ORIGINAL ARTICLE

Evaluation of the oral human abuse potential of Oxycodone DETERx® formulation (Xtampza® ER)

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ABSTRACT

Objective: *To further characterize the human abuse potential and pharmacokinetics (PK) of Oxycodone DETERx (Xtampza® ER) after intact and chewed oral administration.*

Design: *Randomized, double-blind, triple-dummy, active- and placebo-controlled, single-dose, six-period, crossover comparison study.*

Setting: *Clinical research unit.*

Subjects: *Adult, nondependent recreational opioid users who liked the effects of crushed immediate-release (IR) oxycodone in solution and were able to differentiate the effects from placebo solution.*

Interventions: *Oral administration of intact Oxycodone DETERx (fasted and fed), chewed Oxycodone DETERx (fasted and fed), crushed IR oxycodone (fasted), and placebo (fed).*

Main Outcome Measures: *Subject ratings (100-point visual analog scales) of Drug Liking (primary measure) and Take Drug Again (key secondary measure).*

Results: *The pharmacodynamic (PD) analysis included 52 subjects who completed the study; the PK analysis included 71 subjects. Compared with crushed IR oxycodone fasted, the least-squares mean maximum effect (E_{max}) was statistically significant ($p < 0.01$) for Drug Liking and Take Drug Again, respectively, for chewed Oxycodone DETERx fasted (LS mean difference ± standard error of the mean: 13.1 ± 2.2 and 10.0 ± 3.2 points) and fed (10.9 ± 2.2 and 9.7 ± 3.3 points) and intact Oxycodone DETERx fasted (12.2 ± 2.2 and 9.3 ± 3.3 points) and fed (10.3 ± 2.2 and 9.2 ± 3.3 points). Results were consistent for other PD measures (Good Effects, Feeling High). Chewed Oxycodone DETERx fasted and fed treatments were bioequivalent to the respective intact treatments based on PK parameters.*

Conclusions: *This study showed that when chewed or swallowed intact, under fasted or fed conditions, Oxycodone DETERx had statistically significantly lower abuse potential via the oral route compared with IR oxycodone.*

INTRODUCTION

Opioids are an important treatment option for patients with moderate-to-severe pain[1,2]; however, prescription opioids are subject to misuse and abuse.[3,4] The US Food and Drug Administration (FDA) has identified the development of abuse-deterrent opioid formulations as "a high public health priority,"[5] and the introduction of abuse-deterrent opioid formulations has been associated with lower rates of abuse, overdose, and diversion.[6-8]

Oxycodone DETERx® (Xtampza® ER; Collegium Pharmaceutical, Inc., Canton, MA) is

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an extended-release (ER), abuse-deterrent, microsphere-in-capsule formulation of oxycodone approved by the FDA in 2016 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.[9] The DETERx technology uses hydrophobic, waxy microspheres to maintain the ER mechanism while deterring product manipulation.[10,11] Each microsphere (median particle size of ~300 μm) contains oxycodone (as the myristate salt, which is almost insoluble in water) dispersed in a matrix of fatty acid and waxes.[10,11] The abuse-deterrent design features include the microsphere size and waxy quality, which protect against physical manipulation by crushing (for intranasal or oral administration) and chewing, and the lipophilic and waxy excipients, which protect against chemical manipulation using various commonly available solvents (including extraction of oxycodone for intravenous [IV] administration).[12-15] Abuse-deterrent formulation studies found that oxycodone pharmacokinetics (PK) were similar after ingestion of intact Oxycodone DETERx capsules or contents subjected to physical manipulation[12,16] and demonstrated low extractability of oxycodone from the DETERx formulation in water (<12 percent) and resistance to melting and suspension in water for direct (IV) injection.[13]

The oral human abuse potential of Oxycodone DETERx was evaluated in a previous study of recreational opioid users. That study found a statistically significant reduction in the maximum (peak) effect (E_{max}) of Drug Liking for Oxycodone DETERx (intact or chewed) compared with crushed immediate-release (IR) oxycodone, but no statistically significant difference between treatments on a measure of willingness to take the drug again (Take Drug Again E_{max}).[17] Since the first human abuse potential study was conducted, FDA guidance has evolved toward a need to better distinguish potential clinical effects between two drugs with abuse potential.[5,18]

This article presents the results of a second study on the oral human abuse potential and PK of Oxycodone DETERx, comparing intact and chewed administration of Oxycodone DETERx with crushed IR oxycodone solution in recreational, nondependent opioid users. The methodology of the present study was designed to be consistent with updated FDA feedback and recommendations (reflected in published guidance documents[5,18]), to further characterize the human abuse potential of Oxycodone DETERx. Changes to the design of the study included revision of the statistical analysis procedure (including preselection of a clinically meaningful difference for between-treatment comparisons[19]), increased dose of IR oxycodone in the drug discrimination phase (from 20 to 40 mg) to confirm tolerability, more stringent drug discrimination criteria to facilitate selection of subjects for the double-blind treatment phase, and improved training of the subjects on the use of all patient-reported outcomes in the study.

METHODS

This randomized, double-blind, triple-dummy, active- and placebo-controlled, single-dose, six-period crossover study was conducted at one study site in the United States between March 2016 and December 2016. Study conduct was in accordance with the International Conference on Harmonisation guideline for Good Clinical Practice, the principles of the Declaration of Helsinki, and FDA guidance on the assessment of abuse potential of drugs[18] and the evaluation of abuse-deterrent opioids.[5] Study materials were approved by an institutional review board (Midlands IRB, Overland Park, KS); subjects provided written informed consent before any study-related procedure was initiated. Subject recruitment was completed in large part through use of a registry of subjects who participated in previous human abuse potential studies. However, in order to complete enrollment, additional subject advertising media were utilized, including television, radio, online (eg, Facebook), and stationary (eg, bus stop posters) advertisements.

Study subjects

Inclusion criteria were similar to those of the previous oral human abuse potential study.[17] Subjects included healthy, adult (18-55 years), nondependent recreational opioid users with body mass index ≤33.0 kg/m^2. Subjects were not dependent on opioids: they did not exhibit an opioid use disorder as assessed by the investigator using the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) criteria and had not developed a tolerance to opioids. A naloxone challenge test, which included an assessment of withdrawal using the Clinical Opiate Withdrawal Scale (COWS),[20,21] was conducted at the beginning of the drug discrimination phase. Subjects with a COWS score of ≥5,

