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Original Research Article

Pharmacokinetics and Abuse Potential of Benzhydrocodone, a Novel Prodrug of Hydrocodone, After Intranasal Administration in Recreational Drug Users

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Abstract

Objective. Developing an acetaminophen-free, immediate-release hydrocodone product remains an unmet medical need; however, new opioid analgesics should not introduce new abuse risks. Benzhydrocodone is a prodrug of hydrocodone that must be metabolized into hydrocodone by enzymes in the intestinal tract to optimally deliver its pharmacologic effects. This study evaluated the intranasal pharmacokinetics and abuse potential of benzhydrocodone active pharmaceutical ingredient (API) compared with hydrocodone bitartrate (HB) API.

Design. Single-center, randomized, double-blind, crossover study.

Setting. Clinical research site.

Subjects. Healthy adult, nondependent, recreational opioid users.

Methods. Subjects (N = 51 Completers) were randomized to receive 13.34 mg of intranasal benzhydrocodone API and 15.0 mg of intranasal HB API (molar-equivalent doses of hydrocodone). Blood samples were taken, and Drug Liking scores (assessed on a bipolar visual analog scale) were obtained throughout each dosing interval. Nasal irritation and safety were assessed.

Results. Peak hydrocodone plasma concentration (C_{max}) was 36.0% lower, and total hydrocodone exposures (AUC_{last} and AUC_{inf}) were 20.3% and 19.5% lower, respectively, for benzhydrocodone API compared with HB API ($P < 0.0001$). All partial AUC values were lower for benzhydrocodone API, with a $\geq$ 75% reduction in hydrocodone exposure at all time intervals up to one hour postdose ($P < 0.0001$). Median T_{max} of hydrocodone following benzhydrocodone API was delayed by more than one hour compared with HB. Drug Liking score, as assessed by maximal liking (E_{max}), was significantly lower for benzhydrocodone API vs HB API ($P = 0.004$), with 45% of subjects showing a $\geq$ 30% reduction in Drug Liking E_{max}.

Conclusions. Reductions in hydrocodone exposure and associated decreases in Drug Liking relative to HB suggest that the prodrug benzhydrocodone may deter intranasal abuse.

Key Words. Benzhydrocodone; Hydrocodone; Prodrug; Intranasal; Abuse-Deterrent; Drug Liking; Pharmacokinetics

Introduction

Immediate-release (IR) opioids are important tools in modern pain management when nonopioid options do not provide adequate analgesia. Immediate-release, hydrocodone-containing products are among the most commonly prescribed drugs in the United States, with approximately 90 million prescriptions dispensed in 2015 [1]. The only currently approved IR hydrocodone-containing medications are combination therapies, such as those containing acetaminophen (APAP) or nonsteroidal anti-inflammatory drugs (NSAIDs). While the incorporation of nonopioid analgesics can be an important component of multimodal analgesia [2–4], potential hepatotoxicity associated with high daily doses (>4,000 mg) of APAP in opioid combination products has led to certain restrictions on maximal daily APAP doses and maximal dosages of APAP in each tablet [5]. Additionally, in July 2015, the US Food and Drug Administration (FDA) strengthened the warning label of nonaspirin NSAIDs, citing an increased risk of heart attack and stroke associated with higher doses and longer use [6].

While there are many potent, single-ingredient, IR opioids available for the treatment of acute pain (e.g., oxycodone, hydromorphone), there is no IR, single-ingredient, APAP- or NSAID-free hydrocodone product. The availability of efficacious and well-tolerated treatment options is important given the marked variability across patients in responsiveness to opioids. The prototypical μ-opioid receptor agonist morphine, for example, does not provide a satisfactory therapeutic outcome in up to 30% of patients, either because of inadequate analgesia, unacceptable adverse events, or a combination of both [7,8]. The differential sensitivity among patients to the spectrum of opioid-mediated effects is thought to be determined by an interaction between individual genotypic factors (e.g., CYP450 polymorphism, receptor subtype ratios, receptor localization, and tissue distribution) and intrinsic drug-related factors (e.g., differential opioid metabolism, differential opioid receptor affinity, and intrinsic efficacy profiles). As a result, the availability and accessibility of well-tolerated opioid pain medications, including hydrocodone products, are important to adequately treat this diverse patient population.

