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Original Research Article

A Randomized, Double-Blind, Double-Dummy Study to Evaluate the Intranasal Human Abuse Potential and Pharmacokinetics of a Novel Extended-Release Abuse-Deterrent Formulation of Oxycodone

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Abstract

Objective. Evaluate the human abuse potential (HAP) of an experimental, microsphere-in-capsule formulation of extended-release oxycodone (oxycodone DETERx®) (herein "DETERx").

Design. Randomized, double-blind, double-dummy, positive- and placebo-controlled, single-dose, four-phase, four-treatment, crossover study.

Setting. Clinical research site.

Subjects. There were 39 qualifying subjects (72% male, 85% white, mean age of 27 years) with 36 completing all four Double-blind Treatment Periods.

Methods. The four phases encompassed: 1) Screening; 2) Drug Discrimination; 3) Double-blind Treatment; and 4) Follow-up. Drug Discrimination tests ensured that subjects could distinguish placebo from opioid. The four Double-blind Treatments compared DETERx—administered as either a crushed intranasal (IN) or an intact oral (PO) preparation—with immediate-release oxycodone IN (OXY-IR IN) and with an intact IN and PO placebo DETERx control.

Results. For primary pharmacokinetic (PK) assessments, abuse quotient (C_{max}/T_{max}) was lower with DETERx IN than DETERx PO; both treatments were substantially lower than OXY-IR IN (6.24, 8.60, and 69.6 ng/mL/h, respectively). For drug liking, the primary subjective pharmacodynamic (PD) endpoint, both DETERx IN and DETERx PO produced significantly lower scores than OXY-IR IN ($P \leq 0.0001$ for

each); DETERx IN was less liked than DETERx PO ($P \leq 0.05$), mirroring the PK relationships. Objectively assessed pupillometry corroborated the more rapid and significantly greater effect of OXY-IR IN than either DETERx IN or DETERx PO ($P \leq 0.007$ for each). Overall safety profiles of DETERx and OXY-IR were comparable and both were well tolerated.

Conclusions. Pharmacokinetic and pharmacodynamic outcomes suggest that DETERx IN has relatively low HAP; continued research in larger populations is suggested.

Key Words. Oxycodone; Extended-Release Opioid; DETERx; Intranasal; Abuse-Liability; Abuse-Deterrent; Pharmacokinetic; Pharmacodynamic

Introduction

Prescription opioid abuse is an important concern worldwide [1–6]. In the United States, medical emergencies associated with prescription opioid abuse have escalated dramatically, corresponding with increased opioid prescribing [5,7,8], and are amplified by the inherent abuse potential of these medications [9]. Mounting opioid-related mortality has been problematic in North America [10] and has been characterized as a "worsening epidemic" [8].

In partial response, the U.S. Food and Drug Administration [11] has stressed a proactive approach to developing opioid analgesics with lower "abuse potential"—i.e., the likelihood that a drug is attractive for nonmedical use due to positive psychoactive effects—and manufacturers have been formulating such products [11–15]. Assessment of abuse potential is based on drug chemistry, pharmacology, and clinical data from human abuse potential (HAP) studies. Such evaluations typically compare an investigational drug to a known drug of abuse (as a positive control) and to a placebo (PBO, as a negative control); both pharmacodynamic (PD) and pharmacokinetic (PK) characteristics are measured to assess attractiveness as a substance of abuse [14].

Immediate-release (IR) and extended-release (ER) opioid formulations are often abused via oral consumption of intact tablets or capsules [15]. However, abusers may attempt to increase psychoactive effects by tampering (e.g., crushing) and using alternate routes of administration, such as insufflation [15–18]. In the case of ER oxycodone, crushing the tablets often compromises the time-release delivery mechanism, increases the rate of absorption, and thereby increases the desired subjective effects (e.g., drug liking attributable to euphoria) compared with intact tablets of the same dose consumed orally (PO, per os) [19,20].

Intranasal abuse of oxycodone in ER formulations has been well documented in epidemiology studies [16,21–24]. Prevalence rates for intransal (IN) abuse of marketed ER oxycodone have generally decreased [21–24] since the introduction of an abuse-deterrent formulation (ADF) to the market, although the prevalence for abuse via the IN route of administration (ROA) has not disappeared and is still rather significant in some populations surveyed in recent epidemiology studies [22–24]. Furthermore, reports of increased oral ER oxycodone abuse [22], increased oral and IN abuse of IR oxycodone [21], and switching to other prescription and nonprescription opioids [24] has been reported since the introduction of reformulated ER oxycodone ADF.

Oxycodone DETERx® (Xtampza™ ER [oxycodone extended-release]; herein "DETERx") (Collegium Pharmaceutical, Inc., Canton, MA, USA; herein "Collegium") is an experimental, oral, extended-release oxycodone with a novel abuse-deterrent formulation. DETERx is formulated using the proprietary DETERx microsphere-in-capsule technology platform, which resists particle size reduction and "dose dumping" when subjected to crushing or other physical manipulations. Earlier research demonstrated that crushed or chewed DETERx capsule contents were bioequivalent to intact capsules, indicating the physically manipulated microspheres retained their ER mechanism of drug delivery [25]. Furthermore, in an open-label pilot study, PK characteristics of crushed DETERx taken intranasally were compared with intact DETERx taken PO and with immediate-release oxycodone powder (OXY-IR) taken IN as a positive control [26]. Extent of absorption was similar for all three, but the mean peak plasma concentration (C_{max}) was lower for crushed DETERx IN or intact DETERx PO than crushed OXY-IR IN. Moreover, mean times to maximum concentration (T_{max}) for DETERx PO or IN were similar and less rapid than for OXY-IR IN. Taken together, those data suggested that the abuse potential of DETERx IN or DETERx PO was significantly lower than for OXY-IR IN in terms of PK.

The present study compared DETERx IN and DETERx PO with each other, with OXY-IR IN as a positive control, and with PBO as a control to confirm prior PK results in a larger population of subjects and to assess important PD parameters of HAP. Based on the earlier PK data from a pilot study and expected PD effects of DETERx, it was hypothesized that the PK results would be replicated and, for primary PD endpoints, DETERx IN and DETERx PO would demonstrate less abuse liability than OXY-IR IN.

Methods

Study Design

Conducted during 2013, this study evaluated PD and PK parameters assessing HAP of an experimental DETERx formulation using a randomized, double-blind, double-dummy, positive- and PBO-controlled, single-dose, four-treatment, four-period, crossover comparison design that encompassed four phases: 1) Screening; 2)

Drug Discrimination; 3) Double-blind Treatment; and 4) Follow-up. The Double-blind Treatment Phase allowed for comparisons of DETERx—administered either as a crushed IN or an intact PO formulation—with crushed OXY-IR IN and with a PBO control administered both IN and PO.

This study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice, ethical principles that originated with the Declaration of Helsinki, and U.S. clinical research regulations and guidelines. It was approved by the New England Institutional Review Board (NEIRB, 85 Wells Avenue, Suite 107, Newton, MA, 02459, USA); all subjects provided written informed consent before initiation of study procedures and received remuneration for their participation. A Certificate of Confidentiality was granted by the National Institutes of Health (NIH) and was submitted to NEIRB prior to enrollment of subjects. This was a single-center study performed at PRA Health Sciences (3838 South 700 East, Suite 202, Salt Lake City, UT 84106, USA).

Study Subject Selection

A total of 95 prospective subjects were recruited from the investigator's database (PRA Health Sciences, Salt Lake City, UT). Subjects accepted during the Screening Phase were men or nonpregnant, nonlactating women, aged 18 to 55 years, who were recreational opioid users, which was defined as use of opioids for nonmedical purposes (e.g., psychoactive effects) on at least 10 occasions during the past year and at least once in the 12 weeks prior to screening. Additionally, subjects were required to have a history of IN opioid use at least three times within the past year; however, they could not be physically dependent on or tolerant to opioids, alcohol, or other drugs (excepting caffeine and nicotine), based on *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* [27] criteria. Physical dependence on opioids was assessed via a naloxone challenge test at the beginning of the Drug Discrimination Phase. Subjects were required to have a negative urine drug screen and alcohol breath test prior to dosing in the Drug Discrimination Phase and at each Treatment Phase visit; an exception was tetrahydrocannabinol (THC; e.g., cannabis), which could be negative or positive throughout the study, but could not change during the study (recent evidence suggests that THC does not affect subjects' ability to discriminate opioid from PBO) [28]. Prospective subjects testing positive for THC had to pass a targeted neurological exam to demonstrate that they were not cognitively impaired. Urine drug screens for all visits except the screening visit were completed using point-of-care, Clinical Laboratory Improvements Amendment (CLIA) waived, immunoassay drug screens (Alere iCup® Dx Drug Screen Cup, Alere Toxicology Services, Products Division, Portsmouth, VA, USA) without confirmation via mass spectrometry or quantification except in instances where THC tested positive via the urine drug screen.

Prospective subjects were excluded if they had any clinically significant unstable medical condition or chronic disease of the neurological, cardiovascular, endocrine, hematologic, metabolic, gastrointestinal, hepatic, or renal systems; if they tested positive for infectious disease (e.g., human immunodeficiency virus [HIV], hepatitis B virus [HBV], hepatitis C virus [HCV]); or had an anatomical nasal abnormality or infection that could compromise the ability to insufflate drugs. Subjects with any condition for which an opioid was contraindicated (e.g., history of respiratory depression, acute or chronic bronchial asthma or hypercarbia, or suspected or confirmed paralytic ileus) were not included. Heavy smokers unable to abstain from smoking for at least 5 hours during the day and users of other nicotine-containing products (e.g., chewing tobacco, transdermal patch) were excluded. After initial screening, there were additional exclusion criteria imposed during the Drug Discrimination Phase as described below.

Study Procedures/Protocol

The four phases of the study involved six visits to the study research center; four of the visits (Double-blind Treatment Phase) required an inpatient stay lasting up to 48 hours. A minimum of 8 weeks was required by each subject to complete the entire study.

Screening Phase (Visit 1)

Subjects were screened up to 3 weeks prior to dosing in the Double-blind Treatment Phase. After obtaining informed consent, screening procedures included an assessment of inclusion and exclusion criteria, collection of demographic and medical information and recreational drug-use history, a physical exam including 12-lead electrocardiogram and nasal cavity examination, collection of urine and blood samples for laboratory analyses, and an alcohol breath test. Subjects preliminarily accepted into the study were directed to report to the clinical research facility (PRA Health Sciences, Salt Lake City, UT) for a 24-hour stay and, prior to arriving, they were to have refrained from taking medications—prescription (14 days) or over-the-counter (48 hours)—supplements or nutraceuticals for 48 hours, herbs for 14 days, and caffeine or alcohol for 24 hours (subjects would need to adhere to such abstinence for the Drug Discrimination and Double-blind Treatment Phases of the study). If needed, acetaminophen up to 1,000 mg per dose orally was allowed at the discretion of the investigator (e.g., for the treatment of headache).