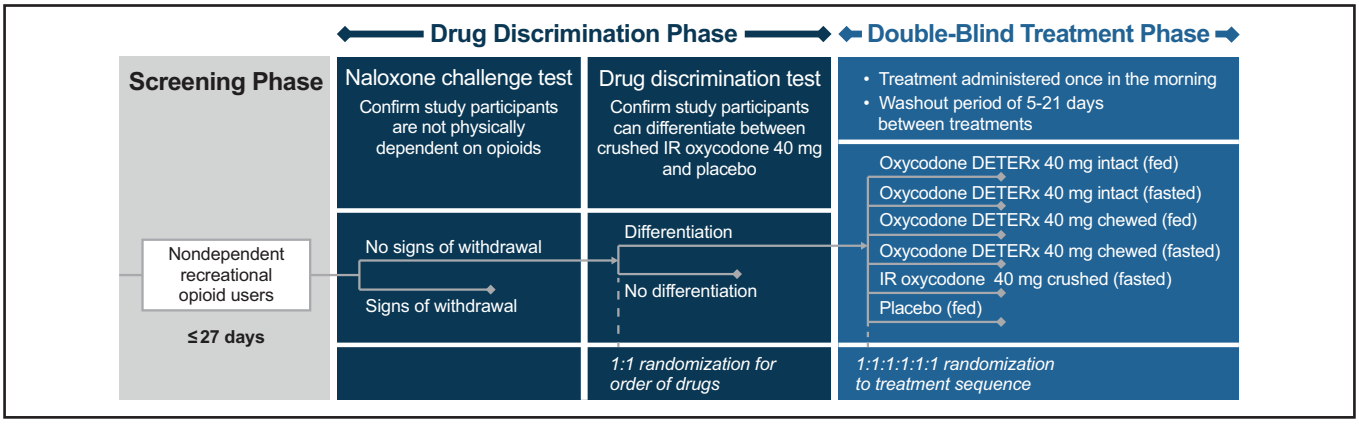

Figure 1. Study design. IR, immediate-release.

indicative of physical dependence on opioids, were precluded from study participation. Recreational use was defined as opioid use for nonmedical purposes on at least 10 occasions within the last year and at least once during the 12 weeks before screening. Eligible subjects had no history of alcohol or drug dependence (other than caffeine and nicotine) and were not heavy users of tobacco products (≤20 cigarettes per day and able to abstain from smoking for at least 5 hours per day).

Study design and treatment

Drug discrimination phase. The naloxone challenge test consisted of sequential IV bolus doses of 0.2 and 0.6 mg. Subjects with no signs or symptoms of withdrawal, based on COWS score <5, were eligible to continue in the study. In the drug discrimination test, subjects received crushed IR oxycodone 40 mg in solution or placebo powder in solution, administered in a randomized double-blind crossover manner under fasted conditions, with each dose separated by at least 24 hours. Ability to differentiate between IR oxycodone and placebo was assessed using the 100-point bipolar Drug Liking visual analog scale (VAS) and defined by the following criteria: Drug Liking E_{max} of ≥75 points in response to IR oxycodone, Drug Liking score of ≥45 and ≤55 points in response to placebo, and ≥15-point difference in Drug Liking score between IR oxycodone and placebo at ≥1 time point. Subjects who met all eligibility requirements, were able to discriminate between IR oxycodone and placebo, and tolerated IR oxycodone 40 mg (eg, no emesis within 12 hours) were eligible for the double-blind treatment phase.

Double-blind treatment phase. Subjects received each of six treatments administered in randomized, crossover, triple-dummy fashion, with a minimum 5-day washout period between treatments (Figure 1). Subjects were admitted to the clinical research unit the day before each treatment was administered and remained in residence at the clinical site until approximately 36 hours after dosing or until discharge was deemed safe by the investigator.

For the fed Oxycodone DETERx and placebo treatments, subjects were provided a standardized high-fat, high-calorie breakfast (approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively), as per FDA guidance,[22] 30 minutes before scheduled administration of study drug and were required to finish the meal within 20 minutes. For the fasted Oxycodone DETERx and oxycodone IR treatments, study drug was administered after an overnight fast of ≥10 hours.

Study drug consisted of Oxycodone DETERx capsules (containing the equivalent of 40 mg oxycodone hydrochloride [HCl]), matching placebo DETERx capsules, crushed IR oxycodone 40 mg (two 20-mg IR oxycodone HCl tablets), and placebo powder. Oxycodone DETERx was administered intact and chewed, under fed and fasted conditions. Administration of oxycodone IR crushed, in solution, under fasted conditions, was selected as the worst-case scenario, which provided high and rapid central exposure to oxycodone; therefore, study treatment did not include intact, chewed, or fed administration of IR oxycodone. For intact administration, subjects ingested intact capsules with 50 mL of IR oxycodone/placebo solution, followed by one rinse of 10 mL and an additional

~90 mL of room temperature, noncarbonated water. For chewed administration, subjects were instructed to chew the study drug capsule contents for 2 minutes without swallowing or talking, which was timed and witnessed by study staff. Following chewing, two additional 50-mL rinses with room temperature, noncarbonated water were administered. Study staff visually inspected the oral cavity, including the buccal and lingual aspects of all four quadrants and under the tongue. If study drug microspheres were seen at the tooth-gum interface or between the teeth, the subject was provided a dental pick to loosen any microspheres to facilitate swallowing of study drug. Subjects completed the dosing procedure within 5 minutes.

Assessments

Measures used for pharmacodynamic (PD) assessment were consistent with FDA guidance document recommendations for abuse potential studies and included the Drug Effects Questionnaire (DEQ), which includes 100-point VAS scales for Drug Liking, Good Effects, Feeling High, Bad Effects, Sick, Nausea, Sleepy, Dizzy, and Any Effects; Take Drug Again VAS; Overall Drug Liking VAS; price value assessment (PVA); and Addiction Research Center Inventory/Morphine Benzedrine Group (ARCI/MBG)[18,23-26] scales. Pupil diameter was measured using a NeurOptic® VIP-200 pupillometer (NeurOptics Inc., Irvine, CA). The DEQ (including Drug Liking), ARCI/MBG, and pupil size were assessed at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours postdose, the Overall Drug Liking and Take Drug Again assessments were completed at 8 and 24 hours postdose, and PVA was completed at 24 hours postdose.

For the PK assessment, blood samples were obtained predose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, and 36 hours postdose. Pharmacokinetic parameters included maximum observed plasma concentration (C_{max}), time to reach maximum plasma concentration (T_{max}), area under the plasma concentration-time curve (AUC) from time 0 to last measurable plasma concentration (AUC_{0-t}), AUC from time 0 to infinity ($AUC_{0-\infty}$), terminal elimination half-life ($t_{1/2}$), and the abuse quotient (AQ). The AQ is a measure of average rate of rise in plasma concentration between dosing and T_{max} (C_{max}/T_{max}).[27,28]

Safety assessments included treatment-emergent adverse events, clinical laboratory tests, physical examination, vital signs, and oxygen saturation.

Statistical analyses

In the sample size determination, a total of 48 completed subjects was estimated to provide at least 90 percent power to detect treatment differences of ≥9.0 points in E_{max} for the Drug Liking VAS, at the 1-sided significance level of 0.025, and estimated abuse deterrence margin,[5] $\delta_1 = 3.5$, using a paired means test and correlation of 0.5, and assuming standard deviation (SD) differences of 11.0 points. The sample size calculation parameters were determined based on data from the previous human abuse potential study using Oxycodone DETERx.[27]

The PD population was defined as all randomized subjects who had ≥1 response on the Drug Liking scale within 2 hours of T_{max} for each treatment. The PK analysis population included subjects who completed ≥2 active treatment periods with sufficient quantifiable data for C_{max} and AUC, and who did not experience emesis (within 12 hours of Oxycodone DETERx dosing and within two times the median T_{max} of 1.07 hours [ie, 2.14 hours] of IR oxycodone dosing). The safety population included subjects who received ≥1 dose of study drug in the double-blind treatment phase and had ≥1 post-treatment safety observation.