While the introduction of an APAP-free, IR hydrocodone product may provide a rational therapeutic option for some patients, careful consideration needs to be given to the marketing of any new opioid product with respect to risks that may not only affect the intended patient population. Among many opioid-related risks, abuse, addiction, and overdose are considered the most serious. The dramatic increase in all three of these related metrics in the last two decades has been well-documented [9]. For IR hydrocodone/APAP combination products, oral administration of intact tablets remains the most common route of abuse, followed by the intranasal route [10]. However, for single-entity IR opioids that contain no APAP and small amounts of inert excipients, there are few, if any, inherent barriers to manipulation of the product for alternate routes of abuse. For example, in treatment-seeking individuals reporting abuse of single-entity, IR oxycodone products in the past 30 days, 41%, 60%, and 38% reported abuse by swallowing (oral), snorting, and injecting, respectively [10]. When examining the class of other (nonoxycodone) single-entity, IR opioids, 26%, 24%, and 65% of abusers reported past 30-day abuse by swallowing (oral), snorting, and injecting, respectively [10]. Nonoral routes of abuse have been associated with a 2.4-fold greater risk of death or major effect (i.e., life-threatening or resulted in significant disability) relative to the oral route [11]. In light of these epidemiological data and given that the abuse-related effects of hydrocodone are similar to other μ-opioid agonists such as oxycodone and morphine [12,13], imparting abuse-deterrent properties to a novel IR hydrocodone product appears essential to avoid unintended consequences.

The prodrug benzhydrocodone (KP201 IR) is being developed as the first single-entity, acetaminophen-(APAP-) and NSAID-free, IR hydrocodone product for the treatment of acute pain in the United States. Benzhydrocodone is a new molecular entity that is formed by covalently bonding hydrocodone to benzoic acid, a widely used food preservative. Benzhydrocodone itself is not pharmacologically active, but must be metabolized to hydrocodone by enzymes in the intestinal tract to optimally deliver its pharmacologic effects. In vitro data indicate that conversion to hydrocodone in intestinal fluid is nearly complete (95%) within five minutes, whereas near-complete conversion in whole blood requires approximately 240 minutes [14]. In rats, intranasal administration of benzhydrocodone resulted in significantly reduced plasma concentrations of hydrocodone when compared with hydrocodone bitartrate [15]. These results suggest that benzhydrocodone has intrinsic molecular properties that can potentially deter abuse by nonoral routes of administration.

The objective of the current study was to assess the pharmacokinetics (PK) and exploratory abuse potential of intranasal (IN), single-entity benzhydrocodone API compared with equimolar doses of hydrocodone bitartrate (HB) API in nondependent, recreational opioid users.

Methods

Study Design and Ethics

This was a randomized, double-blind, single-dose, two-way crossover, single-center study to assess the bioavailability of benzhydrocodone API compared with HB API following IN administration of equimolar doses in nondependent, recreational opioid users. Secondary objectives were to evaluate the comparative abuse potential and safety of benzhydrocodone API vs HB API following IN administration. The study was composed of a screening phase (visit 1), a Naloxone challenge test

within 28 days of the screening visit to verify nondependence on opioids (visit 2, check-in), an in-clinic treatment phase (visit 2), and a follow-up phase (visit 3). The Naloxone challenge test was conducted on the day prior to the first dose of the treatment phase, and a minimum 12-hour washout was required before first study drug administration during the treatment phase. Although the FDA Guidance for Evaluation and Labeling of Abuse-Deterrent Opioids recommends that clinical abuse potential studies include a drug discrimination test to assess whether subjects can distinguish between placebo and active opioid treatment in a clinical laboratory setting, such testing was not administered as the primary purpose of this study was to determine and compare PK parameters of the two study drugs.

During the treatment phase, eligible subjects were assigned in a 1:1 ratio to one of two in-clinic single treatment sequences (benzhydrocodone followed by HB or HB followed by benzhydrocodone) in crossover fashion. The follow-up phase was conducted approximately four to eight days following discharge from the clinic.

The study protocol, amendments, informed consent form, and investigator and treatment information were reviewed and approved by an institutional review board. This study was conducted in full accordance with the International Conference on Harmonisation (now known as the International Council for Harmonisation) guidelines for good clinical practice, in compliance with the Declaration of Helsinki and all its accepted amendments regarding medical research in humans, and in accordance with guidelines for clinical trials of the United States Code of Federal Regulations and the European Agency for Evaluation of Medicinal Products.