Drug Discrimination Phase (Visit 2)

Subjects who were preliminarily accepted into the study during the Screening Phase returned to the research clinic as inpatients for a 24-hour stay for

the Drug Discrimination Phase. Each subject was first administered a naloxone challenge test to confirm lack of physiological opioid dependence. A 0.2 mg intravenous (IV) naloxone bolus dose was administered; signs of opioid withdrawal denoting dependence were assessed using the Clinical Opiate Withdrawal Scale (COWS) [29]. If no withdrawal was evident, a 0.6 mg IV bolus dose was administered as confirmation of no opioid dependence. Subjects judged as non-opioid-dependent were administered the drug discrimination test. In a double-blind, two-treatment, randomized design, each subject received either a single IN dose of crushed OXY-IR 20 mg or a single IN dose of crushed PBO-IR and was later crossed-over to the other treatment. All doses were administered following a high-fat, high-calorie (HFHC) meal, as recommended by FDA Guidance for Industry: Food Effect Bioavailability and Fed Bioequivalence Studies [30] in order to assure uniform effects on drug bioavailability and bioequivalence in cases of residual gut absorption from post-nasal drip following IN administration and to confirm the ability of subjects to consume the meal within the allotted time and to tolerate the meal. Each dose of either OXY-IR IN or PBO-IR IN was separated by at least 24 hours to allow for a washout period before crossover to the alternate treatment, which allowed for a minimum of nearly five half-lives of OXY-IR ($T_{1/2}$ for OXY-IR at doses of 20 mg or 0.28 mg/kg has been shown to be 3.2 and 5.1 hours, respectively) [31,32].

During this phase, subjects were immediately excluded from the study if they had not, as previously instructed, refrained from taking medications, supplements, nutraceuticals, herbs, caffeine or alcohol, or if they had a positive urine drug screen or alcohol breath test. Also excluded were those subjects failing the naloxone challenge test and subjects unable to discriminate between OXY-IR opioid and PBO during the drug discrimination test. Ability to discriminate was defined as: 1) a response to PBO-IR between $\geq$40 and $\leq$60 points for Drug Liking—scoring in the neutral range on a 100 point bipolar visual analog scale (VAS, Strong Disliking to Strong Liking)—during the first 2 hours following drug administration; 2) minimum 65 points of maximum effect (E_{max}) for Drug Liking in response to OXY-IR; and 3) $\geq$ 15-point difference on Drug Liking between OXY-IR and PBO-IR treatments at one or more time points during the first 2 hours following drug administration. Additional causes for exclusion were intolerance to study treatments in the Drug Discrimination Test (e.g., emesis within the first 6 hours after dosing), inability to completely insufflate the entire volume of drug or PBO doses, or unacceptable responses to other study assessments or inability to successfully complete the study as judged by the Investigator (e.g., inability to consume the HFHC meal within 20 minutes or emesis following the meal).

Subjects successfully completing the Drug Discrimination Phase were directed to return to the research center within a minimum of 5 days to begin the Double-blind Treatment Phase. Subjects were reminded to refrain from taking medications, supplements, nutraceuticals, herbs, caffeine, alcohol, or other drugs.

Double-Blind Treatment Phase (Visits 3–6)

During this phase, subjects reported to the research center for a 48-hour stay and were randomized by an unblinded pharmacist, or designee, and a quality control representative at the site in a 1:1:1:1 ratio to receive each of four treatments (1–4) according to a 4×4 Williams square design [33] to assure a balanced and unbiased crossover strategy during the course of four such visits:

1. Crushed DETERx 40 mg IN + Intact PBO-ER PO
2. Crushed PBO-ER IN + Intact DETERx 40 mg PO
3. Crushed OXY-IR 40 mg IN *(active control)* + Intact PBO-ER PO
4. Crushed PBO-ER IN *(PBO control)* + Intact PBO-ER PO

The highest strength of DETERx that is manufactured was selected for use in the study (capsules contain 36 mg oxycodone, equivalent to 40 mg oxycodone HCl). This meets FDA guidance for selecting a positive control including a known and robust drug liking response; earlier data from the PK pilot study noted above [26] had found that these DETERx and OXY-IR dosages were equivalent based on overall area under the concentration versus time curves (AUC). Subjects received their randomly assigned treatments once in the morning after an overnight fast of at least 10 hours, followed by consumption of a standardized HFHC breakfast (as in the Drug Discrimination Phase), which was completed within 10 minutes prior to study-drug dosing. Insufflation of IN study drugs was self-administered by subjects through a short straw within a maximum insufflation time of 4 minutes. After each treatment, subjects remained in the clinic for approximately 36 hours for testing and observation. A minimum of 5 days between each treatment was allowed to provide ample time for a washout of study drug before subjects returned to the research center and were crossed over to the next randomized treatment (PK data from the earlier pilot study suggested that 5 days would encompass 22 or more half-lives of study drug; mean $T_{1/2}$ DETERx IN 5.54 ± 1.52 hours; DETERx PO 5.39 ± 1.90 hours; OXY-IR IN 4.44 ± 0.83 hours) [26].

Follow-Up Phase (Telephone Call)

Approximately 1 week after completion of the Double-blind Treatment Phase, subjects were called by the investigator or a clinic staff member as a final check to assess any safety concerns

associated with participation in the study. This follow-up marked the end of the study.

Study Medications and Blinding

The experimental formulation for this study was DETERx (Collegium), an extended-release, abuse-deterrent, microsphere-in-capsule, oral formulation intended for use in the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. This novel formulation consists of encapsulated ER microspheres designed to resist particle size reduction and "dose dumping" when subjected to rigorous physical manipulations such as breaking, cutting, chewing, crushing, or preparation for IV injection. The microspheres have a median particle size of approximately 300 microns and are comprised of active drug, fatty acid, and wax excipients; the drug is released over an extended period of time in the digestive tract by diffusion from the microspheres into gastrointestinal fluids. Earlier research demonstrated that both crushed and chewed contents of the DETERx capsules were bioequivalent to intact DETERx capsules in vivo, and that DETERx microspheres retained their ER mechanism of drug delivery in vitro when subjected to crushing and grinding using readily available household utensils [25].

Generic, commercially available OXY-IR tablets (Sun Pharmaceutical Industries, Ltd., Mumbai, India) were used as the active control in both the Drug Discrimination and Double-blind Treatment Phases. For treatment by insufflation, DETERx microspheres (removed from capsules), OXY-IR tablets, and PBO (ER PBO microspheres supplied by Collegium) were prepared by the onsite pharmacist using a procedure that had been determined in a previous study [25] to be the optimal condition in terms of reducing particle size and increasing drug release in an in vitro dissolution study. Neither study investigators/clinicians nor subjects were aware of powder or capsule contents, facilitating the double blind. To attain double-dummy control conditions, ER PBO was administered as either IN powder or PO capsule in conjunction with active DETERx (Treatments 1 and 2) and OXY-IR (Treatment 3); as a validation check, both IR and IN PBO treatments also were administered together (Treatment 4).

Outcome Assessments and Endpoints

Pharmacokinetic Measures

Important PK characteristics of opioids that correlate with attractiveness for abuse include a high peak plasma concentration (C_{max}) and a shortened time period (T_{max}) to achieve C_{max} because tampering with opioid formulations may increase subjective PD effects by increasing C_{max} and/or decreasing T_{max} [9,34–37]. Given this relationship, the ratio of mean C_{max}/T_{max}, known as the abuse quotient (AQ), has been shown to be useful for helping to gauge a drug's attractiveness for abuse; a relatively high AQ typically predicts increased Drug Liking [38,39].

Primary outcome metrics included: C_{max}, T_{max}, AUC_{last} (within 36 hours following dosing), AUC_{INF} (from time 0 to infinity), $T_{1/2}$ (terminal elimination half-life), and AQ. Partial AUC (PAUC) values were estimated from time zero to all blood sampling time points during the 36 hours of observation and plotted for comparison purposes.

Pharmacodynamic Measures

Pharmacodynamic assessments included subjective and objective parameters. A number of subjective parameters of interest were assessed on 100-mm VAS: Drug Liking (bipolar VAS); Overall Drug Liking (bipolar VAS); Take Drug Again (bipolar VAS); Drug Effects Questionnaire (DEQ, unipolar VAS questions [scored none to extremely] on Any Drug Effects, High, Good Effects, Bad Effects, Sick, Nausea, Sleepy, and Dizzy); the Addiction Research Center Inventory/Morphine Benzedrine Group (ARCI/MBG), assessing euphoric drug effects [39,40]; and a Price-Value Assessment Questionnaire (PVAQ). As an objective measure of drug effects, pupillometry was assessed using a NeurOptics® VIP™-200 pupillometer (NeurOptics, Inc., Irvine, CA, USA). Constriction in pupil diameter in millimeters (mm) was calculated by subtracting the diameter after treatment administration from the baseline diameter; larger decreases indicate more pupil constriction denoting a greater central drug effect.

The PD population included subjects who completed all four Treatment Periods with at least one PD assessment in each Treatment Period. The primary PD endpoint of interest was Drug Liking ("Do you like the effect that you are feeling now?") VAS score; primary outcomes compared crushed OXY-IR 40 mg IN (positive control - Treatment 3) with crushed DETERx 40 mg IN (Treatment 1) for Drug Liking. Secondary comparisons of Drug Liking were examined between crushed DETERx IN (Treatment 1) and intact DETERx PO (Treatment 2), and between crushed OXY-IR IN (Treatment 3) and intact DETERx PO (Treatment 2). An examination of Drug Liking between crushed OXY-IR 40 mg IN (Treatment 3) and PBO (Treatment 4) was used for validation of the appropriateness of the positive control.

Additionally, PD outcomes reflecting Drug Liking, Drug High, and Good Drug Effects were summarized as maximum drug effects (E_{max}), time-to-E_{max} ($TE_{max,}$ hours), and area under the drug-effect curve (AUE) at 0–1 hour ($AUE_{0–1h}$), 0–2 hours ($AUE_{0–2h}$), 0–4 hours ($AUE_{0–4h}$), 0–8 hours ($AUE_{0–8h}$), and 0–24 hours ($AUE_{0–24h}$). Increasing time intervals from 0 were used to determine the initial onset of positive subjective effects and the cumulative effects of these effects over time.