The primary endpoint was Drug Liking E_{max} during the 24 hours after dosing. Take Drug Again E_{max} was the key secondary endpoint. For the Drug Liking VAS, other DEQ VAS scales, and ARCI/MBG, the maximum (peak) effect (E_{max}) was calculated through 24 hours after dosing; for pupillometry, E_{max} was calculated through 8 hours postdose; and for Take Drug Again VAS and Overall Drug Liking VAS, E_{max} was based on assessments at 8 and 24 hours postdose. The primary analysis was a pairwise comparison between chewed Oxycodone DETERx treatments (fed or fasted) and crushed IR oxycodone fasted. Comparison between crushed IR oxycodone (fasted) and placebo (fed) was used to establish validity. Secondary comparisons included chewed versus intact Oxycodone DETERx. Other analyses included comparisons of intact Oxycodone DETERx treatments versus IR oxycodone and each Oxycodone DETERx treatment versus placebo.

The PD endpoints were analyzed using a mixed-effects model with fixed effects for sequence,

period, and treatment, with subject nested within sequence as a random effect. Least-squares (LS) mean and 95 percent confidence intervals (CIs) were calculated for each treatment, and LS mean differences and 95 percent CIs were generated for each pair-wise comparison. If the normality assumption was rejected, a nonparametric analysis using ranked values was performed. Pair-wise comparisons were not adjusted for multiplicity. The primary analysis of Drug Liking E_{max} was hypothesis-driven, using the hypothesis specified in the FDA guidance[5]:

$$Ho: \mu_c - \mu_T \leq (\mu_c - 50)\ \delta^* \text{ versus } Ha: \mu_c - \mu_T > (\mu_c - 50)\ \delta^*$$

where μ_C is the mean of the control treatment (crushed IR oxycodone 40 mg in solution, fasted), μ_T is the mean of the test treatment (chewed Oxycodone DETERx, fed or fasted), and $0.1 < \delta^* < 1$. Values for δ^* represent the percentage difference between the two treatments (eg, δ^* of 0.20 indicates a > 20 percent difference). A δ^* of 0.1 was used in the primary statistical analysis; if results were statistically significant, the δ^* value was incremented by 0.05 until a statistically nonsignificant result was obtained, and the last δ^* prior to nonsignificance was identified.[29] Statistical significance between control and test drug for the Drug Liking primary endpoint (E_{max}) was declared if the lower bound of the 95 percent CI was greater than $(\mu_C - 50)\ \delta^*$. Significance testing for other endpoints and comparisons used two-tailed tests with a nominal $\alpha = 0.05$.

A responder analysis was based on percent reduction in Drug Liking E_{max} for Oxycodone DETERx treatments relative to IR oxycodone. A responder was defined as a subject who had at least a prespecified level of reduction, with levels from 0 to 100 percent in 10 percent increments presented in a sensitivity analysis. The binomial test of proportions was used to test the null hypothesis that ≤50 percent of subjects were responders.

Pharmacokinetic parameters for oxycodone were compared among treatments using an analysis of variance model with sequence, treatment, and period as fixed effects and subject within sequence as a random effect, using the natural logarithms of the data. Bioequivalence in C_{max} and AUC_{0-t} was defined according to criteria established by the FDA (90 percent CI of the LS geometric mean ratio for a specific comparison falls entirely within 80-125 percent boundaries).[22]

Treatment-emergent adverse event data, clinical laboratory test results, physical examination findings, vital signs, and oxygen saturation data were analyzed descriptively.

RESULTS

Subject disposition and demographics

Seventy-five subjects passed the naloxone challenge and drug discrimination tests and proceeded to the double-blind treatment phase (Figure 2). All 75 subjects were included in the safety population, 71 subjects were included in the PK population, and 52 subjects were included in the PD analysis population. Study subjects were predominantly male and black/African American; average age was 29 years (Table 1).

PD measures

At early time points, mean Drug Liking VAS scores were higher for IR oxycodone compared with all Oxycodone DETERx treatments (Figure 3). Mean peak effects were delayed with all Oxycodone DETERx treatments relative to IR oxycodone. The statistically significant difference in LS mean ± standard error of the mean (SEM) Drug Liking E_{max} for crushed IR oxycodone fasted versus placebo (30.7 ± 2.2 points; $p < 0.0001$) confirmed study validity (Table 2). In the primary analysis of the primary outcome measure, the LS mean difference ± SEM in Drug Liking E_{max} for crushed IR oxycodone fasted compared with chewed Oxycodone DETERx fasted was 13.1 ± 2.2 points ($p = 0.0025$, using $\delta^* = 0.20$; $p < 0.0001$, using $\delta^* = 0$). For crushed IR oxycodone fasted compared with chewed Oxycodone DETERx fed, the LS mean difference ± SEM was 10.9 ± 2.2 points ($p = 0.0048$, using $\delta^* = 0.15$; $p < 0.0001$, using $\delta^* = 0$). The LS mean difference ± SEM in Drug Liking E_{max} was also statistically significant for crushed IR oxycodone fasted compared with intact Oxycodone DETERx fasted (12.2 ± 2.2 points; $p < 0.0001$) and fed (10.3 ± 2.2 points; $p < 0.0001$). No statistically significant differences in LS mean E_{max} were observed for chewed versus intact Oxycodone DETERx. All active treatments had statistically significantly higher LS mean E_{max} than placebo ($p < 0.0001$). Median time to E_{max} interval was shortest for crushed IR oxycodone fasted (1.0 hour), followed by Oxycodone DETERx fasted treatments (2.0-3.0 hours), and longest for Oxycodone DETERx fed treatments (4.0 hours).