Study Subjects

Subjects considered eligible for this study were men and women age 18 to 55 years; opioid users who were not dependent on opioids, based on criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Test Revision (DSM-IV-TR) [16], but who had experience in nontherapeutic opioid use (i.e., for psychoactive effects) on ≥ 10 occasions within the past year and more than once in the 12 weeks prior to screening. Eligible subjects were also required to have had experience with IN opioid administration, defined as IN use on three or more occasions within the past year prior to screening. Subjects were also required to be overall healthy; if female, to not be pregnant, or if of childbearing potential, to be using accepted birth control methods; if male, to be using birth control or having had a vasectomy; and with a body mass index (BMI) within 19.0–33.0 kg/m^2 and weight $\geq$55 kg inclusive.

At screening, subjects were excluded who had previously received, were currently receiving, or were seeking to participate in treatment for a substance-related disorder (excluding nicotine and caffeine); had a history of drug or alcohol dependence, regardless of participation in drug rehabilitation programs; had a positive urine drug screen at screening or check-in, although subjects testing positive for opioids, amphetamines, cocaine, and benzodiazepines at screening were allowed, provided the drug screen at check-in was negative; had a known history of or current respiratory disease, although subjects with histories of mild childhood asthma or bronchitis could be approved at the discretion of the investigator; had an anatomical nasal abnormality that may have compromised the ability to insufflate drugs or abnormal nasal exam (e.g., infection, rhinorrhea); had a hemoglobin level $<$12.6 g/dL (men) or $<$ 11.1 g/dL (women); were heavy smokers ($>$20 cigarettes per day) or unable to abstain from use of nicotine products; had ingested alcohol within 48 hours prior to check-in for the Naloxone challenge test and treatment phase; or had oxygen saturation $<$94% as confirmed by repeat testing that was clinically significant in the judgment of the investigator. Subjects who fulfilled the screening criteria were administered the Naloxone challenge test at check-in. Only subjects with Clinical Opiate Withdrawal Scale scores $<$5 were eligible to enter the treatment phase of this study.

Treatment Phase

Subjects who passed the Naloxone challenge test were randomized, based on a Williams Square design, into a double-blind, crossover treatment sequence to receive 13.34 mg of IN benzhydrocodone API and 15.0 mg of IN HB API (doses are equivalent with respect to hydrocodone), separated by a 72-hour washout period. Nasal insufflation was to be completed in five minutes. Subjects fasted for eight or more hours before each dose and for four hours afterwards. Subjects remained in the study clinic for $\geq$24 hours following the last treatment phase dose of study medication. As the pharmacodynamic end points were exploratory, there was no placebo control arm in the treatment phase. However, regardless of whether the hydrocodone dose resulted in absolute Drug Liking effects substantially higher relative to placebo, direct comparison of the treatments still allowed for an assessment of which drug was liked more following intranasal administration. Moreover, doses of 15 mg oral hydrocodone have been shown to produce greater Drug Liking than placebo in recreational opioid abusers, and were thus deemed to be in the abuseable range [12].

No concomitant medications that may have had a PK or pharmacodynamic (PD) interaction with the study medications were permitted during the study. Ibuprofen was provided as needed during the study except for the 72-hour period prior to day –1 (the day before the screening visit).

Pharmacokinetic Assessments and Sample Collection

On dosing days during the treatment phase (days 1 and 4), one 6-mL blood sample was collected for analysis at one hour predose, and at 0.083 (5 minutes), 0.25

(15 minutes), 0.5 (30 minutes), 0.75 (45 minutes), 1, 1.5, 2, 3, 4,6, 8, 10, 12, and 24 hours postdose. Blood samples were immediately placed on ice, processed according to the clinical site's established procedures, and frozen within one hour of collection; they remained frozen until assayed. Plasma sample analysis was conducted by Worldwide Clinical Trials Early Phase Services/Bioanalytical Sciences, Inc. (Austin, TX, USA) using validated liquid chromatography-tandem mass spectrometry procedures.