Safety/Tolerability Assessment and Endpoints

Safety and tolerability were assessed in the Drug Discrimination and Double-blind Treatment Phases via treatment-emergent adverse events (TEAEs), nasal cavity examination, nasal effects assessment, vital signs measurements, oxygen saturation, hematology, chemistry, and

urinalysis laboratory parameters. The Safety Population included all subjects randomized into the Double-blind Treatment Phase who received at least one dose of study drug during the Double-blind Treatment Phase and for whom there was at least one post-treatment safety observation in this phase. Adverse events were coded by investigators by system organ class (SOC) and preferred term based on the Medical Dictionary for Regulatory Activities reporting system (MedDRA, http://www.meddra.org) (MedDRA MSSO, McLean, VA, USA). Each TEAE was assigned to the respective study phase and/or specific Double-blind Treatment according to the date and time of onset. A TEAE in the Double-blind Treatment Phase was defined as an adverse event (AE) with an onset date on or after the start of dosing in the Double-blind Treatment Phase. Nasal cavity inspection was conducted by the investigator and the nasal effects assessments associated with insufflation—including intranasal irritation, burning, facial pain/pressure, nasal congestion, runny nose/nasal discharge, and need to blow nose—were assessed during each treatment by self-report of subjects.

Statistical Analyses

Statistical analyses in this study were performed using SAS® Version 9.3 (SAS Institute, Inc., Carey, NC, USA); all significance tests were two-tailed using $\alpha \leq 0.05$. An adequate number of subjects were screened for enrollment in the study so that up to 42 subjects would be randomly assigned into the Double-blind Treatment Phase and at least 36 subjects would complete the study for PD analyses. This would provide at least 90% power to detect mean treatment differences of $\geq$11.2 points in E_{max} on the primary Drug Liking variable at a two-sided significance level of 0.05, assuming a standard deviation (SD) of mean E_{max} differences of 20 points; this allowed detection of at least a moderate, potentially clinically important effect size (i.e., standardized mean difference, or SMD $\geq$ 0.50) [41].

For primary PK assessments of oxycodone (DETERx IN and PO, and OXY-IR IN), mean values by treatment received were calculated using non-compartmental methods for C_{max} and T_{max}, and AQ was calculated for each subject and then summarized across subjects within treatment group to derive mean values. Secondary PK measures included: AUC_{last}, AUC_{INF}, $T_{1/2}$, and PAUC from time 0 to all blood sample time points. Analyses of variance (ANOVA) included calculation of least square (LS) means, differences between treatment LS means, and standard errors associated with differences. LS means ("marginal means") are arithmetic means adjusted by using a linear mixed model with fixed effects for sequence, period, and treatment, and random effects for patients nested in sequence. This approach is less sensitive to missing data and may better estimate the population mean in small groups [42]. T_{max} was analyzed using nonparametric analysis (Walsh averages and appropriate quantile of the Wilcoxon Signed Rank Test statistic). A plot was developed for mean ($\pm$ standard deviation) plasma oxycodone concentrations (ng/mL) versus time (hours) on linear axes.

For PD endpoints, LS mean differences were estimated by the method of Hodges and Lehman [43], and 95% confidence intervals (CIs) were calculated as recommended by Moses and Lehmann [44] for each pairwise treatment. Select PD parameters of interest collected over time also were graphed for visual inspection. Secondarily, percent reduction in Drug Liking E_{max} data were examined in a responder analysis; a responder was defined as a subject who had a specified level of reduction in Drug Liking E_{max} for DETERx IN relative to OXY-IR IN. Levels from 0% to 100% in 10% increments were examined in the analysis.

For safety assessments, TEAEs were tabulated for each of the four double-blind treatments by most severe and by most closely related to study drug. If a subject experienced the same event more than once during a Treatment Period, only the first occurrence was tabulated. Nasal effects assessments were summarized for each treatment as the number and percentage of subjects within each category (e.g., irritation, burning, etc.).

Results

Subject Disposition and Demographics

There were 95 subjects recruited and screened for participation in this study; 64 met eligibility criteria to proceed to the Drug Discrimination Phase (Figure 1). All of these subjects passed the naloxone challenge test; however, there were 25 subjects discontinued at this phase: 15 were unable to adequately distinguish between low-dose OXY-IR IN and PBO-IR IN; six experienced emesis and were withdrawn in accordance with protocol mandated criteria; three decided to withdraw from the study; and one violated the protocol. Therefore, 39 qualifying subjects entered into the Double-blind Treatment Phase and comprised the Safety Population for safety analyses. Two of the 39 subjects (one male, one female) were withdrawn following the first Treatment Period (both subjects had received OXY-IR IN) and one female subject was withdrawn during the third Treatment Period (this subject received placebo, DETERx IN, and OXY-IR IN). Consequently, 36 subjects completed all four Treatment Periods with at least one PD and PK assessment in each period; these subjects make up the PD/PK assessment Population for these analyses. There were no PK assessments performed in the PBO group (PBO-ER IN and PO; Treatment 4).

Demographically (Table 1), most subjects for the Safety Population were male (72%), White (85%), and not Hispanic or Latino (90%). Mean age was about 27 years and ranged from 19 to 54 years. Demographic and baseline characteristics were not remarkably different across the Drug Discrimination, Safety, and PD/PK assessment Populations. The only notable differences were a slightly lower percentage of subjects who were not Hispanic/Latino and a larger percentage of Whites in the Drug Discrimination Population.

In accordance with study entry criteria, all subjects had a history of recreational opioid use, but none were

determined to be physiologically dependent. Cannabinoids were the most frequently used recreational drug; the majority of subjects (N = 30) had used IN administration of other recreational drugs during the prior 12 weeks. Medical history revealed no clinically significant abnormalities and was representative of an otherwise healthy population of adult recreational drug users. Prior medications used by subjects included health supplements, ibuprofen, contraceptives, and sleep aids. The most frequent concomitant medication was acetaminophen; used by four subjects for headache, one subject for earache, and one subject for menstrual cramps. Additionally, one subject had received loratadine, hydroxyzine, and permethrin cream for acarodermatitis and was discontinued from the study at the investigator's discretion due to ongoing use of these medications.

Pharmacokinetic Outcomes

Summary statistics for relevant PK parameters are shown in Table 2. C_{max} values for crushed DETERx IN were lower in comparison with those observed for the other two active treatments: crushed DETERx IN resulted in approximately 74% of the peak exposure of intact DETERx PO and only 49% of the peak exposure of crushed OXY-IR IN. At the same time, median T_{max} for DETERx IN and PO administration were equivalent (5.08 hours for both treatments); both were longer than OXY-IR IN (2.48 hours). The consequent mean AQ value for crushed DETERx IN was lower than for intact DETERx PO—mean AQs were 6.24 and 8.60 ng/mL/h, respectively—and both were much lower than for OXY-IR IN (69.6 ng/mL/h; based on the mean of summed AQ values calculated for each subject).

DETERx IN and DETERx PO were bioequivalent with respect to AUC_{last} and AUC_{INF} values; due to fluctuations in plasma concentrations at later time points, AUC_{INF} (and $T_{1/2}$), could be accurately derived only for 31 DETERx IN subjects and 29 DETERx PO subjects (Table 2), which did not statistically bias the relationships. Looking at the trend for mean drug concentrations over time (Figure 2), the mean concentration following administration of crushed DETERx IN initially rose higher than for intact DETERx PO, but both were much less than crushed OXY-IR IN, such that by 5 hours following administration, the mean cumulative $PAUC_{(0–5h)}$ value of crushed DETERx IN was similar to that of intact DETERx PO and much less than for crushed OXY-IR IN: mean (SD) cumulative $PAUC_{(0–5h)}$ for crushed DETERx IN, intact DETERx PO, and crushed OXY-IR IN were 88.0 (24.0), 83.6 (41.8), and 243 (41.7) h*ng/mL, respectively.

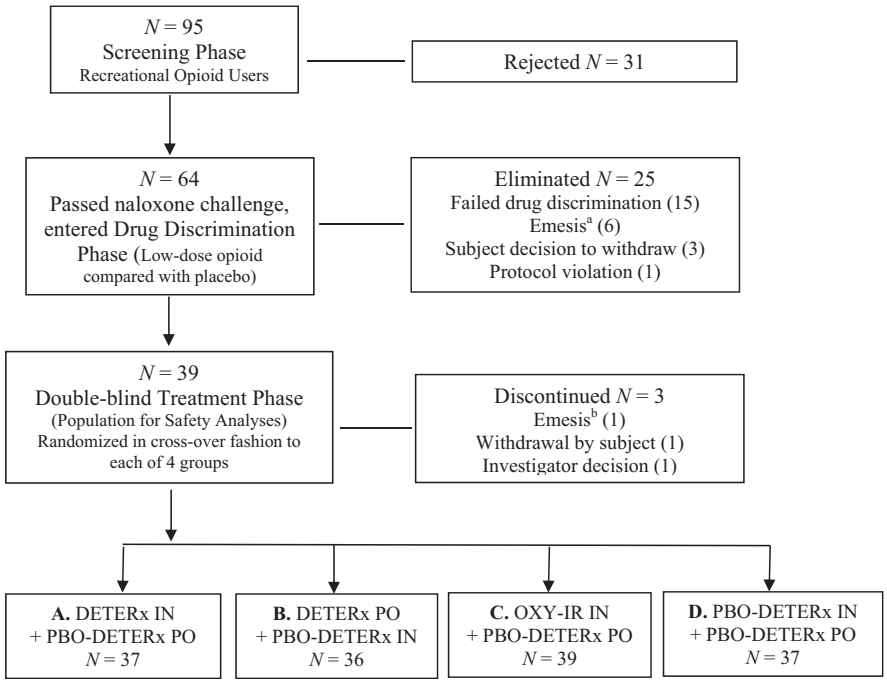

Figure 1 Disposition of subjects during the course of the study. [a] Study entry criteria required that subjects who experienced emesis within the first 6 hours of dosing were not eligible to continue to the Double-blind Treatment Phase. [b] The protocol stated that subjects who experienced emesis after the HFHC meal prior to dosing or within the first 6 hours of dosing were to be discontinued from the study. HFHC = high-fat, high-calorie; IN = intranasal; N = number of observations; OXY = oxycodone; OXY-IR = immediate-release oxycodone; PBO = placebo; PO = oral (per os).

Table 1 Demographic and baseline characteristics

Characteristic	Drug discrimination population (N = 64)	Safety population (N = 39)	PD/PK population (N = 36)
Age; mean yrs (SEM)	26.38 (0.88)	26.77 (1.07)	26.89 (1.13)
Gender, N (%)			
Male	48 (75.0%)	28 (71.8%)	27 (75.0%)
Female	16 (25.0%)	11 (28.2%)	9 (25.0%)
Ethnicity, N (%)			
Non-Hispanic/Latino	54 (84.4%)	35 (89.7%)	32 (88.9%)
Hispanic or Latino	10 (15.6%)	4 (10.3%)	4 (11.1%)
Race, N (%)			
Asian	3 (4.7%)	2 (5.1%)	2 (5.6%)
Black/African American	4 (6.3%)	2 (5.1%)	2 (5.6%)
White	51 (79.7%)	33 (84.6%)	31 (86.1%)
Other	6 (9.4%)	2 (5.1%)	1 (2.8%)
Weight, mean kg (SEM)	75.37 (2.16)	77.35 (2.81)	78.07 (3.00)
Height, mean cm (SEM)	174.13 (1.22)	174.75 (1.32)	175.16 (1.26)
BMI, mean kg/m^2 (SEM)	24.73 (0.58)	25.27 (0.81)	25.38 (0.88)

BMI = body mass index; kg = kilogram; m^2 = meter squared; N = number of observations; PD = pharmacodynamic; PK = pharmacokinetic; SEM = standard error of the mean.