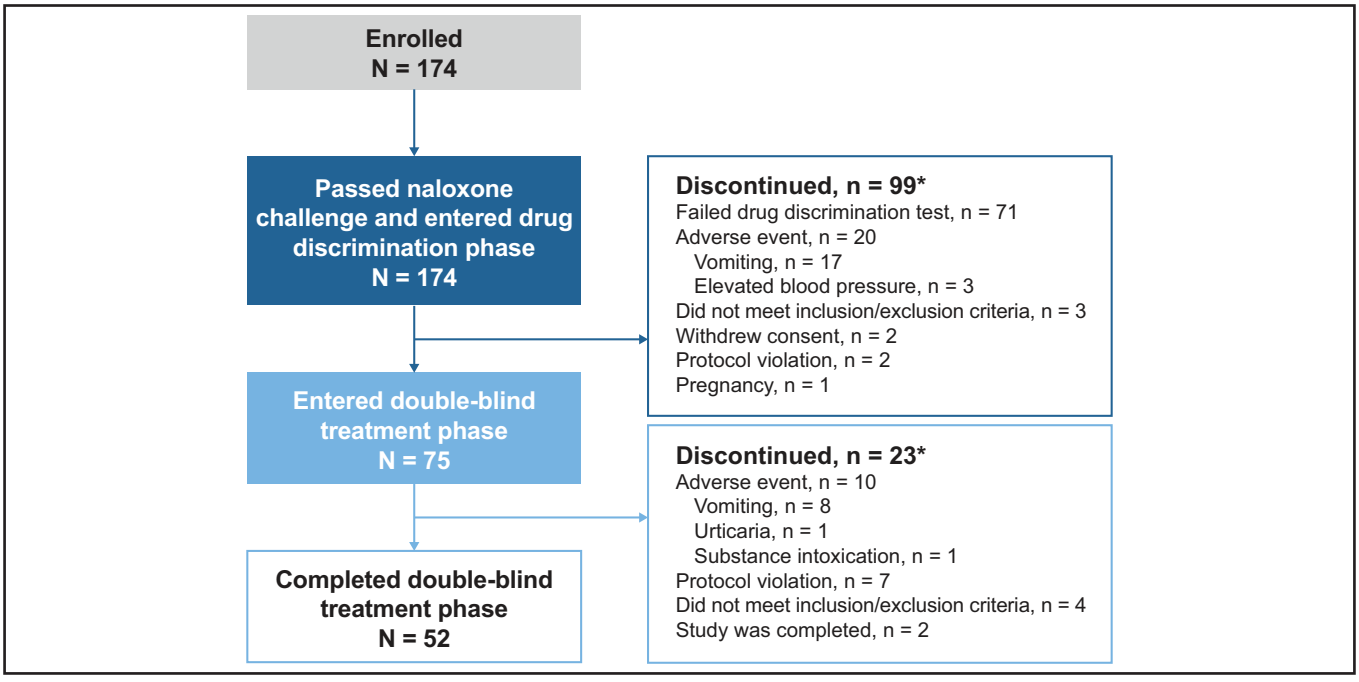

Figure 2. Disposition of subjects over the course of the study. *Patients could have discontinued for more than one reason.

Table 1. Subject demographic and baseline characteristics

Characteristic	PD population (n = 52)	PK population (n = 71)	Safety population (N = 75)
Male, n (percent)	45 (86.5)	58 (81.7)	62 (82.7)
Age, y, mean (SD)	28.9 (6.0)	29.0 (6.0)	29.0 (5.8)
Race, n (percent)			
Black/African American	44 (84.6)	58 (81.7)	59 (78.7)
White	8 (15.4)	12 (16.9)	15 (20.0)
Other	0 (0)	1 (1.4)	1 (1.3)
Latino/Hispanic ethnicity, n (percent)	1 (1.9)	2 (2.8)	2 (2.7)
Weight, kg, mean (SD)	76.3 (14.0)	75.2 (14.0)	75.3 (14.0)
Height, cm, mean (SD)	174.8 (8.3)	173.8 (8.7)	173.8 (8.5)
BMI, kg/m^2, mean (SD)	24.9 (3.9)	24.8 (3.7)	24.8 (3.8)

Abbreviations: BMI, body mass index; PD, pharmacodynamic; PK, pharmacokinetic; SD, standard deviation.

In the responder analysis, the majority of subjects showed ≥10 percent reduction in Drug Liking E_{max} after administration of chewed Oxycodone DETERx fasted (65.4 percent; p = 0.0133) or intact Oxycodone DETERx fasted (67.3 percent; p = 0.0063) compared with crushed IR oxycodone fasted (Figure 4A). Similarly, the majority of subjects showed ≥10 percent reduction in Drug Liking E_{max} after administration of chewed Oxycodone DETERx fed (61.5 percent; p = 0.0480) or intact Oxycodone DETERx fed (59.6 percent; p = 0.0828), compared with crushed IR oxycodone fasted (Figure 4B).

For the key secondary outcome measure of Take Drug Again, LS mean E_{max} was statistically

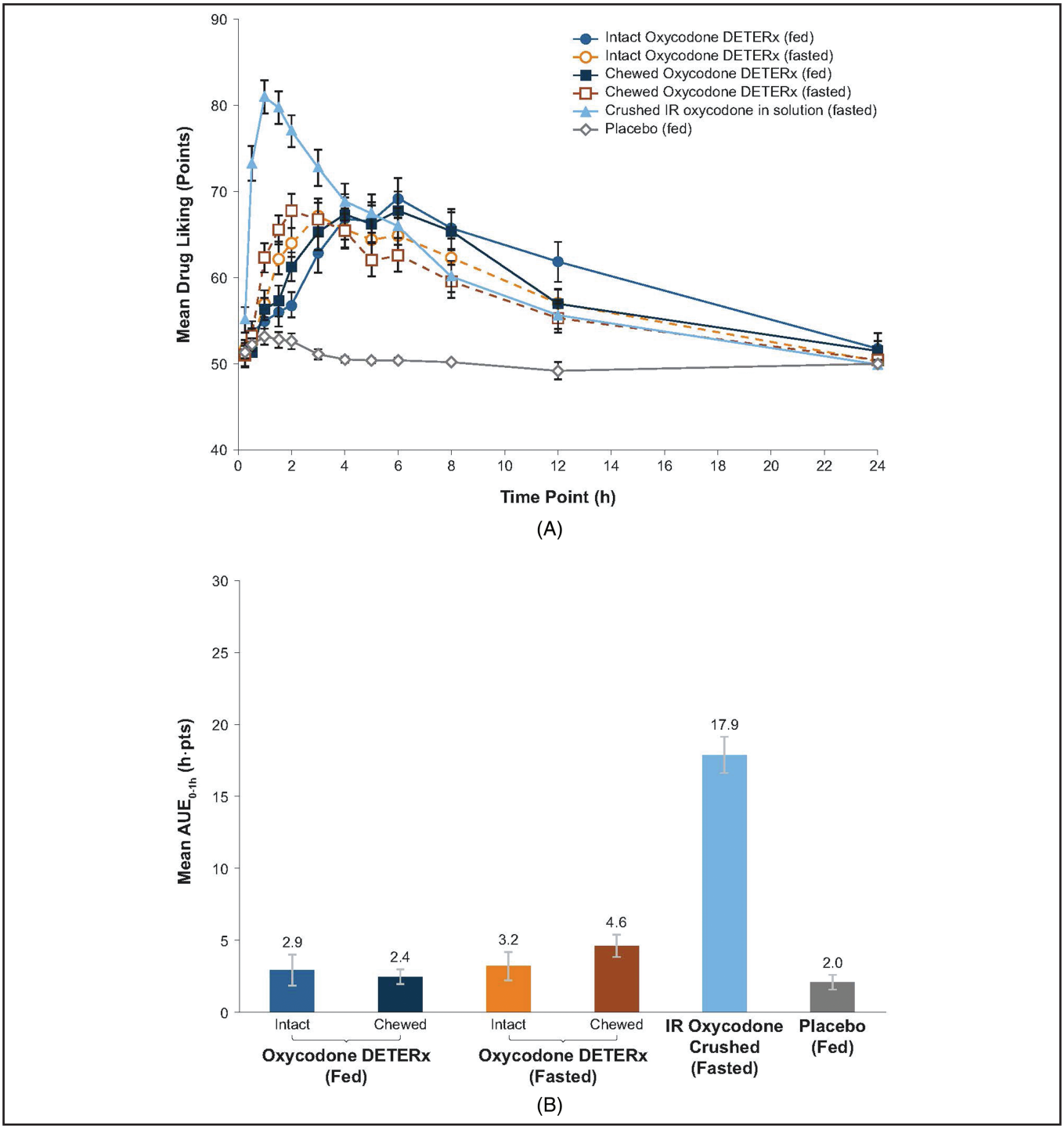

Figure 3. Primary PD measure (PD population, n = 52). (A) Mean Drug Liking VAS scores over time and (B) Drug Liking $AUE_{0\text{-}1h}$. Error bars, ± SEM. $AUE_{0\text{-}1h}$, area under the drug effect curve from time 0 to 1 hour; IR, immediate-release; PD, pharmacodynamic; pts, points; SEM, standard error of the mean; VAS, visual analog scale.