For each treatment, the following PK parameters were calculated for hydrocodone released from benzhydrocodone and HB, using standard noncompartmental methods: area under the plasma concentration vs time curve (AUC) from time zero to x hours (AUC_{0-x}), where x was 0.083 (5 minutes), 0.25 (15 minutes), 0.5 (30 minutes), 0.75 (45 minutes), 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours postdose; AUC from time zero to the last measurable concentration (AUC_{last}); AUC from time zero extrapolated to infinity (AUC_{inf}); maximum observed plasma concentration (C_{max}); time to maximum observed plasma concentration (T_{max}); apparent first-order terminal elimination rate constant (K_{el}); apparent first-order terminal elimination half-life ($t_{1/2}$). Individual plasma concentration vs time data was calculated using Phoenix WinNonlin (Version 6.3, Certara, Inc.). C_{max} and T_{max} were determined directly from the observed concentration data. An additional post hoc measure of the abuse quotient ($AQ = C_{max}/T_{max}$) was calculated for each active treatment arm. A high AQ, produced by increases in C_{max} and/or decreases in T_{max}, has been shown to correspond to plasma drug concentrations that elicit robust subjective and reinforcing effects [17]. The K_{e1} was estimated by linear regression through at least three data points in the terminal phase of the log concentration time profile. The $t_{1/2}$ was calculated as $0.693/K_{e1}$. The AUC_{last} and AUC_{0-x} measures were calculated using the linear trapezoidal method; AUC_{inf} was estimated as $AUC_{inf} = AUC_{last} +$ the last measured plasma quantification (C_{last}/K_{el}).

Pharmacodynamic Parameters

The primary PD measure for this study was a Drug Liking visual analog scale (DL-VAS), an FDA-recommended measure of drug abuse liability [18]. For this assessment, taken at 0.25, 1, 1.5, 2, 3, 4, 6, and 8 hours after each dose, subjects were asked "Do you like the drug effect you are feeling now?" and were instructed to mark their answer on the 0–100 point bipolar DL-VAS that was anchored on the left with "strong disliking" on one end (score of 0); "neither like nor dislike in the middle (score of 50); and anchored on the right with "strong liking" (score of 100). Pupil diameter was assessed using a NeurOptic VIP-200 pupillometer within one hour predose and at 0.083, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours postdose. The main PD end points of interest for Drug Liking VAS and pupillometry included peak effect (E_{max}) and time of E_{max} (TE_{max}). In addition, the area under the effect curve was calculated for both measures from time zero to x hours (AUE_{0-x}), where x was 0.5, 1, 2, 4, 8, and 24 hours (pupillometry only). Lastly, within five minutes postdose, subjects were asked to respond to an Ease of Insufflation (snorting) VAS following each treatment during the treatment phase. For this measure, subjects were asked to respond to the question "Insufflation of the drug was:" by marking their answer on a 0–100 unipolar VAS anchored on the left with "very easy" (score of 0) and on the right with "very difficult" (score of 100).

Safety Assessments

Safety and tolerability assessments included the monitoring and reporting of all adverse events (AEs), with categorization by severity and relatedness to treatment, and serious AEs (SAEs). A medical history of each prospective participant was obtained at screening and was updated for enrolled subjects at admission to the treatment phase and at follow-up. Physical examinations were conducted at screening, at check-in, following the Naloxone challenge test, at discharge of the treatment phase, and at the follow-up visit. Vital signs were obtained at screening, at check-in, and at follow-up visits; a 12-lead electrocardiogram (ECG) was also obtained at those study points, as well as at discharge from the treatment phase. Clinical laboratory tests were obtained at the screening and follow-up visits, including hematology, serum chemistry, urinalysis, and serology. In addition, an assessment for abnormal nasal anatomy was performed at screening, check-in, treatment phase, and follow-up or early termination. A nasal effects assessment was also performed for nasal safety during the treatment phase at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours postdose. Individual subject-rated measures included nasal irritation, burning, runny nose/nasal discharge, facial pain/pressure, nasal congestion, and need to blow nose, each measured on a four-point Likert scale (0–3).

Study Populations and Statistical Considerations

Enrolled subjects were those who were screened and returned for check-in. Analysis populations in this study included the Safety population, defined as all subjects who received any amount of study medication during the treatment phase; the Completer population, including all randomized subjects who completed both crossover treatments and contributed at least one postdose PK time point from each period; and the PK population, which included all randomized subjects who completed both active treatments and had sufficient data for PK analysis for hydrocodone. Descriptive statistics were used for continuous variables, and frequency and percentages were calculated for categorical variables.