Pharmacodynamic Outcomes

Subjective Effects

The primary subjective endpoint, Drug Liking, was assessed via 0- to 100-mm bipolar VAS, where 0 = strong disliking, 50 = neither like nor dislike, and 100 = strong liking. Study validity of the OXY-IR IN positive control during the Double-blind Treatment Phase was confirmed by the E_{max} LS mean for Drug Liking being higher for crushed OXY-IR 40 mg IN than PBO (82.57 vs 54.63 mm, $P < 0.0001$). The difference of LS means between OXY-IR IN and PBO was also higher for minimum effect (E_{min}, $P = 0.0276$) and all other PD parameters ($P < 0.0001$) except TE_{max} ($P = 0.3680$ for ranked analysis). Table 3 presents statistical summary comparisons of PD parameters between active-drug treatment groups for Drug Liking. Based on the LS mean E_{max} for Drug Liking, crushed DETERx 40 mg IN was less liked than crushed OXY-IR 40 mg IN ($P \leq 0.0001$); the calculated SMD of this relationship represents a large and potentially clinically important effect size of 1.24 [41]. This primary PD finding for DETERx IN versus OXY-IR IN was corroborated by all AUE parameters, with statistically significant less Liking for DETERx IN than OXY-IR IN. Furthermore, LS mean TE_{max} was shorter for OXY-IR IN compared with DETERx IN ($P = 0.0019$).

For comparisons of intact DETERx 40 mg PO with OXY-IR 40 mg IN, LS mean E_{max} and all AUE parameters demonstrated less Liking for DETERx PO than OXY-IR IN ($P \leq 0.05$ for all comparisons). LS mean TE_{max} was shorter for OXY-IR IN compared with DETERx PO ($P \leq 0.0001$). Comparing crushed DETERx IN with intact DETERx PO, LS mean E_{max} and AUEs at later time points (i.e., $AUE_{0–8h}$ and $AUE_{0–24h}$) showed significantly less Liking for DETERx IN; however, the LS mean AUEs at earlier time points (i.e., $AUE_{0–1h}$ through $AUE_{0–4h}$) were not significantly different between the DETERx PO and IN treatments. Overall, these data suggest that abuse potential of DETERx will likely not be augmented by crushing and insufflation.

Figure 3A graphically depicts arithmetic mean scores for Drug Liking during the Double-blind Treatment Phase. Early, at the 15-minute post-dose time point, subjects showed comparably mild disliking for DETERx IN, DETERx PO, and PBO (scores = 43.56, 47.97, and 47.31 mm, respectively), but a high Drug Liking for OXY-IR IN (score = 75.25 mm). At each following time point—except at 90 minutes, and 6 and 8 hours—mean Drug Liking scores with DETERx IN were less than 50 mm, which represents disliking of DETERx IN; the highest mean Drug Liking score for this treatment was only 51.19 mm at the 6-hour time point.

In terms of responder analyses for the primary outcome measure, only two subjects (5.6%) had any percent increase in Drug Liking E_{max} with DETERx IN compared with OXY-IR IN. In all other instances, there was a *reduction* to some extent in Drug Liking E_{max} with DETERx IN relative to OXY-IR IN (Figure 4): more than three-quarters of subjects (N = 28; 77.8%) had a reduction of 30% or more in Drug Liking E_{max} with DETERx IN versus OXY-IR IN; more than half of subjects (N = 21, 58.3%) had a 50% or greater reduction; more than a quarter of subjects (N = 10; 27.8%) had a reduction of 100% or more.

Table 4 summarizes statistical comparisons of LS mean E_{max} for secondary subjective endpoints including the

Table 2 Summary statistics: oxycodone PK parameters

Treatment		C_{max} (ng/mL)	T_{max} (h)	AUC_{last} (h*ng/mL)	AUC_{INF} (h*ng/mL)	$T_{1/2}$ (h)	AQ[a] ng/mL/h
Crushed DETERx IN	N	36	36	36	31[b]	31[b]	36
	Mean	29.8	5.78	440	459	6.02	6.24
	SD	6.58	2.40	101	106	1.52	3.72
	Min	15.5	1.58	215	219	4.01	2.12
	Median	29.2	5.08	416	436	5.57	5.66
	Max	43.5	12.10	712	738	9.38	22.2
	CV%	22.1	41.5	22.9	23.0	25.2	59.6
Crushed OXY-IR IN	N	36	36	36	36	36	36
	Mean	60.9	2.48	568	577	3.92	69.6
	SD	11.9	1.75	124	124	0.523	84.1
	Min	44.7	0.28	359	362	3.00	8.60
	Median	56.6	2.58	573	584	3.94	23.0
	Max	94.5	6.05	944	949	5.50	284
	CV%	19.5	70.5	21.8	21.5	13.3	120.9
Intact DETERx PO	N	36	36	36	29[b]	29[b]	36
	Mean	41.0	5.37	470	477	5.07	8.60
	SD	9.95	1.50	93.1	89.6	0.728	4.67
	Min	27.6	1.58	329	345	4.15	3.79
	Median	38.4	5.08	448	466	4.90	7.45
	Max	68.8	8.08	666	680	6.92	27.6
	CV%	24.3	27.9	19.8	18.8	14.4	54.3

[a]AQ parameters are calculated from C_{max}/T_{max} values separately determined for each subject and then summarized for all individuals within the respective treatment group.

[b]Due to fluctuations in plasma concentrations at later time points, AUC_{INF} and $T_{1/2}$ could be accurately derived only for 31 DETERx IN subjects and 29 DETERx PO subjects.

AQ = abuse quotient; AUC_{INF} = area under the plasma concentration-time course profile from time 0 (dosing) to infinity; AUC_{last} = area under the plasma concentration-time course profile from time 0 (dosing) to last quantifiable concentration; C_{max} = maximum observed plasma concentration; CV = coefficient of variation; IN = intranasal; IR = immediate-release; max = maximum; mL = milliliter; N = number of observations; ng = nanogram; OXY = oxycodone; PK = pharmacokinetic; PO = per os; SD = standard deviation; T_{max} = time from dosing to maximum observed concentration; $T_{1/2}$ = terminal elimination half-life.

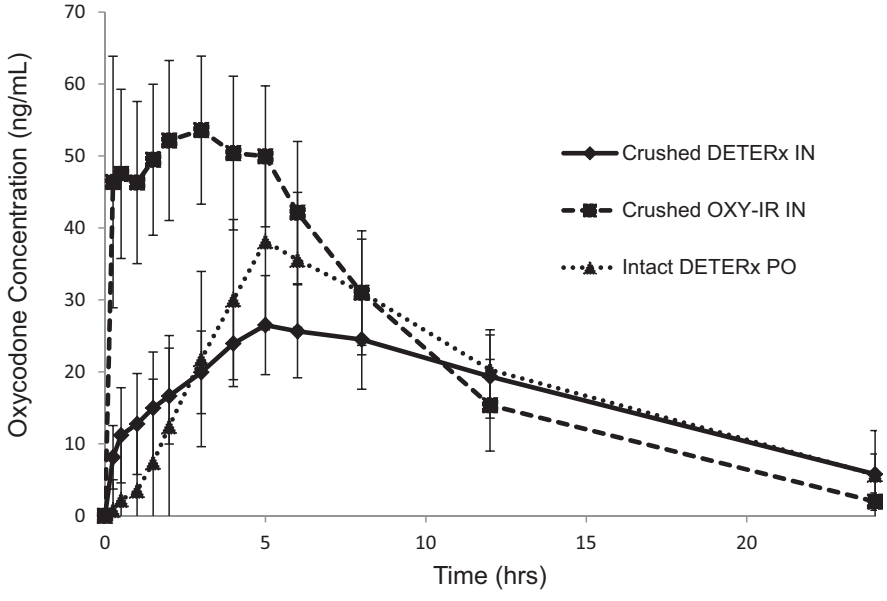

Figure 2 Mean plasma oxycodone concentration (ng/mL) over time (hours) for crushed DETERx IN, intact DETERx PO, and crushed OXY-IR IN recorded at multiple time points following administration of study drug. Error bars = ±Standard Deviation. hrs = hours; IN = intranasal; mL = milliliter; ng = nanogram; OXY = oxycodone; OXY-IR = immediate-release oxycodone; PO = per os.

Table 3 LS mean differences for PD parameters on the primary endpoint "drug liking" (N = 36)

Group comparisons	E_{max} (mm)	$AUE_{0–1h}$ (mm)	$AUE_{0–2h}$ (h*mm)	$AUE_{0–4h}$ (h*mm)	$AUE_{0–8h}$ (h*mm)	$AUE_{0–24h}$ (h*mm)	TE_{max} (h)
OXY-IR IN vs DETERx IN[a]	20.69*	22.39*	43.23*	72.66*	99.90*	97.96*	−0.75**
DETERx IN vs DETERx PO[b]	−5.99**	0.14[c]	0.00[c]	−7.52[c]	−28.36**	−45.25**	−1.00[c]
OXY-IR IN vs DETERx PO[a]	14.70*	22.55*	43.20*	64.06*	68.37*	52.29**	−2.50*

AUE = area under the effect curve; E_{max} = maximum (peak) effect; h = hour; IN = intranasal; IR = immediate-release; LS = least squares; mm = millimeters; N = number of observations; OXY = oxycodone; PD = pharmacodynamic; PO = per os; TE_{max} = time-to-peak effect.

[a]Positive values for E_{max} and AUE indicate less Drug Liking for DETERx IN and DETERx PO than OXY-IR IN; negative values for TE_{max} indicate longer periods of time to reach peak effects with DETERx IN and DETERx PO than OXY-IR IN.

[b]Negative values for E_{max} and select AUE time points indicate less Drug Liking for DETERx IN compared with DETERx PO; negative value for TE_{max} indicates longer period of time-to-reach peak effect with DETERx PO vs DETERx IN.

[c]Not significant.

*$P \leq 0.0001$.

**$P \leq 0.05$.

DEQ, Overall Drug Liking, Take Drug Again, ARCI/MBG, and PVAQ. Outcomes on positive subjective effects of Drug High and Good Drug Effects were generally consistent with results of the Drug Liking assessment, with both DETERx IN and PO demonstrating less abuse potential than OXY-IR IN, but greater than PBO up to 24 hours post-dose. Specifically, differences in E_{max} between OXY-IR IN and DETERx IN, as well as differences between OXY-IR IN and DETERx PO, were statistically significant for each of those effects ($P < 0.0001$).