significantly lower for chewed Oxycodone DETERx (fasted or fed) and for intact Oxycodone DETERx (fasted or fed) compared with crushed IR oxycodone fasted (Figure 5). The LS mean difference ± SEM in Take Drug Again E_{max} for crushed IR oxycodone fasted compared with chewed Oxycodone DETERx fasted was 10.0 ± 3.2 points ($p < 0.01$) and compared with chewed Oxycodone DETERx fed was 9.7 ± 3.3 points ($p < 0.01$). The LS mean difference ± SEM in Take Drug Again E_{max} was also statistically significant for crushed IR oxycodone fasted compared with intact Oxycodone DETERx fasted (9.3 ± 3.3 points;

Table 2. PD measures: Peak effect (PD population, n = 52)*

Measure	Intact Oxycodone DETERx fed	Chewed Oxycodone DETERx fed	Intact Oxycodone DETERx fasted	Chewed Oxycodone DETERx fasted	Crushed IR oxycodone fasted	Placebo fed
Drug Liking†	74.9 (17.3)‡	75.4 (14.7)§	73.9 (15.1)‡	73.3 (14.9)§	86.4 (12.0)	55.8 (9.9)‡
Take Drug Again‖	78.2 (21.2)§	77.8 (17.7)¶	78.0 (21.1)§	77.8 (18.3)¶	87.7 (12.9)	50.8 (21.4)‡
Good Effects**	44.8 (33.8)‡	42.7 (31.7)‡	44.1 (32.1)‡	45.4 (32.6)‡	74.4 (25.8)	10.9 (20.7)‡
Feeling High**	44.3 (33.1)‡	44.4 (30.7)‡	42.7 (30.2)‡	43.8 (30.8)‡	73.9 (26.1)	9.7 (18.1)‡
Bad Effects‖**	7.4 (18.7)	8.4 (20.6)	8.1 (17.8)	6.8 (18.6)	11.4 (20.6)	2.7 (10.1)§
Sick**	3.2 (12.4)	6.0 (17.5)	4.6 (17.4)	4.4 (14.7)	6.8 (17.8)	0.7 (7.9)§
Nausea‖**	5.1 (15.0)§	6.8 (19.2)§	2.4 (7.6)††	3.2 (11.7)‡	7.5 (15.7)	1.3 (8.0)‡
Sleepy**	29.9 (33.4)§	34.9 (31.9)	31.3 (33.0)§	30.4 (31.9)§	42.2 (34.2)	10.4 (24.3)‡
Dizzy‖**	6.8 (17.4)††	10.5 (22.6)††	6.6 (18.8)§	6.7 (17.4)	13.9 (22.2)	0.4 (2.1)‡
Any Effects**	43.2 (32.9)‡	43.7 (31.8)‡	41.8 (30.2)‡	42.3 (30.3)‡	73.9 (25.5)	9.7 (18.1)‡
Overall Drug Liking†	77.5 (17.5)¶	76.3 (18.0)‡	76.7 (17.3)¶	75.7 (17.8)‡	86.5 (12.4)	55.5 (13.1)‡
Price Value‖	11.6 (11.2)¶	14.9 (16.1)††	12.6 (14.5)¶	14.0 (17.1)§	18.1 (17.5)	3.5 (7.6)‡
ARCI/MBG score	4.6 (4.8)§	5.1 (4.8)	5.0 (4.7)††	5.4 (4.6)	6.2 (5.1)	1.6 (3.5)‡
Pupil diameter, mm	3.1 (0.9)‡	3.1 (0.8)‡	2.7 (0.9)‡	2.9 (0.9)‡	3.9 (0.8)	0.8 (0.6)‡

Abbreviations: ARCI/MBG, Addiction Research Center Inventory/Morphine Benzedrine Group; IR, immediate-release; PD, pharmacodynamic.
*All data are mean (standard deviation); all values are peak effect (E_{max}) except for price value, which was assessed only once (24 hours postdose). The p values are based on mixed-effects model analysis.
†Bipolar, 100-point visual analog scale anchored with "strong disliking" at 0, "neither like nor dislike" at 50, and "strong liking" at 100.
‡Statistically significantly lower score vs crushed IR oxycodone ($p < 0.0001$).
§Statistically significantly lower score vs crushed IR oxycodone ($p < 0.01$).
‖Nonparametric analysis of ranked data.
¶Statistically significantly lower score vs crushed IR oxycodone ($p < 0.001$).
**Unipolar, 100-point scales anchored with "none" at 0 and "extremely" at 100.
††Statistically significantly lower score vs crushed IR oxycodone ($p < 0.05$).

$p < 0.01$) and fed (9.2 ± 3.3 points; $p < 0.01$). No statistically significant differences in LS mean Take Drug Again E_{max} were observed for chewed versus intact Oxycodone DETERx. All active treatments had statistically significantly higher LS mean Take Drug Again E_{max} than placebo ($p < 0.0001$).

Mean scores on other secondary outcome measures are summarized in Table 2. Chewed Oxycodone DETERx treatments (fasted or fed) were associated with statistically significantly lower E_{max} values than crushed IR oxycodone fasted on most secondary outcome measures, including positive effects (Feeling High, Good Effects), pharmacologic effects (Any Effects, Nausea), Overall Drug Liking, and pupil diameter. For chewed Oxycodone DETERx treatments (fasted or fed), the differences compared with crushed IR oxycodone fasted were less marked on the ARCI/MBG, Sleepy, and Dizzy endpoints, although directionally supportive. Consistent with the findings with chewed Oxycodone DETERx treatments, administration of intact Oxycodone DETERx under fasted or fed conditions was associated with statistically significantly lower E_{max} values relative to crushed IR oxycodone fasted for the majority of secondary endpoints. There were