For pharmacokinetic data, a linear mixed effect model was used to analyze natural log-transformed C_{max} and all AUC parameters with fixed effects for sequence, period, and treatment, and a random effect for subject nested in sequence. The least square geometric mean

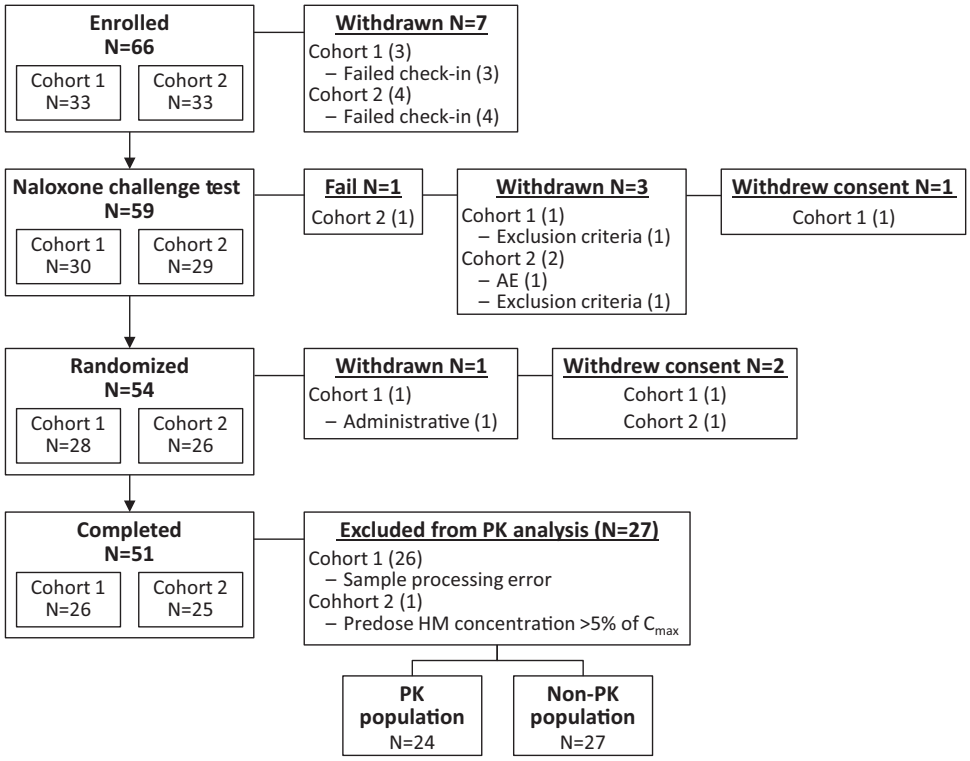

Figure 1 Subject disposition. AE = adverse event; HM = hydromorphone; PK = pharmacokinetics.

ratios (benzhydrocodone API over HB API) along with the corresponding 90% confidence intervals (CIs) were calculated. The same method was used for K_{el} and $t_{1/2}$, but this analysis was conducted with the untransformed parameters. The Wilcoxon signed rank test was used to determine the statistical significance of the median difference for T_{max} for the treatment comparisons. All significance testing for PK parameters was two-tailed, using a significance threshold of $\alpha = 0.05$.

As the primary objective of this study was to assess the pharmacokinetics of benzhydrocodone API, all pharmacodynamic parameters were analyzed in an exploratory fashion using a standard mixed effects model for a 2×2 crossover design for all subjects in the Completer population. Responder analyses of percent reduction in Drug Liking E_{max} were conducted for benzhydrocodone API compared with HB API. The percentage of responders was plotted vs cumulative percent reduction. All statistical analyses were completed using SAS (version 9.3).

Results

Subject Disposition and Baseline Characteristics

Figure 1 shows subject disposition throughout the course of the study. A total of 66 subjects were enrolled in two cohorts (33 each). Due to mishandling of blood samples for PK analysis, subjects of the first cohort were excluded from all PK analyses; these subjects were designated as Cohort 1. Of the remaining 33 subjects, designated Cohort 2, 24 had evaluable PK data and comprised the PK population. In total, 54 subjects (28 from Cohort 1 and 26 from Cohort 2) were randomized and received at least one dose of study drug, comprising the Safety population. Of the Safety population (N = 54), 51 (94.4%) subjects completed both treatment periods and comprised the Completer population.

Demographic and baseline clinical characteristics of the Safety and PK populations are shown in Table 1. Subjects in the Safety population were primarily male (75.9%), white (88.9%), and had a mean age of 27.7 years (SD = 7.3 years). With regard to drug abuse profile, subjects in the Safety population most commonly abused opioids (44.4%) and had abused drugs intranasally on a median of 36.0 (range = 5–570) occasions over the preceding 12 months. Demographic and clinical characteristics were generally similar for the smaller PK population (N = 24) compared with Safety population subjects. Demographic and baseline characteristics for the 51 Completers were very similar to the Safety population.