Figures 3B and 3C graphically depict arithmetic mean scores for Drug High and Good Effects. These generally reflect the same trends as for the Drug Liking variable; however, during the early post-dose time period (up to 2 hours), DETERx IN exhibited relatively higher Drug High and Good Effects than DETERx PO. This is consistent with the PK results, showing an early rise in mean plasma concentration of crushed DETERx IN relative to intact DETERx PO, which reverses within several hours; these initial Drug High and Good Effects scores favoring IN administration are significantly lower than OXY-IR IN scores and did not appear to affect the lower Drug Liking scores exhibited for DETERx IN.

Other secondary endpoints (Table 4), including Overall Drug Liking, Any Drug Effects, Take Drug Again assessments, and ARCI/MBG also showed significantly higher E_{max} values for OXY-IR IN than DETERx administered either IN or PO ($P \leq 0.029$ for all). On the DEQ, compared with both DETERx treatments, OXY-IR IN produced statistically higher LS mean E_{max} for Nausea, Sleepiness, and Dizziness, but differences for Bad Drug Effects were not statistically significant. LS mean E_{max} for Sick was significantly higher for OXY-IR IN than DETERx PO, but there was no statistically significant difference on this measure between OXY-IR IN and DETERx IN. In most comparisons of crushed DETERx IN with intact DETERx PO, outcomes for secondary endpoints were consistent with the results for the primary endpoint of Drug Liking. Additionally, LS mean E_{max} for High, Good Drug Effects, Overall Drug Liking, Take Drug Again, and ARCI/MBG were significantly higher for intact DETERx PO than crushed DETERx IN.

For Price-Value Assessments, 24 hours following treatment, subjects were asked to estimate how much they would pay (street value) for each of the medications they received if those were available illicitly. Street value was selected from a $0 to $100 scale divided into $5 increments. As depicted in Table 4, subjects indicated that they would pay significantly more for OXY-IR IN than either DETERx IN ($P < 0.0001$ based on ranked data) or DETERx PO ($P = 0.012$ based on ranked data), while differences between DETERx IN and PO were not statistically significant.

Objective Pupillometry. Statistical comparisons of LS mean E_{max} for the objective pupillometry endpoint are summarized in Table 4; Figure 5 graphically depicts arithmetic mean pupil diameter measures over time. Outcomes for pupillometry over time were similar to the results for the primary Drug Liking endpoint, with both DETERx treatments falling between PBO and OXY-IR IN treatments. OXY-IR IN demonstrated a more immediate and significantly greater drug effect than either DETERx IN or DETERx PO, but differences between DETERx treatments themselves were not statistically significant (LS mean $P = 0.349$).

Safety Outcomes

TEAEs considered by the investigator to be treatment-related are summarized in Table 5. Nausea, vomiting,

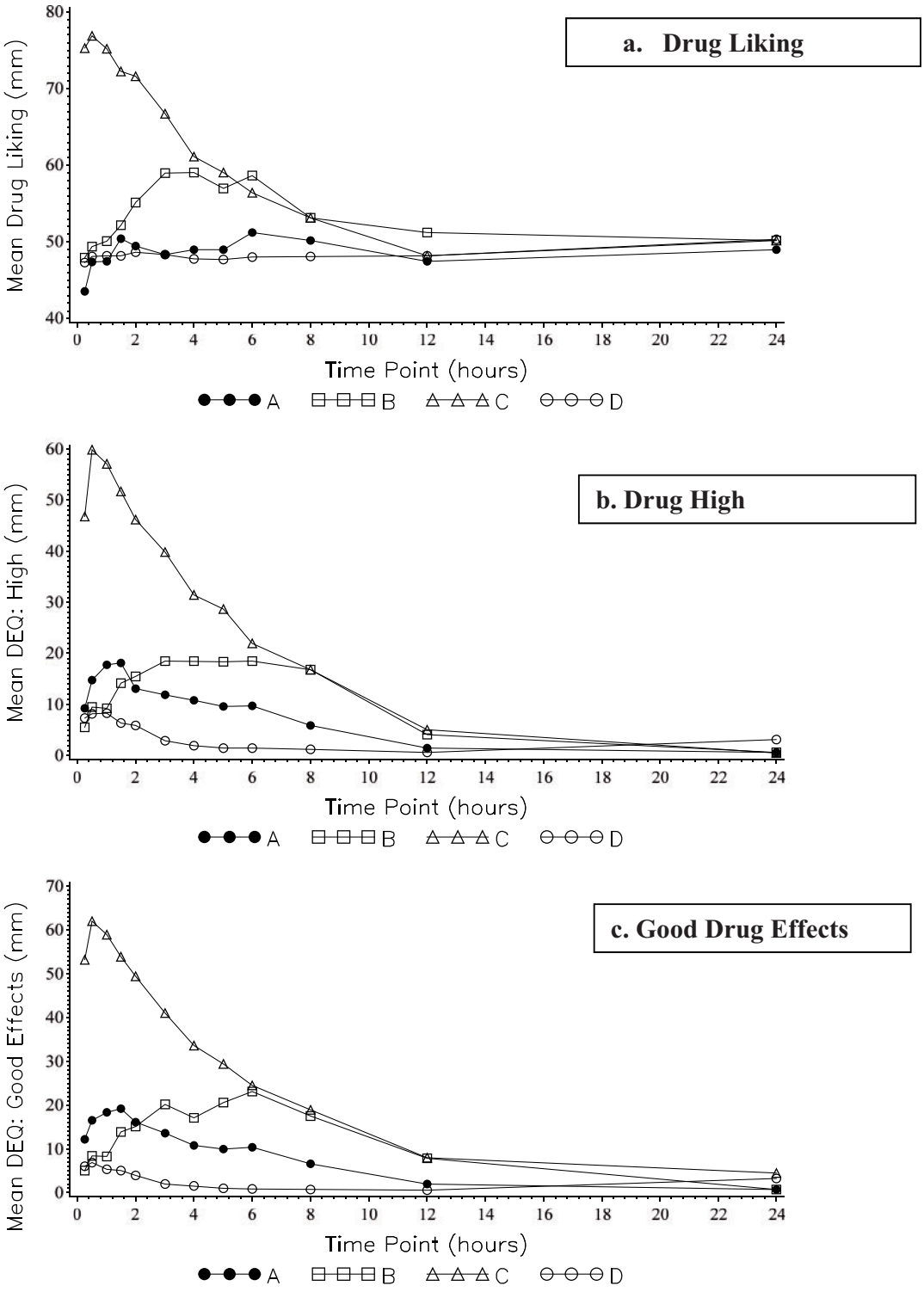

Figure 3 Mean VAS scores for (a) Drug Liking (bipolar VAS), (b) Drug High (unipolar VAS), and (c) Good Effects (unipolar VAS) during the Double-blind Treatment Phase (N = 36). Each graph shows arithmetic mean VAS results observed during 24 hours for the four treatment conditions: A (●) = crushed DETERx IN; B (□) = intact DETERx PO; C (△)= crushed OXY-IR IN; D (○) = Placebo. Higher scores denote greater response on the respective PD drug-attractiveness variable; error bars are omitted for clarity purposes. DEQ = drug effects questionnaire; IN = intranasal; mm = millimeter; N = number of observations; OXY = oxycodone; OXY-IR = immediate-release oxycodone; PD = pharmacodynamic; PO = per os; VAS = visual analog scale.

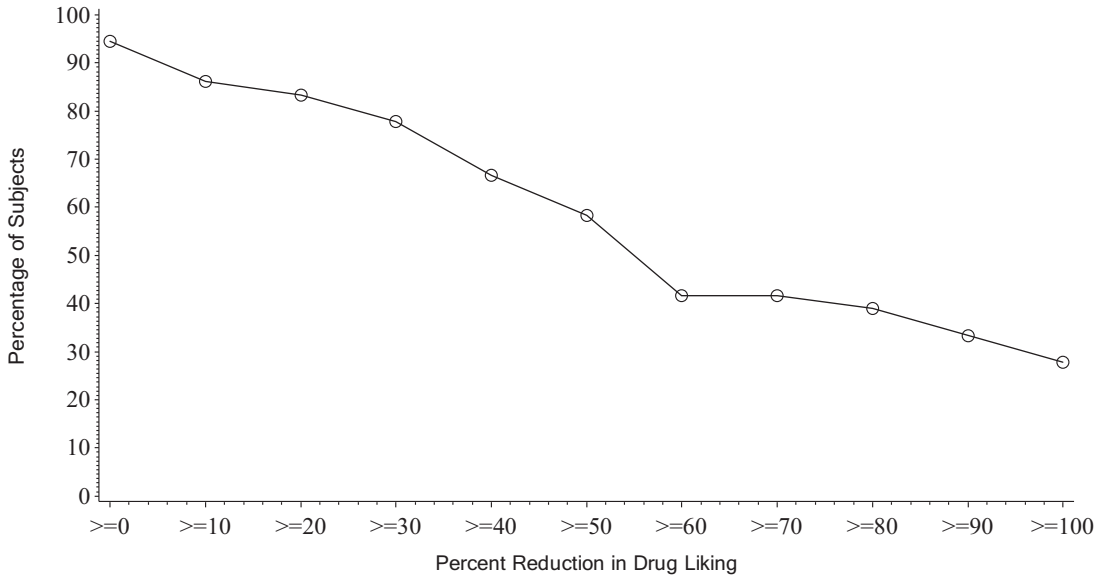

Figure 4 Cumulative plot of percent reduction in Drug Liking E_{max} for DETERx IN relative to OXY-IR IN in the Double-blind Treatment Phase (N = 36). The vertical Y-axis represents the percent of subjects attaining a percent reduction of Drug Liking for DETERx IN vs OXY-IR IN equal to or greater than the value on the horizontal X-axis. '> =' symbol = greater than or equal to; E_{max} = peak effect; IN = intranasal; IR = immediate-release; N = number of observations; OXY = oxycodone.