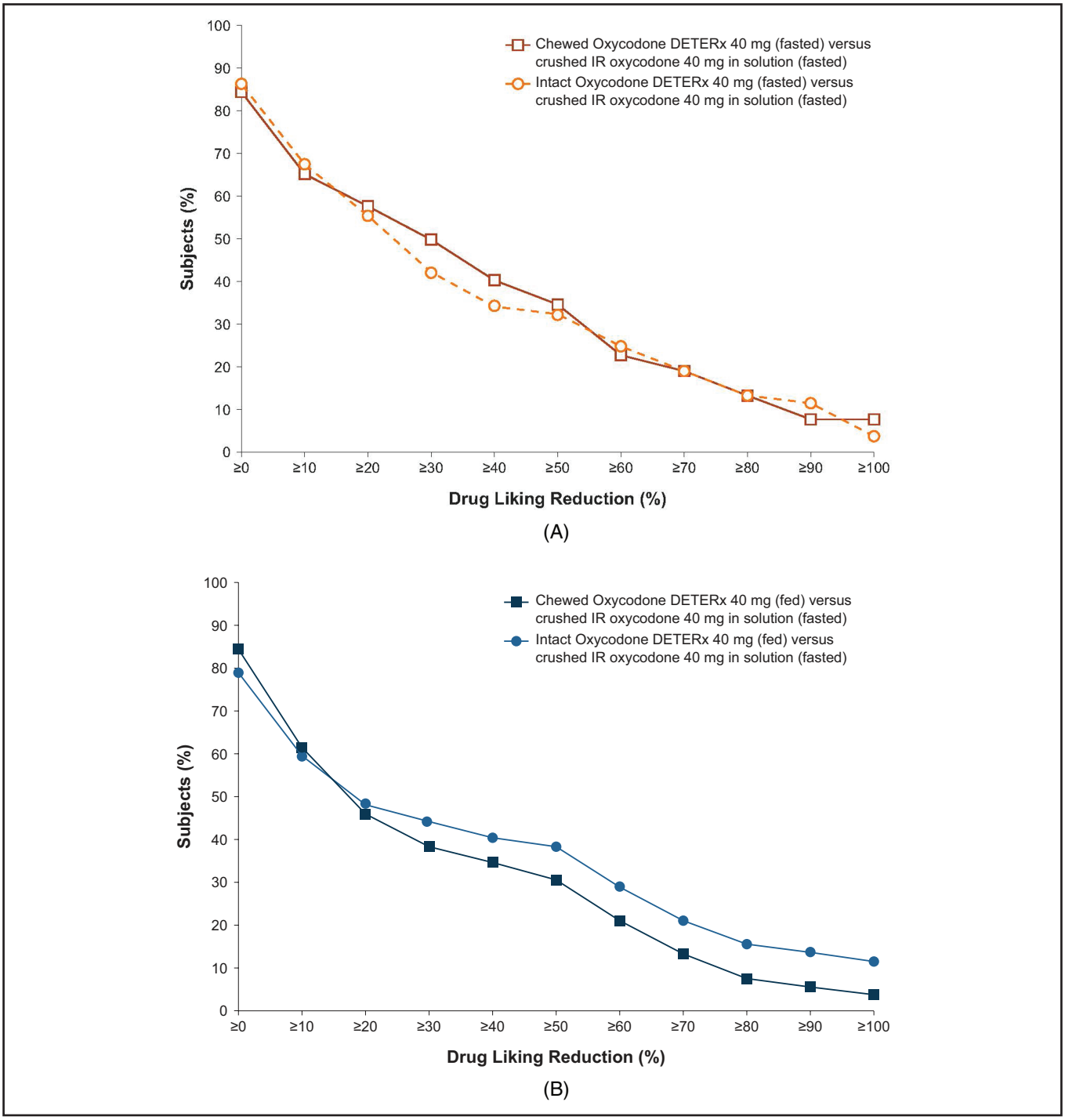

Figure 4. Proportion of responders based on percent reduction in Drug Liking E_{max} for Oxycodone DETERx treatments relative to IR oxycodone (PD population, n = 52). Administration of Oxycodone DETERx under (A) fasted and (B) fed conditions. E_{max}, maximum (peak) effect; IR, immediate-release; PD, pharmacodynamics.

no statistically significant differences between chewed and intact Oxycodone DETERx treatments in mean E_{max} for any of the secondary measures. All Oxycodone DETERx treatments were associated with statistically significantly greater effects compared with placebo for the majority of secondary endpoints (ie, Feeling High, Good Effects, Sleepy, Dizzy, Any Effects, Overall Drug Liking, PVA, ARCI/MBG score, and pupil diameter); IR oxycodone differed statistically significantly from placebo for all secondary PD endpoints ($p < 0.01$).

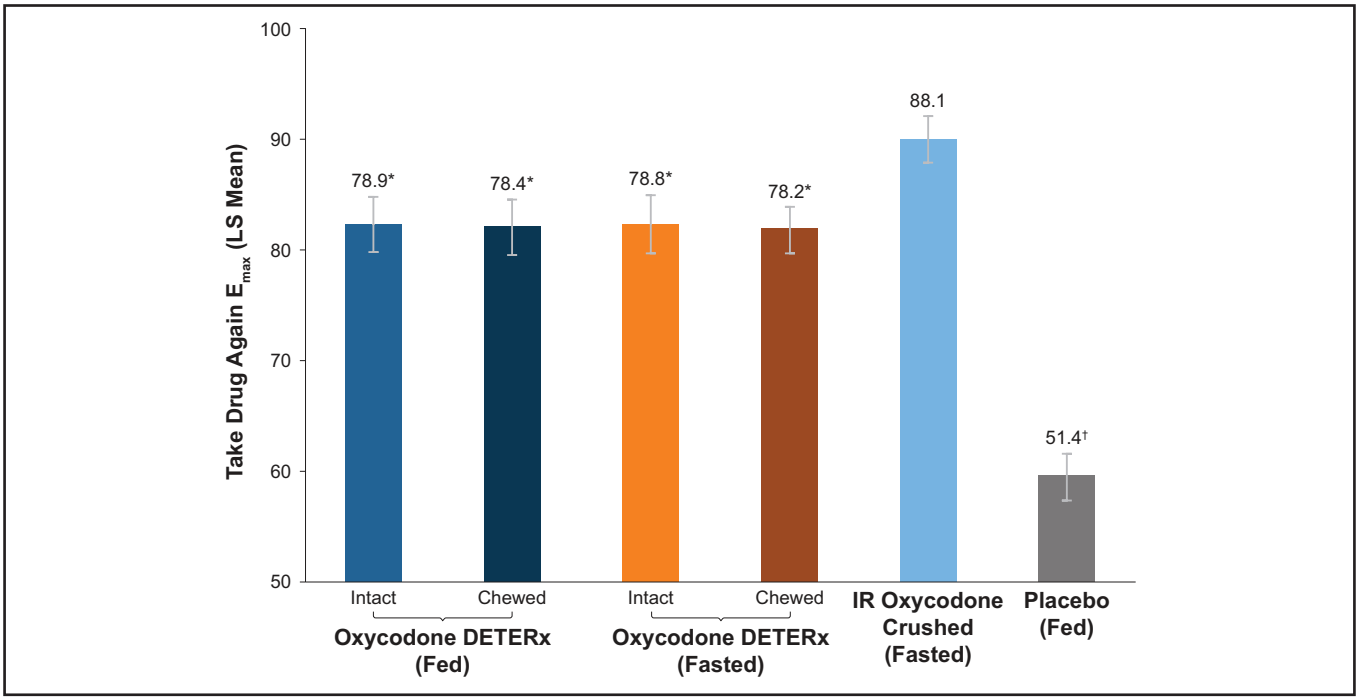

Figure 5. Key secondary PD measure (PD population, n = 52): LS mean maximum (peak) effect (E_{max}) for Take Drug Again. Error bars, ± SEM. *p < 0.01 versus IR oxycodone. †p < 0.0001 versus IR oxycodone. E_{max}, maximum (peak) effect; IR, immediate-release; LS, least-squares; SEM, standard error of the mean.