Pharmacokinetic Findings

Mean hydrocodone plasma levels for the first six hours postdose are illustrated in Figure 2, and associated pharmacokinetic parameters are shown in Table 2.

Table 1 Demographic/baseline clinical characteristics and opioid abuse profiles of study subjects

Characteristic	Safety Population (N = 54)	PK Population (N = 24)
Age, y		
Mean (SD)	27.7 (7.3)	27.5 (6.5)
Sex, No. (%)		
Male	41 (75.9)	18 (75.0)
Female	13 (24.1)	6 (25.0)
Race, No. (%)		
White	48 (88.9)	20 (83.3)
Black/African American	4 (7.4)	2 (8.3)
Other	2 (3.7)	2 (8.3)
Ethnicity, No. (%)		
Hispanic or Latino	9 (16.7)	1 (4.2)
Not Hispanic or Latino	45 (83.3)	23 (95.8)
Weight, kg		
Mean (SD)	76.8 (14.6)	78.3 (15.4)
BMI, kg/m^2		
Mean (SD)	25.0 (3.6)	25.3 (3.6)
Drug class most often abused during the past 12 wk, No. (%)		
Opioids/morphine derivatives	24 (44.4)	12 (50.0)
Stimulants	16 (29.6)	7 (29.2)
Other	14 (25.9)	5 (20.8)
Frequency of drug abuse during the past 12 wk, total		
Mean (SD)	144.9 (219.0)	114.9 (219.2)
Median [range]	91 [3–1036]	45 [6–1017]
Frequency of IN drug abuse during the past 12 mo		
Mean (SD)	54.5 (83.5)	36.0 (25.3)
Median [range]	36 [5–570]	36.5 [6–100]

BMI = body mass index; IN = intranasal; PK = pharmacokinetics.

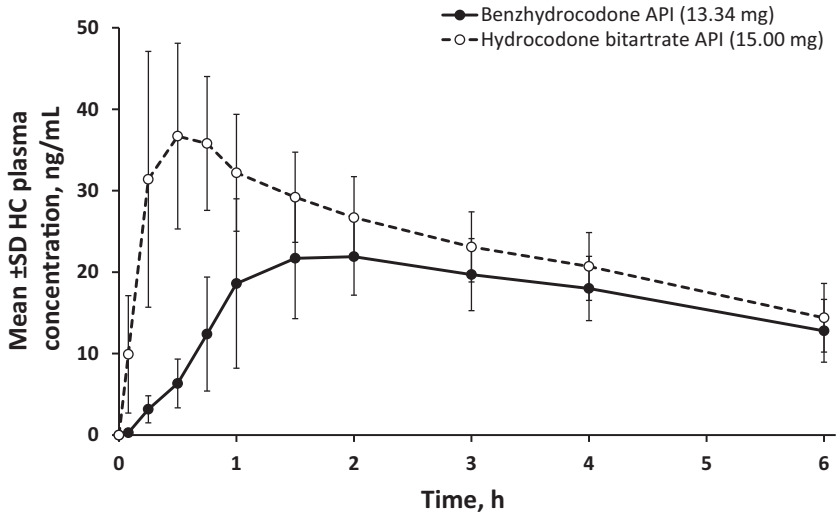

Figure 2 Mean (SD) hydrocodone plasma levels after administration of intranasal (IN) benzhydrocodone API and IN hydrocodone bitartrate API in the pharmacokinetics population (N = 24). HC = hydrocodone.

Table 2 Pharmacokinetic parameters for intranasal benzhydrocodone API and intranasal HB API

Parameter	IN Benzhydrocodone (N = 24)	IN HB (N = 24)	*P*
C_{max}, mean (SD), ng/mL	25.6 (6.4)	40.4 (11.8)	<0.001
AUC_{last}, mean (SD), h*ng/mL	185.5 (50.5)	231.0 (54.6)	<0.001
AUC_{inf}, mean (SD), h*ng/mL	194.7 (55.7)	239.4 (58.4)	<0.001
T_{max}, median (range), h	1.75 (0.75, 4.0)	0.50 (0.25, 2.0)	<0.001
$t_{1/2}$, mean (SD), h	5.29 (0.78)	5.13 (0.74)	0.2738
AQ, mean, ng/mL/h	17.0	31.9	N/A

AQ = abuse quotient, as determined by C_{max}/T_{max}; AUC_{inf} = area under the plasma concentration vs time curve extrapolated to infinity; AUC_{last} = area under the plasma concentration vs time curve from 0 to the last quantifiable concentration; C_{max} = maximum plasma concentration; HB = hydrocodone bitartrate; T_{max} = time to maximum plasma concentration; $t_{1/2}$ = terminal elimination half-life.