Table 4 Summary of LS mean E_{max} comparisons for secondary PD endpoints (N = 36)

Measure	OXY-IR IN vs DETERx IN	DETERx IN vs DETERx PO	OXY-IR IN vs DETERx PO
Drug effects questionnaire (mm)			
Any drug effects	69.34 v 38.53, $P < 0.0001$	38.53 v 36.85, $P = 0.7759$	69.34 v 36.85, $P < 0.0001$
Drug high	69.05 v 23.78, $P < 0.0001$	23.78 v 34.70, $P = 0.0470$	69.05 v 34.70, $P < 0.0001$
Good drug effects	68.93 v 27.25, $P < 0.0001$	27.25 v 39.65, $P = 0.0299$	68.93 v 39.65, $P < 0.0001$
Bad drug effects	25.50 v 36.59, $P = 0.7996$	36.59 v 25.11, $P = 0.4274$	25.50 v 25.11, $P = 0.5887$
Sick	17.36 v 14.36, $P = 0.1635$	14.36 v 8.51, $P = 0.3263$	17.36 v 8.51, $P = 0.0187$
Nausea	17.90 v 11.74, $P = 0.0179$	11.74 v 11.03, $P = 0.5757$	17.90 v 11.03, $P = 0.0037$
Sleepy	48.14 v 20.56, $P < 0.0001$	20.56 v 25.11, $P = 0.1284$	48.14 v 25.11, $P = 0.0001$
Dizzy	19.65 v 10.71, $P = 0.0022$	10.71 v 11.84, $P = 0.3015$	19.65 v 11.84, $P = 0.0384$
Overall drug liking (mm)	71.78 v 48.42, $P < 0.0001$	48.42 v 62.20, $P = 0.0037$	71.78 v 62.20, $P = 0.0292$
Take drug again (mm)	71.25 v 47.77, $P < 0.0001$	47.77 v 58.98, $P = 0.0128$	71.25 v 58.98, $P = 0.0154$
ARCI/MBG	5.93 v 1.34, $P < 0.0001$	1.34 v 3.10, $P = 0.0185$	5.93 v 3.10, $P = 0.0024$
Price-value assessment ($)	8.54 v 2.92, $P < 0.0001$	2.92 v 4.54, $P = 0.0708$	8.54 v 4.54, $P = 0.0119$
Pupillometry (mm)	3.08 v 2.60, $P = 0.0004$	2.60 v 2.73, $P = 0.3488$	3.08 v 2.73, $P = 0.0070$

ARCI/MBG = Addiction Research Center Inventory-Morphine Benzedrine Group; E_{max} = maximum (or peak) effect; IN = intranasal; LS = least square; mm = millimeter; N = number of observations; OXY = oxycodone; OXY-IR = immediate-release oxycodone; PO = per os; PD = pharmacodynamic; $= U.S. dollars; vs = versus.

headache, and generalized pruritus were the only individual TEAEs other than nasal discomfort that occurred in more than 10% of subjects during any treatment. Most TEAEs were mild or moderate in severity; eye irritation and nasal discomfort were the only severe TEAEs. Respiratory, Thoracic, and Mediastinal disorders occurred more frequently with DETERx treatments than OXY-IR IN: 18.9% of subjects with DETERx IN, 13.5% of subjects with PBO (which included PBO-ER IN), 5.6% of subjects with DETERx PO (which included PBO-ER IN), and 2.6% of subjects with OXY-IR IN. AEs in this system organ class may have resulted from IN administration of the microsphere formulation contained in both the active and PBO ER capsules; although it is

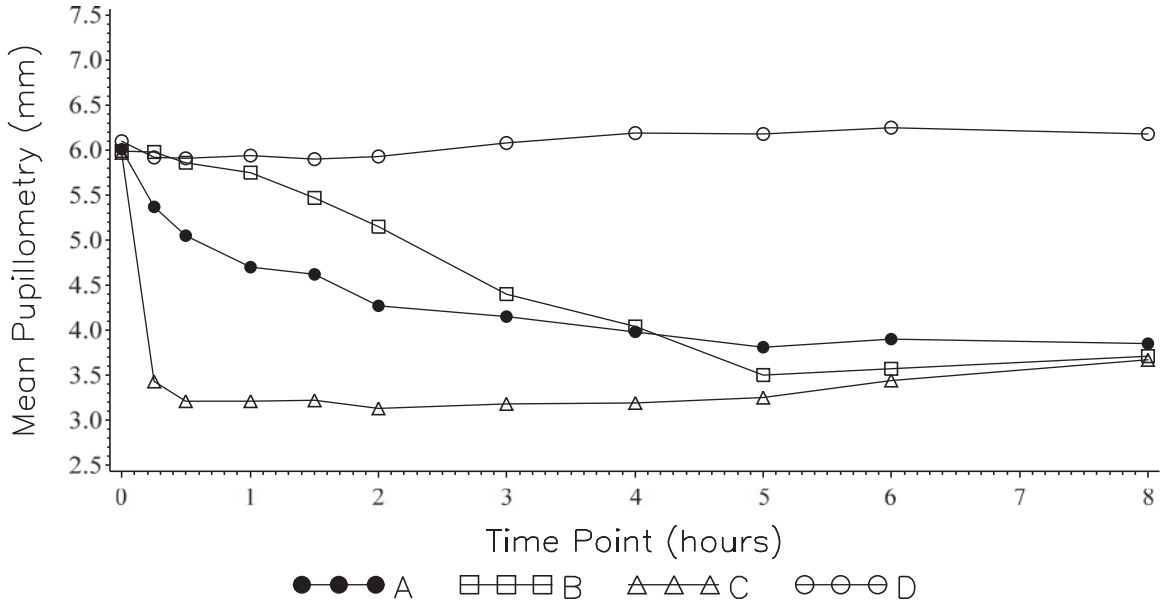

Figure 5 Arithmetic mean results of pupillometry measures during the Double-blind Treatment Phase, encompassing 8 hours of observation in study subjects (N = 36). Treatments: A (●) = crushed DETERx IN; B (□) = intact DETERx PO; C (△) = crushed OXY-IR IN; D (○) = Placebo. Larger decreases indicate more pupil constriction denoting a greater drug effect; error bars are omitted for clarity purposes. IN = intranasal; IR = immediate-release; mm = millimeter; N = number of observations; OXY = oxycodone; PO = per os.

unclear why the DETERx PO treatment, which also included PBO-ER IN, had a lower incidence of these types of TEAEs than the other DETERx IN treatments.

Nasal cavity examinations completed by the clinicians were normal for all subjects. The influence of the microsphere formulation was evident in results of the Nasal Effects Assessment based on subject self-report of irritation, burning, facial pain pressure, nasal congestion, nasal discharge, and need to blow nose following insufflation. At earlier time points, subjects reported the highest frequencies and severity of nasal effects with DETERx IN, DETERx PO, and PBO (the latter two included PBO-ER IN) compared with OXY-IR IN. As time passed, moderate or severe nasal effects were reported by fewer subjects with all Treatments. For example, at 15-minutes post-dose, severe "nasal irritation" was reported by 24.3%, 19.4%, 2.6%, and 21.6% of subjects with DETERx IN, DETERx PO, OXY-IR IN, and PBO, respectively. By 1 hour, the frequencies of severe effects had diminished to 5.4%, 11.1%, 0.0%, and 5.4%, respectively. The frequencies continued to decline until at 12 hours no severe effects were reported and only mild effects were reported by 10.8%, 5.6%, 0.0%, and 2.7% of subjects, respectively. Comparable patterns were observed for all other nasal effects.

Discussion

This randomized, double-blind, double-dummy clinical study examined the relative HAP of a novel formulation of ER oxycodone (formulated using the DETERx microsphere-in-capsule technology platform)—administered orally and intranasally following crushing—in comparison with intranasally administered OXY-IR as a positive control, and with a PBO ER control. Safety outcomes were evaluated in a population of 39 qualifying recreational opioid users; PK and PD parameters were assessed in 36 of those subjects who were randomized to and sufficiently participated in the four different Treatment Periods.

DETERx was designed for oral administration as an intact capsule; whereas, recreational drug abusers are likely to open a capsule and attempt to crush and insufflate its contents —oxycodone microspheres. This study presents the first PK and PD data to show that crushing DETERx and administering it nasally is not associated with increased Drug Liking scores when compared with taking the drug as intended, via oral administration.

Pharmacokinetic results in this study demonstrate that DETERx PO and IN appear to be equivalent in terms of overall absorption, but administration of crushed DETERx IN results in a lower mean C_{max} than with either intact DETERx PO or crushed OXY-IR IN. Absorption of DETERx IN was initially more rapid than DETERx PO, as might be expected with intranasal exposure; however, mean T_{max} for DETERx administered PO and IN were comparable to each other and less than half as rapid as for OXY-IR IN. The subsequent mean abuse quotient ($AQ = C_{max}/T_{max}$) in this study was lower with DETERx IN than DETERx PO (6.24 vs 8.60 ng/mL/h, respectively) and more than

Table 5 Investigator-rated treatment-emergent adverse events (TEAEs) related to therapy during the double-blind treatment phase—safety population[a]

System organ class/preferred term[b]	DETERx IN (N = 37)	DETERx PO (N = 36)	OXY-IR IN (N = 39)	Placebo (N = 37)
Eye disorders	**1 (2.7%)**	**2 (5.6%)**	**0 (0.0%)**	**0 (0.0%)**
Eye irritation	1 (2.7%)	2 (5.6%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders	**6 (16.2%)**	**5 (13.9%)**	**14 (35.9%)**	**0 (0.0%)**
Dyspepsia	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)
Nausea	5 (13.5%)	5 (13.9%)	8 (20.5%)	0 (0.0%)
Vomiting	1 (2.7%)	2 (5.6%)	10 (25.6%)	0 (0.0%)
General and administration site conditions	**3 (8.1%)**	**1 (2.8%)**	**0 (0.0%)**	**2 (5.4%)**
Facial pain	2 (5.4%)	0 (0.0%)	0 (0.0%)	1 (2.7%)
Irritability	1 (2.7%)	0 (0.0%)	0 (0.0%)	1 (2.7%)
Pain	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)
Investigations	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (2.7%)**
Blood pressure increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.7%)
Nervous system disorders	**8 (21.6%)**	**8 (22.2%)**	**6 (15.4%)**	**3 (8.1%)**
Burning sensation	0 (0.0%)	2 (5.6%)	0 (0.0%)	0 (0.0%)
Disturbance in attention	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dizziness	1 (2.7%)	1 (2.8%)	1 (2.6%)	0 (0.0%)
Headache	6 (16.2%)	5 (13.9%)	5 (12.8%)	2 (5.4%)
Sinus headache	3 (8.1%)	0 (0.0%)	0 (0.0%)	1 (2.7%)
Somnolence	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)
Respiratory, thoracic, and mediastinal disorders	**7 (18.9%)**	**2 (5.6%)**	**1 (2.6%)**	**5 (13.5%)**
Epistaxis	1 (2.7%)	0 (0.0%)	0 (0.0%)	1 (2.7%)
Hiccups	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)
Nasal congestion	1 (2.7%)	0 (0.0%)	0 (0.0%)	1 (2.7%)
Nasal discomfort	5 (13.5%)	2 (5.6%)	0 (0.0%)	4 (10.8%)
Skin and subcutaneous tissue disorders	**3 (8.1%)**	**10 (27.8%)**	**20 (51.3%)**	**0 (0.0%)**
Pruritus	0 (0.0%)	1 (2.8%)	3 (7.7%)	0 (0.0%)
Pruritus generalized	3 (8.1%)	9 (25.0%)	17 (43.6%)	0 (0.0%)
Vascular disorders	**0 (0.0%)**	**1 (2.8%)**	**0 (0.0%)**	**0 (0.0%)**
Hot flush	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)

IN = intranasal; N = number of observations; OXY = oxycodone; OXY-IR = immediate-release oxycodone; PO = per os; TEAEs = treatment-emergent adverse events.

