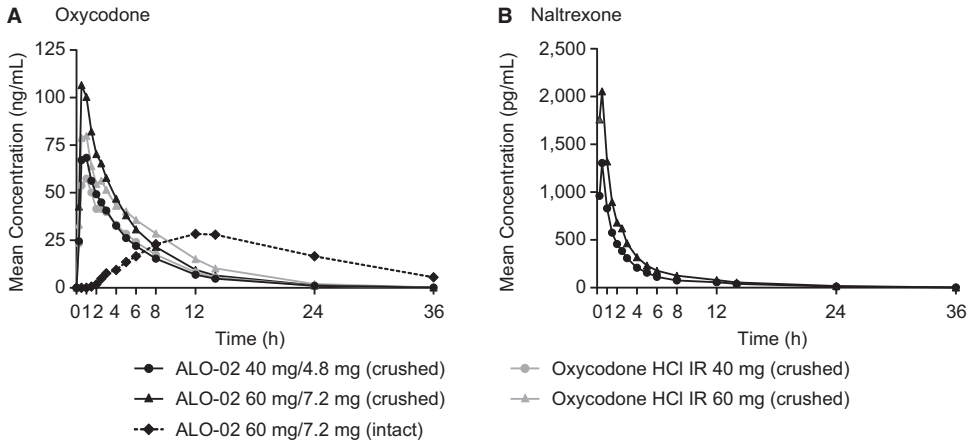

Figure 3 Mean plasma concentration-time profiles. IR = immediate release.

hour postdose. The objective measurements of pupillometry indicate lower physiologic opioid activity with crushed ALO-02 in comparison with crushed oxycodone IR, despite similar oxycodone plasma exposures. Together, the pupillometry and pharmacokinetic results suggest that the C_{max} of naltrexone coincides with and antagonizes the physiologic effects of oxycodone.

Naltrexone levels were undetected in participants receiving intact ALO-02. In this case, the unique pharmacodynamic profile of intact ALO-02 is likely attributable to its ER properties, as confirmed by the lower (and delayed) oxycodone C_{max} and the delayed, incremental effects (over time) on pupillometry. The time course profiles for Drug Liking and High were relatively flat and similar to placebo, and although intact ALO-02 demonstrated significantly greater E_{max} scores on Drug Liking and High compared with placebo, a similar significant difference was not observed for $AUE_{0\text{-}2h}$. For the global measures of Take Drug Again and Overall Drug Liking, E_{max} scores associated with intact ALO-02 were not significantly different from placebo but were significantly lower than crushed oxycodone IR. These results suggest less abuse potential with orally administered intact ALO-02 compared with oxycodone IR, a difference likely attributable to the preserved ER properties of ALO-02.

There were fewer opioid-related AEs following treatment with intact and crushed ALO-02 compared with oxycodone IR. This was particularly noteworthy for euphoric mood, a pattern consistent with the pharmacodynamic results of intact and crushed ALO-02. The incidence of other AEs, such as pruritus, dizziness, and nausea, was also less in the intact and crushed ALO-02 groups relative to respective doses of crushed oxycodone IR.

The difference between the effects of crushed oxycodone IR 40 and 60 mg on Drug Liking and High (E_{max} and $AUE_{0\text{-}2h}$) were small and not statistically significant. The inability of participants to discriminate between doses is referred to as a plateau effect, and in this study, may be attributed to the population having been selected for sensitivity to the oxycodone IR 40 mg dose during the drug discrimination phase. Eligible participants sensitive to the oxycodone IR 40 mg dose may not differentiate higher doses very well. This finding reinforces the need to consider discrimination doses that are similar or intermediate to those being tested in the main clinical phase of these studies.

There are limitations associated with this study. While conducting the study in nondependent, recreational opioid users was consistent with the FDA Guidance, generalization to other populations, such as individuals with pain or substance abuse disorders and physical dependence on opioids, may be limited [6]. The study was performed in a confined, in-clinic, and highly controlled setting and limited to doses of 40 and 60 mg oxycodone; misuse or abuse may occur in situations with more variable and confounding factors. The results of this study and its extrapolation to real-world abuse will need to be evaluated with longitudinal epidemiologic studies.

Conclusions

The results of this abuse-potential study demonstrate that ALO-02 (crushed or intact) significantly lowers pharmacodynamic effects on subjective measures of Drug Liking and High compared with equivalent doses of crushed oxycodone IR. The reduced effects associated with crushed ALO-02 are likely attributable to naltrexone, whereas the effects of intact ALO-02 may be mediated by its ER properties. These data support less abuse potential with orally administered crushed or intact ALO-02 in comparison with equivalent doses of crushed oxycodone IR.