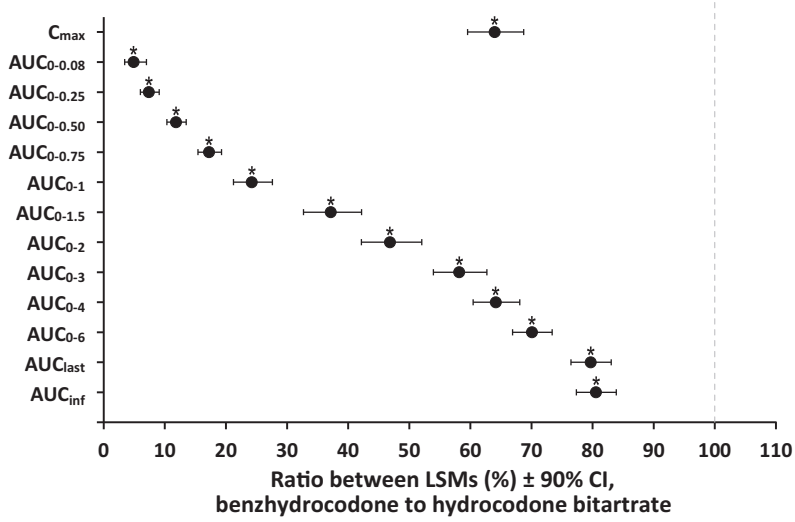

Figure 3 Ratios of log-transformed geometric least square mean values of hydrocodone parameters for IN benzhydrocodone API and IN hydrocodone bitartrate API in the PK population (N = 24). *$P < 0.0001$, linear mixed-effect model. $AUC_{0–0.083}$, $AUC_{0–0.25}$, $AUC_{0–0.5}$. . .$AUC_{0–6}$ = area under the plasma concentration-time curve from time zero to the specified time point, in hours; CI = confidence interval; LSM = least square mean.

Overall, the C_{max} of hydrocodone released from benzhydrocodone API was markedly lower than hydrocodone released from HB API. Time to C_{max} (T_{max}) was more than threefold longer for benzhydrocodone API vs HB API, with a median T_{max} of 1.75 hours (range = 0.75–4.0 hours) vs 0.5 hours (range = 0.25–2.0 hours), respectively. The abuse quotient of hydrocodone was 47% lower for benzhydrocodone API (17.0) relative to HB API (31.9). After reaching peak plasma levels, hydrocodone plasma concentrations of both treatments declined in a log-linear manner. The mean $t_{1/2}$ values of hydrocodone were similar for benzhydrocodone API (5.29 hours, SD = 0.78 hours) and HB API (5.23 hours, SD = 0.74 hours).

Ratios between log-transformed geometric least square (LS) mean values of selected PK parameters are displayed in Figure 3; they show that peak hydrocodone plasma concentration (C_{max}) was 36.0% lower for benzhydrocodone API than for HB API ($P < 0.0001$). Total hydrocodone exposures (AUC_{last} and AUC_{inf}) for benzhydrocodone API were 20.3% and 19.5% lower, respectively, than those for HB API ($P < 0.0001$ for both ratios). All partial AUC values (AUC_{0-x}) were also lower for benzhydrocodone API than for HB API ($P < 0.0001$ for each ratio), with a ≥ 50% reduction in hydrocodone exposure for all time intervals up to two hours postdose.

Pharmacodynamic Findings

Drug Liking

Mean Drug Liking values over time for IN benzhydrocodone API and HB API, as recorded on the DL-VAS, are