Pharmacokinetic parameters

Crushed IR oxycodone fasted exhibited statistically significantly higher mean ± SD C_{max} (91.1 ± 26.6 ng/mL) and shorter median T_{max} (0.5 hours) than all Oxycodone DETERx treatments (mean ± SD C_{max}, 33.9 ± 9.8 to 45.4 ± 11.6 ng/mL; median T_{max}, 3.1-5.1 hours); overall exposure to oxycodone (AUC) was similar across treatments (Figure 6; Table 3). The mean AQ for crushed IR oxycodone was approximately 10-fold higher than the AQ for chewed and intact Oxycodone DETERx. Chewed Oxycodone DETERx fasted and fed treatments were bioequivalent to the respective intact treatments based on C_{max} (fasted: 90 percent CI, 104.4-117.5; fed: 90 percent CI, 90.4-102.1), AUC_{0-t} (fasted: 90 percent CI, 100.1-111.5; fed: 90 percent CI, 94.2-105.3), and $AUC_{0-\infty}$ (fasted: 90 percent CI, 97.4-106.0; fed: 90 percent CI, 96.7-106.3).

Safety

Oxycodone DETERx treatments and IR oxycodone were generally well tolerated in this study; all treatment-emergent adverse events were mild or moderate in severity. The adverse event profile was consistent with known opioid-class effects (Table 4). No clinically significant differences were observed between treatments for changes in clinical laboratory test results, vital signs measurements, or physical examination findings. Three subjects experienced a clinically significant increase in blood pressure; these incidents were not treatment-specific and resolved without intervention. Three subjects experienced oxygen desaturation below 90 percent after receiving Oxycodone DETERx; repeat saturation test results were 98 percent for all three subjects; no intervention was required.

DISCUSSION

This study demonstrated that administration of chewed Oxycodone DETERx in both the fed and fasted states resulted in statistically significantly lower Drug Liking and lower willingness to Take Drug Again than did crushed IR oxycodone. Similarly, intact Oxycodone DETERx resulted in statistically significantly lower Drug Liking and lower willingness to Take Drug Again than crushed IR oxycodone. Importantly, the abuse potential of Oxycodone DETERx was not meaningfully changed following manipulation via chewing compared with the intact formulation, under fasted and fed conditions. The observed lower ratings of Drug Liking and Take Drug Again for both chewed and

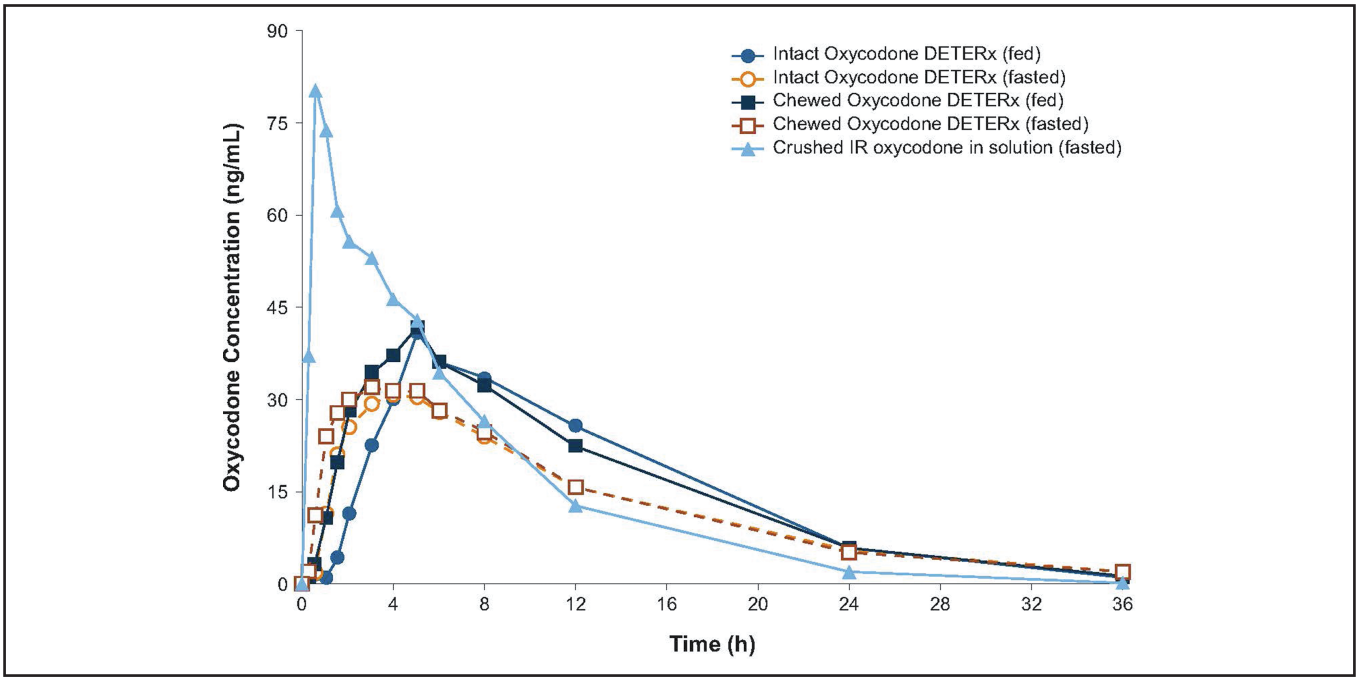

Figure 6. Mean oxycodone plasma concentration over time (PK population, n = 71). IR, immediate-release; PK, pharmacokinetic.

Table 3. Summary of pharmacokinetic measures (PK population, n = 71)*

Parameter	Intact Oxycodone DETERx fed (n = 61)	Chewed Oxycodone DETERx fed (n = 66)	Intact Oxycodone DETERx fasted (n = 67)	Chewed Oxycodone DETERx fasted (n = 67)	Crushed IR oxycodone fasted (n = 64)
C_{max}, ng/mL	45.4 (11.6)	44.3 (10.9)	33.9 (9.8)	37.6 (11.5)	91.1 (26.6)
T_{max}, h	5.1 (2.1-12.1)	5.1 (1.5-8.1)	4.1 (1.5-8.1)	3.1 (0.5-8.1)	0.5 (0.3-5.2)
AUC_{0-t}, ng·h/mL	541 (127)	553 (149)	447 (119)	466 (145)	543 (131)
$AUC_{0-\infty}$, ng·h/mL†	546 (134)	568 (138)	478 (122)	480 (126)	549 (132)
$t_{1/2}$, h†	5.3 (0.7)	5.4 (0.8)	8.1 (2.5)	7.6 (2.5)	4.2 (0.6)
AQ, ng/(mL·h)	8.9 (5.3)	10.6 (5.7)	10.5 (4.9)	17.6 (14.8)	138 (84.5)

Abbreviations: AQ, abuse quotient; $AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-t}, area under the plasma concentration-time curve from time 0 to last measurable plasma concentration; C_{max}, maximum observed plasma concentration; IR, immediate-release; PK, pharmacokinetic; $t_{1/2}$, terminal elimination half-life; T_{max}, time to reach maximum plasma concentration.
*All measures are mean (standard deviation) except for T_{max}, which is median (range).
†n = 52 for intact Oxycodone DETERx fed, n = 54 for chewed Oxycodone DETERx fed, n = 63 for intact Oxycodone DETERx fasted, n = 63 for chewed Oxycodone DETERx fasted, and n = 63 for crushed IR oxycodone fasted.

intact oral administration in both the fasted and fed states suggests that the relative abuse potential of Oxycodone DETERx is lower when compared with a non-abuse-deterrent formulation of crushed IR oxycodone. Secondary PD and PK measures were supportive of the primary endpoint, indicating that Oxycodone DETERx under all conditions had lower positive effects and was associated with statistically significantly lower and delayed peak exposure compared with IR oxycodone.