Table 3 Summary of oxycodone and naltrexone pharmacokinetic parameters (pharmacokinetic population)

	Oxycodone					Naltrexone		
	ALO-02 40 mg/4.8 mg (crushed) (n = 36)	ALO-02 60 mg/7.2 mg (intact) (n = 38)	ALO-02 60 mg/7.2 mg (crushed) (n = 37)	Oxycodone IR 40 mg (crushed) (n = 37)	Oxycodone IR 60 mg (crushed) (n = 37)	ALO-02 40 mg/4.8 mg (crushed) (n = 36)	ALO-02 60 mg/7.2 mg (intact) (n = 38)	ALO-02 60 mg/7.2 mg (crushed) (n = 37)
C_{max}, ng/mL								
Geometric mean	76.3	28.5	111.5	65.0	87.0	1.1	0.0	1.8
(Geometric CV, %)	(29)	(31)	(26)	(24)	(31)	(76)	(0)	(75)
T_{max}, h								
Median (range)	1.0 (0.5–2.6)	12.1 (3.0–14.1)	0.6 (0.5–1.6)	1.0 (0.3–3.1)	1.0 (0.3–2.6)	0.6 (0.3–1.6)	NR	0.6 (0.3–1.1)
$AUC_{0\text{-}2h}$, ng·h/mL								
Geometric mean	100.0	0.7	153.4	85.8	114.9	1.2	0.00	2.0
(Geometric CV, %)	(27)	(77)	(23)	(24)	(31)	(67)	(0)	(67)
AUC_{inf}, ng·h/mL								
Geometric mean	348.1	629.4	503.5	350.5	516.6	2.9	NR	4.7
(Geometric CV, %)	(31)	(28)	(28)	(28)	(33)	(56)		(54)
$t_{1/2}$, h								
Mean ± SD	4.4 ± 0.7	9.3 ± 1.6	4.4 ± 0.6	4.3 ± 0.7	4.2 ± 0.5	5.4 ± 1.7	NR	5.6 ± 2.1

$AUC_{0\text{-}2h}$ = area under the concentration time curve from time 0 to 2 hours; AUC_{inf} = area under the concentration time curve from time 0 extrapolated to infinity; C_{max} = maximal plasma drug concentration; CV = coefficient of variation; IR = immediate release; NR = not reported; SD = standard deviation; $t_{1/2}$ = terminal half-life; T_{max} = time to C_{max}.

Table 4 Treatment-emergent adverse events during treatment phase occurring ≥ 10% with any treatment (safety population, all causalities; n(%))

MedDRA (v16.0) Preferred Term	Placebo (n = 37)	ALO-02 40 mg/4.8 mg (crushed) (n = 36)	ALO-02 60 mg/7.2 mg (intact) (n = 38)	ALO-02 60 mg/7.2 mg (crushed) (n = 37)	Oxycodone IR 40 mg (crushed) (n = 37)	Oxycodone IR 60 mg (crushed) (n = 36)
Euphoric mood	1 (2.7)	19 (52.8)	11 (28.9)	23 (62.2)	31 (83.8)	31 (86.1)
Pruritus	0	5 (13.9)	14 (36.8)	8 (21.6)	18 (48.6)	24 (66.7)
Somnolence	4 (10.8)	14 (38.9)	10 (26.3)	14 (37.8)	13 (35.1)	17 (47.2)
Dizziness	0	6 (16.7)	7 (18.4)	7 (18.9)	8 (21.6)	10 (27.8)
Nausea	3 (8.1)	4 (11.1)	5 (13.2)	6 (16.2)	6 (16.2)	7 (19.4)
Feeling hot	1 (2.7)	2 (5.6)	1 (2.6)	7 (18.9)	5 (13.5)	2 (5.6)
Headache	2 (5.4)	1 (2.8)	7 (18.4)	5 (13.5)	4 (10.8)	4 (11.1)
Dry mouth	0	0	1 (2.6)	3 (8.1)	4 (10.8)	5 (13.9)
Fatigue	1 (2.7)	2 (5.6)	4 (10.5)	4 (10.8)	5 (13.5)	4 (11.1)
Pruritus generalised	0	1 (2.8)	1 (2.6)	0	4 (10.8)	3 (8.3)
Vomiting	0	0	2 (5.3)	1 (2.7)	2 (5.4)	4 (11.1)

IR = immediate release.

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