[a]The initial Safety Population was N = 39; however, due to discontinuation of three subjects at differing points during the Double-blind Treatment Phase of the study, there were TEAE data for fewer subjects in the DETERx IN, DETERx PO, and Placebo groups.

[b]If a subject experienced the same event more than once during a Treatment Period, the most closely related event was tabulated. Individual subjects may be counted in more than one TEAE category during a Treatment Period.

10-fold lower than OXY-IR IN (6.24 vs 69.6 ng/mL/h), suggesting that crushing and insufflating DETERx does not produce the relatively high plasma concentrations during a short period of time and the abuse potential that opioid misusers might seek and expect when manipulating and administering this agent via the nasal route.

Overall PK outcomes in this study confirm important relationships evident in an earlier pilot study of DETERx by Kopecky et al. [26]. In that open-label, randomized, active-controlled, pilot study, 13 nondependent, recreational opioid users experienced with intranasal administration of opioids participated. PK characteristics of crushed DETERx 40 mg taken IN were compared with intact DETERx 40 mg PO and with OXY-IR 40 mg IN (oxycodone HCl powder in that study). Results indicated that the extent of absorption was similar for all three opioid treatments with respect to AUC time-course profiles; however, administration of crushed DETERx IN resulted in a lower mean C_{max} than either intact DETERx PO or crushed OXY-IR IN; i.e., C_{max} for crushed DETERx IN was approximately 80% that of intact DETERx PO and only 60% of OXY-IR IN powder. Moreover, mean T_{max} for DETERx IN was slightly shorter than for DETERx PO (5.19 vs 6.27 hour, respectively), as might be expected, but DETERx IN T_{max} was only about half as rapid as for OXY-IR IN (5.19 vs 2.82 hour,

respectively). Therefore, crushing DETERx IN produced relatively lower plasma oxycodone concentrations than either DETERx PO or OXY-IR IN, which suggested that a concentration-driven euphoric effect sought by opioid abusers may not be achieved when manipulating and administering DETERx via the nasal route.

Due to the open-label design of the pilot study, there were no PD assessments, such as of Drug Liking; however, lower AQs for DETERx formulations suggested there may be diminished attractiveness for abuse of this product. OXY-IR IN powder had the highest AQ value (42.49 ng/mL/h); whereas, AQs for crushed DETERx IN and intact DETERx PO were of similar magnitude (8.46 and 8.37 ng/mL/h, respectively) and about 5-fold lower than OXY-IR IN. Adverse events were mild across all treatment groups and without any cases of significant changes in oxygen saturation, laboratory values, vital signs, or physical exam results. Similar to the current study, there were more spontaneously reported nasal-related AEs post insufflation of DETERx IN than OXY-IR IN. Nasal effects assessments showed greater incidence of need to blow nose at early time points when DETERx IN and OXY-IR IN were compared, as well as a greater incidence of facial pain/pressure at 15 minutes following administration.

The current study went beyond PK assessments and was the first investigation to evaluate PD parameters of PO versus IN administration of DETERx; several subjective questionnaires were used for this purpose, as well as more objective pupillometry, in accordance with the "Guidance for Industry: Abuse-Deterrent Opioids Evaluation and Labeling" from the U.S. FDA [14]. Fundamentally, PK outcomes translated directly to important PD findings; for example, on the primary PD endpoint of Drug Liking, DETERx IN and DETERx PO produced much lower scores (less Liking) than OXY-IR IN. Furthermore, DETERx IN was less Liked then DETERx PO based on E_{max} while the LS mean AUEs for Drug Liking at earlier time points (i.e., $AUE_{0–1h}$ through $AUE_{0–4h}$) were not significantly different between the DETERx PO and DETERx IN treatments indicating that tampering and insufflating DETERx did not produce psychotropic effects (ie., liking) beyond those of the baseline condition—oral consumption of DETERx, which may be contrary to expectation, but expected based on the abuse-deterrent attributes of the DETERx formulation. The Drug Liking outcomes in this study generally mirrored the relationships for C_{max} and AQ values in the PK assessment. This association was supported by other recently reported research, which noted strong correlations between AQ and E_{max} for Drug Liking, Drug High, and Good Drug Effects, and even stronger correlations of C_{max} with E_{max} values [45].

Outcomes on key secondary PD endpoints—e.g., Drug High, Good Drug Effects, Take Drug Again, ARCI/MBG, and Price-Value Assessments—were generally consistent with those for Drug Liking. DETERx IN and DETERx PO demonstrated significantly less abuse potential (lower scores) than OXY-IR IN, but greater than PBO, during periodic assessments through 24 hours post-dose. The objective assessment, using pupillometry, corroborated the more immediate and greater effect of OXY-IR IN than either DETERx IN or DETERx PO. At early post-dose time points (up to 2 hours), DETERx IN exhibited relatively higher scores than DETERx PO for Drug High and Good Drug Effects, which appeared to reflect the initially larger rise in mean plasma concentration during drug exposure via nasal mucus membranes. However, following this initial 2 hour interval, plasma concentrations and scores for both Drug High and Good Drug Effects increased for DETERx PO, resulting in higher C_{max} and E_{max} values than those observed for DETERx IN. E_{max} values for Drug High and Good Drug Effects were significantly higher statistically for DETERx PO than for DETERx IN (Table 4), but calculated SMDs (0.33 Drug High; 0.36 Good Drug Effects) for these relationships denote small effect sizes that are unlikely to be clinically relevant [41].

Safety profiles of the 40 mg formulations of DETERx and OXY-IR tested in this study were comparable, with the most common AEs being mild-to-moderate and consistent with opioid-containing drugs in general. However, mild respiratory AEs (e.g., nasal discomfort, nasal congestion, and epistaxis) were common and subject-reported nasal effects—e.g., irritation, burning facial pain, nasal congestion—were more frequent and severe with DETERx IN administration (whether active or PBO), suggesting that this microsphere formulation may have an important role in producing undesirable nasal effects following crushing and insufflation of DETERx. This may be a desirable feature for an extended-release opioid product, because it may serve as a nuisance to an abuser who tries to crush and insufflate the drug, without the addition of potentially harmful antagonist or aversive agents (e.g., irritants); although, differences in frequencies of subject-reported nasal effects need verification in larger samples.

Past efforts in developing tamper-resistant and/or abuse-deterrent opioid formulations have included barriers to crushing, grinding, dissolution, and extraction of active drug by incorporating nasal irritants to discourage insufflation or integrating sequestered opioid antagonists (e.g., naltrexone) that release from the formulation to neutralize opioid effects if the formulation is compromised [46,47]. The impact of these formulations in the community will be evaluated through epidemiologic studies, but approaches that include addition of harmful irritants or opioid antagonists are not without risk and may result in unintended consequences or harm for dependent drug abuse populations. Prior studies have shown that when ER opioid formulations lacking abuse-deterrent technology are crushed or grated, their effects closely mimic those of highly abused IR opioid formulations [19,20], whereas, studies among recreational drug users suggest that some ER opioids formulated to resist tampering [19] or to delay release of opioid after administration [48] may diminish positive subjective effects,

including Drug Liking and High, and are less attractive for abuse. Hence, the available evidence suggests that tamper-resistance mechanisms may reduce the frequency of oral and non-oral abuse of those opioids that incorporate effective abuse-deterrent mechanisms [22].

The novel, microsphere-in-capsule DETERx formulation tested in this study was designed to release active drug over time by diffusion into gastrointestinal fluids and to retain its time-release mechanism following common tampering methods such as chewing, crushing, grinding, and preparation for IV injection. The results of this study suggest that such tampering prior to nasal administration would be ineffective, but further research may be necessary to confirm this. In addition to the administration as an intact capsule, the DETERx formulation can be sprinkled onto food or administered via enteral tube, benefiting patients with dysphagia/odynophagia as well as special populations such as young children and the elderly [25]. Outcomes of this present study suggest DETERx may have important abuse-deterrent characteristics evidenced by both PK and PD outcomes, including lower AQ and reduced Drug Liking during insufflation and exposure of crushed DETERx IN to nasal mucus membranes, as well as possibly being an irritant to those sensitive tissues—effects that would reduce the abuse liability of this opioid product. Certainly, both DETERx IN and DETERx PO exhibited lower abuse potential in comparison with OXY-IR IN on all PK and PD measures. Still, abuse of opioids frequently involves consumption of intact tablets [17,18,22,49]; therefore, the availability of an opioid formulation with a PD profile that diminishes positive subjective effects when taken intact orally could be important for reducing risks of abuse; it is important that the subjective responses to the unique DETERx PO formulation in this study were significantly lower than for OXY-IR IN in all instances.

An important strength of this study was its strict adherence to FDA guidance for the design of clinical studies investigating abuse-deterrent opioids [14]; the study may serve as a model for how future studies might be implemented to facilitate those recommendations that evaluate the HAP of new agents. Although consistent with current methodology and typical of studies assessing human abuse potential, the total number of subjects evaluated is relatively small. The rigorous research protocol—with its careful selection and qualification of subjects to minimize potential sources of bias, confounding, and intersubject variability—possibly resulted in a sample of subjects that may not have been universally representative of recreational abusers of opioids. Also, while the study population was large enough to provide adequate statistical power, and there were clear differences in PK parameters between DETERx IN, DETERx PO, and OXY-IR IN, there was also some high variability in data for OXY-IR IN; for example, percent coefficient of variation (CV%; CV = SD/mean) for OXY-IR IN AQ was >100% (Table 2). This appears to be most influenced by more widely fluctuating T_{max} for OXY-IR IN, which may be typical of opioid formulations without any time-release mechanism and that are subject to metabolism by liver enzymes, as is oxycodone; however, this PK parameter was still significantly and multiple-times higher on average for OXY-IR IN than for DETERx IN or PO ($P \leq 0.0001$, post hoc unpaired t-test).

Postmarketing surveillance data encompassing larger populations will be important for determining whether the features of DETERx demonstrated in this study will impact the misuse of this formulation, or whether determined opioid abusers will find ways to defeat the formulation or simply take excessive intact capsules, or the microsphere contents, to achieve desired effects. Also, in real-world situations, opioid abusers may take larger amounts of DETERx than the 40 mg doses used in this study, which could affect PK and PD profiles as well as safety factors.

Conclusion

A most important finding of this study was that administration of either crushed DETERx IN or intact DETERx PO resulted in less Liking than crushed OXY-IR IN. This and other significant PD outcomes were supported by PK results, suggesting a favorable HAP profile of either crushed IN or intact PO DETERx. Administration of crushed DETERx IN was not associated with increased Drug Liking scores when compared with taking intact DETERx PO, implying that physical manipulations followed by intranasal administration are not expected to be a significant route of abuse and confirming the hypothesis from an earlier pilot PK study [26]. The DETERx formulation was well tolerated by subjects; although, the occurrence of adverse nasal effects occurred more frequently with IN administration of DETERx microspheres, which may be an added abuse-deterrent effect of this drug formulation when not used via the intended oral ROA. Other than those AEs, the safety profile of DETERx was consistent with an opioid-containing drug. Continuing research is recommended to assess abuse potential of DETERx via other routes of administration and to monitor HAP and safety outcomes in larger populations.