Table 4. Adverse events occurring in ≥5 percent of subjects for any treatment in the double-blind treatment phase (safety population, N = 75)

Adverse event, n (percent)	Intact Oxycodone DETERx fed (n = 64)	Chewed Oxycodone DETERx fed (n = 66)	Intact Oxycodone DETERx fasted (n = 68)	Chewed Oxycodone DETERx fasted (n = 69)	Crushed IR oxycodone fasted (n = 67)	Placebo fed (n = 65)
Any adverse event	43 (67.2)	37 (56.1)	22 (32.4)	31 (44.9)	44 (65.7)	16 (24.6)
Pruritus	27 (42.2)	22 (33.3)	11 (16.2)	17 (24.6)	30 (44.8)	0
Euphoric mood	13 (20.3)	11 (16.7)	7 (10.3)	4 (5.8)	10 (14.9)	0
Somnolence	8 (12.5)	13 (19.7)	6 (8.8)	6 (8.7)	8 (11.9)	3 (4.6)
Nausea	5 (7.8)	4 (6.1)	2 (2.9)	3 (4.3)	6 (9.0)	1 (1.5)
Feeling hot	3 (4.7)	2 (3.0)	1 (1.5)	1 (1.4)	5 (7.5)	1 (1.5)
Headache	3 (4.7)	1 (1.5)	1 (1.5)	4 (5.8)	4 (6.0)	4 (6.2)

Abbreviation: IR, immediate-release.

The results of this study support and extend the results of the first human oral abuse potential study of Oxycodone DETERx.[17] Statistical significance on the primary endpoint (Drug Liking E_{max}) was confirmed, as were findings for multiple secondary endpoints. In addition, the key secondary endpoint of Take Drug Again was met. Changes to study design/methodology included revision of the statistical analyses to be consistent with the final FDA guidance,[5] preselection of a clinically meaningful margin (δ*),[19] and a closed testing procedure for the primary and key secondary endpoint comparisons. In addition, the FDA made a recommendation to the Sponsor to use a dose of 40 mg IR oxycodone (versus the 20 mg dose used in the previous study) in the drug discrimination phase to ensure that subjects could tolerate the oxycodone dose that was to be administered in the double-blind treatment phase.[30] The study design was also revised to make the drug discrimination phase qualification criteria more stringent to reduce variability in Drug Liking (for IR oxycodone and placebo) and to facilitate selection of subjects with better discrimination ability for the double-blind treatment phase of the study, by requiring a higher minimum Drug Liking E_{max} response to IR oxycodone and a narrower placebo response range, as well as initiating improved training on PD assessments.

This study included both fed and fasted conditions because Oxycodone DETERx has a known food effect; bioavailability is increased in the presence of food.[9] This study found statistically significantly reduced E_{max} on Drug Liking and Take Drug Again VAS scales for Oxycodone DETERx, in both fed and fasted conditions, compared with IR oxycodone. Although there was a modest numerical difference (2 points) between fed and fasted conditions in LS mean E_{max} for Drug Liking, a similar pattern was not observed for Take Drug Again. In addition, for chewed Oxycodone DETERx, the fed condition was associated with slightly increased mean scores on the Bad Effects, Sick, and Nausea scales relative to the fasted condition. Based on these small numerical differences, it seems unlikely that consumption of a large meal would exert a meaningful effect on the abuse liability of Oxycodone DETERx.

Oral administration, nasal inhalation, and injection are common routes for abuse of prescription opioids, including ER oxycodone.[3,31] A study of recreational opioid users demonstrated reduction in the intranasal abuse potential of crushed capsule contents for Oxycodone DETERx compared with crushed IR oxycodone.[27] The development of opioid formulations with reduced oral abuse potential has important public health implications, including the potential to alter opioid addiction trajectories.[6-8,32] The reduced abuse potential of Oxycodone DETERx administered via the oral route (either intact capsules or chewed microspheres) compared with crushed IR oxycodone was demonstrated in this study and the previous oral abuse study of recreational opioid users.[17] To our knowledge, this is the first study to confirm the results of a previous

human abuse potential study. Currently, Oxycodone DETERx is the only single-agent oxycodone medication with oral human abuse potential data demonstrating a reduction in both Drug Liking and willingness to Take Drug Again.

There are some limitations associated with this study. Although the study was powered based on the final FDA guidance and is consistent with the current, updated methodology for human abuse potential studies,[5,18] the number of subjects is still relatively small. Due to the smaller sample size, demographic variables potentially associated with opioid abuse (eg, age, race, socioeconomic status) could not be fully accounted for in this study, as is the case with all similar abuse liability studies. Moreover, results from single-dose administration of oxycodone in a highly controlled setting to a specific population (nondependent recreational users) may not be generalizable to other recreational opioid users or real-world settings. Additionally, while the protocol was designed to minimize bias, intersubject variability, and confounding, this may have resulted in a cohort of subjects who may not be representative of all recreational opioid abusers. Lastly, the addiction potential of Oxycodone DETERx was not assessed in this study; longitudinal epidemiologic studies are required to assess the addiction potential of marketed opioid analgesics. Epidemiological studies will be conducted as soon as they are feasible.

CONCLUSIONS

In this study of recreational opioid users, ratings of both Drug Liking and willingness to Take Drug Again were statistically significantly lower for chewed or intact Oxycodone DETERx than IR oxycodone. Overall plasma exposure to oxycodone was similar among treatments, but the magnitude of peak exposure was reduced and the time to peak exposure was delayed for all Oxycodone DETERx treatments relative to IR oxycodone. Chewing Oxycodone DETERx did not compromise the abuse-deterrent formulation or alter the PK profile. The results of the present study support that when chewed or swallowed intact, under fasted or fed conditions, Oxycodone DETERx has statistically significantly lower abuse potential via the oral route compared with IR oxycodone. Research studies such as this one, which demonstrate the reduced abuse potential of an opioid analgesic in a population of recreational opioid abusers, represent one step in the development of abuse-deterrent opioid formulations. Additional research, including epidemiologic studies, is necessary to evaluate the potential benefits of abuse-deterrent opioids in real-world settings.

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