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References

1 Hertz JA, Knight JR. Prescription drug misuse: A growing national problem. Adolesc Med Clin 2006; 17:751–69.

2 Manchikanti L, Singh A. Therapeutic opioids: A ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids. Pain Physician 2008;11:s63–88.

3 Manchikanti L. Prescription drug abuse: What is being done to address this new drug epidemic? Testimony before the subcommittee on criminal justice, drug policy and human resources. Pain Physician 2006;9:287–321.

4 National Center on Addiction and Substance Abuse. Controlled prescription drug abuse at epidemic level. J Pain Palliat Care Pharmacother 2006;20:61–4.

5 U.S. Substance Abuse and Mental Health Services Administration. Drug Abuse Warning Network, 2011: National Estimates of Drug-Related Emergency Department Visits. HHS Publication No. SMA-13-4760, DAWN Series D-39. Rockville, MD: U.S. Department of Health and Human Services; 2013. Available at: http://www.samhsa.gov/data/sites/default/files/DAWN2k11ED/DAWN2k11ED/DAWN2k11ED.htm (accessed February 6, 2015).

6 U.S. Substance Abuse and Mental Health Services Administration. Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings. HHS Publication No. SMA-13-4795, NSDUH Series H-46. Rockville, MD: U.S. Department of Health and Human Services; 2013. Available at: http://www.samhsa.gov/data/NSDUH/2012SummNatFindDetTables/Index.aspx (accessed February 6, 2015).

7 Manchikanti L, Helm S 2nd, Fellows B, et al. Opioid epidemic in the United States. Pain Physician 2012; 15:ES9–38.

8 Paulozzi LJ, Jones CM, Mack KA, Rudd RA. Vital Signs: Overdoses of Prescription Opioid Pain Relievers—United States, 1999-2008. MMWR 2011; 60 (early release). Available at: http://www.cdc.gov/mmwr/pdf/wk/mm60e1101.pdf (accessed February 6, 2015).

9 Butler SF, Fernandez KC, Chang A, et al. Measuring attractiveness for abuse of prescription opioids. Pain Med 2010;11:67–80.

10 King NB, Fraser V, Boikos C, Richardson R, Harper S. Determinants of increased opioid-related mortality in the United States and Canada, 1990-2013: A systematic review. Am J Public Health 2014;104:e32–42.

11 U.S. General Accounting Office. Prescription Drugs. OxyContin Abuse and Diversion and Efforts to Address the Problem. GAO Publication No. GAO-04-110. Washington, DC: U.S. General Accounting Office; 2003. Available at: http://www.gao.gov/new.items/d04110.pdf (accessed February 6, 2015).

12 Casty FE, Wieman MS, Shusterman N. Current topics in opioid therapy for pain management: Addressing the problem of abuse. Clin Drug Investig 2013; 33:459–68.

13 Peppin JF, Coleman JJ, Kirsh KL. Issues and critiques of the forthcoming risk evaluation and mitigation strategy (REMS) for opioids in pain management. Issues Law Med 2011;27:91–119.

14 U.S. Food and Drug Administration. Guidance for Industry: Abuse-Deterrent Opioids—Evaluation and Labeling [draft]. Rockville, MD: U.S. FDA Center for Drug Evaluation and Research; 2013. Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf (accessed February 6, 2015).

15 Webster LR, Bath B, Medve RA. Opioid formulations in development designed to curtail abuse: Who is the target? Expert Opin Investig Drugs 2009;18:255–63.

16 Butler SF, Black RA, Cassidy TA, Dailey TM, Budman SH. Abuse risks and routes of administration of different prescription opioid compounds and formulations. Harm Reduct J 2011;8:29.

17 Carise D, Dugosh KL, McLellan AT, et al. Prescription OxyContin abuse among patients entering addiction treatment. Am J Psychiatry 2007; 164:1750–6.

18 Katz N, Fernandez K, Chang A, Benoit C, Butler SF. Internet-based survey of nonmedical prescription opioid use in the United States. Clin J Pain 2008; 24:528–35.

19 Setnik B, Roland CL, Cleveland JM, Webster L. The abuse potential of Remoxy®, an extended-release formulation of oxycodone, compared with immediate- and extended-release oxycodone. Pain Med 2011;12:618–31.

20 Webster LR, Bath B, Medve RA, Marmon T, Stoddard GJ. Randomized, double-blind, placebo-controlled study of the abuse potential of different formulations of oral oxycodone. Pain Med 2012; 13:790–801.

21 Havens JR, Leukefeld CG, DeVeaugh-Geiss AM, Coplan P, Chilcoat HD. The impact of a reformulation of extended-release oxycodone designed to deter abuse in a sample of prescription opioid abusers. Drug Alcohol Depend 2014;139:9–17.

22 Butler SF, Cassidy TA, Chilcoat H, et al. Abuse rates and routes of administration of reformulated extended-release oxycodone: Initial findings from a sentinel surveillance sample of individuals assessed for substance abuse treatment. J Pain 2013; 14:351–8.

23 Cassidy TA, DasMahapatra P, Black RA, Wieman MS, Butler SF. Changes in prevalence of prescription opioid abuse after introduction of an abuse-deterrent opioid formulation. Pain Med 2014;15:440–51.

24 Cicero TJ, Ellis MS. Abuse-deterrent formulations and the prescription opioid abuse epidemic in the United States: Lessons learned from OxyContin. JAMA Psychiatry 2015;72:424–30.

25 Kopecky E, Fleming A, Varanasi R, et al. Oxycodone DETERx, an extended-release, tamper-resistant formulation for management of chronic pain. J Pain 2013;14:S68.

26 Kopecky E, Fleming A, Findlen K, Varanasi R, Saim S. Assessment of the pharmacokinetics and safety of oxycodone DETERx administered intranasally in recreational opioid users. Poster/abstract presented at PAINweek 2013, September 5–6, 2013, Las Vegas, NV. Available at: http://conference.painweek.org/media/mediafile_attachments/00/650-painweek2013acceptedabstracts.pdf (abstract 52, pp 92–93) (accessed February 6, 2015).

27 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.

28 Smith M, Jenkins J, Iverson M, Webster LR. Preliminary Report of THC Influence on Subject Ability to Discriminate Between Active Opioid and Placebo in Human Abuse Liability Study. Presentation at the CPDD 76th Annual Scientific Meeting, June 14–19, 2014, San Juan, Puerto Rico. Available at: http://www.cpdd.org/Pages/Meetings/CPDD14AbstractBook.pdf (poster #673, pp 169) (accessed February 7, 2015).

29 Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). J Psychoactive Drugs 2003;35:253–9.

30 Guidance for Industry: Food Effect Bioavailability and Fed Bioequivalence Studies. Rockville, MD: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER); 2002. Available at: http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126833.pdf (accessed February 6, 2015).

31 Mandema JW, Kaiko RF, Oshlack B, Reder RF, Stanski DR. Characterization and validation of a pharmacokinetic model for controlled-release oxycodone. Br J Clin Pharmacol 1996;42:747–56.

32 Poyhia R, Vainio A, Kalso E. A review of oxycodone's clinical pharmacokinetics and pharmacodynamics. J Pain Symptom Manage 1993;8:63–7.

33 Williams EJ. Experimental designs balanced for the estimation of residual effects of treatments. Aust J Sci Res 1949;2:148–68.

34 Comer SD, Ashworth JB, Sullivan MA, et al. Relationship between rate of infusion and reinforcing strength of oxycodone in humans. J Opioid Manag 2009;5:203–12.

35 de Wit H, Bodker B, Ambre J. Rate of increase of plasma drug level influences subjective response in humans. Psychopharmacology 1992;107:352–8.

36 Marsch LA, Bickel WK, Badger GJ, et al. Effects of infusion rate of intravenously administered morphine on physiological, psychomotor, and self-reported measures in humans. J Pharmacol Exp Ther 2001;299:1056–65.

37 Schoedel KA, McMorn S, Chakraborty B, et al. Positive and negative subjective effects of extended-release oxymorphone versus controlled-release oxycodone in recreational opioid users. J Opioid Manag 2011;7:179–92.

38 Moorman-Li R, Motycka CA, Inge LD, et al. A review of abuse-deterrent opioids for chronic nonmalignant pain. PT (Pharm & Ther) 2012;37:412–21.

39 Perrino PJ, Colucci SV, Apseloff G, Harris SC. Pharmacokinetics, tolerability, and safety of intranasal administration of reformulated OxyContin® tablets compared with original OxyContin® tablets in healthy adults. Clin Drug Investig 2013;33:441–9.

40 Haertzen CA, Hickey JE. Addiction Research Center Inventory (ARCI): Measurement of euphoria and other drug effects. In MA Bozarth, ed. Methods of Assessing the Reinforcing Properties of Abused Drugs. New York: Springer-Verlag; 1987:489–524.

41 Cohen JA. Power primer. Psych Bull 1992;112:155–9.

42 SAS OnlineDoc®, Ver 8 [Chap 30, Sec 1]. Cary, NC: SAS Institute Inc.; 1999. Available at: https://v8doc.sas.com/sashtml/stat/chap30/sect1.htm (accessed February 6, 2015).

43 Hodges JL Jr, Lehmann EL. Estimates of location based on rank tests. Ann Math Stat 1963;34:598–611.

44 Moses LE, Shapiro D, Littenberg B. Combining independent studies of a diagnostic test into a summary ROC curve: Data-analytic approaches and some additional considerations. Stat Med 1993;12:1293–316.

45 Webster LR, Morton T, Kostenbader K, et al. Abuse Quotient of Orally Administered MNK-795 Extended-Release Oxycodone/Acetaminophen (XR OC/APAP) Tablets Versus Immediate-Release Oxycodone/Acetaminophen (IR OC/APAP) Tablets in Recreational Users of Prescription Opioids. Presentation at the 2014 Annual Meeting of the American Academy of Pain Medicine, March 7, 2014, Phoenix, AZ (poster #193). Available at: http://www.painmed.org/2014posters/abstract-193/ (accessed February 6, 2015).

46 Romach MK, Schoedel KA, Sellers EM. Update on tamper-resistant drug formulations. Drug Alcohol Depend 2013;130:13–23.

47 Stanos SP, Bruckenthal P, Barkin RL. Strategies to reduce the tampering and subsequent abuse of long-acting opioids: Potential risks and benefits of formulations with physical or pharmacologic deterrents to tampering. Mayo Clin Proc 2012; 87:683–94.

48 Shram MJ, Sathyan G, Khanna S, et al. Evaluation of the abuse potential of extended release hydromorphone versus immediate release hydromorphone. J Clin Psychopharmacol 2010;30:25–33.

49 Cicero TJ, Ellis MS, Surratt HL. Effect of abuse-deterrent formulation of OxyContin. N Engl J Med 2012;367:187–9.