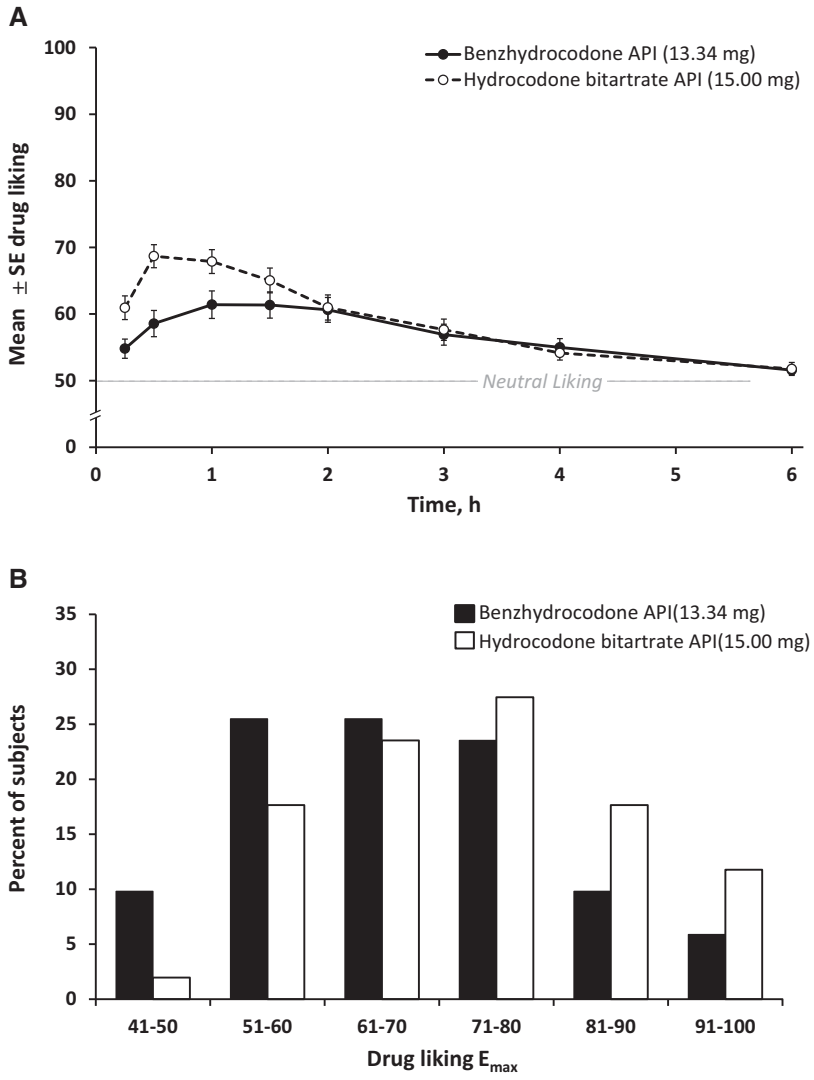

Figure 4 Mean (SE) Drug Liking over time for intranasal (IN) benzhydrocodone API and IN hydrocodone bitartrate API (**A**), and frequency distribution of Drug Liking E_{max} scores for IN benzhydrocodone API and IN hydrocodone bitartrate API (**B**), Completer population (N = 51). VAS = visual analog scale.

shown in Figure 4A. Mean Drug Liking E_{max} was significantly lower for IN benzhydrocodone API vs IN HB API (67.4, SD = 13.3, vs 73.2, SD = 12.7, respectively); the difference between LS mean values was 5.8 points (95% CI = –1.9 to –9.6, $P = 0.004$). The frequency distribution of E_{max} values for benzhydrocodone API and HB API is shown in Figure 4B. The distribution for benzhydrocodone API is shifted leftward relative to HB API, with a greater percentage of subjects having E_{max} values in the 40–50 and 50–60 range compared with HB API, and a smaller percentage of subjects having E_{max} values in the 80–90 and 90–100 range. In parallel with the threefold longer T_{max} value for benzhydrocodone API than that for HB API, the TE_{max} was also longer for benzhydrocodone API vs HB API (median of 1.1 hours vs 0.5 hours, respectively). DL-VAS scores declined to near neutral levels by six hours postdose for both treatments.

The proportion of subjects with various magnitudes of Drug Liking E_{max} reduction with benzhydrocodone API vs HB API, expressed as percent reduction from E_{max} values for benzhydrocodone API relative to HB API, are presented in Figure 5. Overall, 69% (35 of 51 Completers) of subjects showed some reduction (i.e., >0) in drug liking, 43% (21) demonstrated a ≥30% reduction, and 29% (15) demonstrated a ≥50% reduction.

Pupillometry

Mean change in pupil diameter over time is illustrated in Figure 6. Mean pupil diameter for IN HB API declined rapidly to a nadir of ~4.4 mm at one hour postdose, whereas mean pupil diameter decreased more gradually following IN administration of benzhydrocodone API, with a minimum diameter

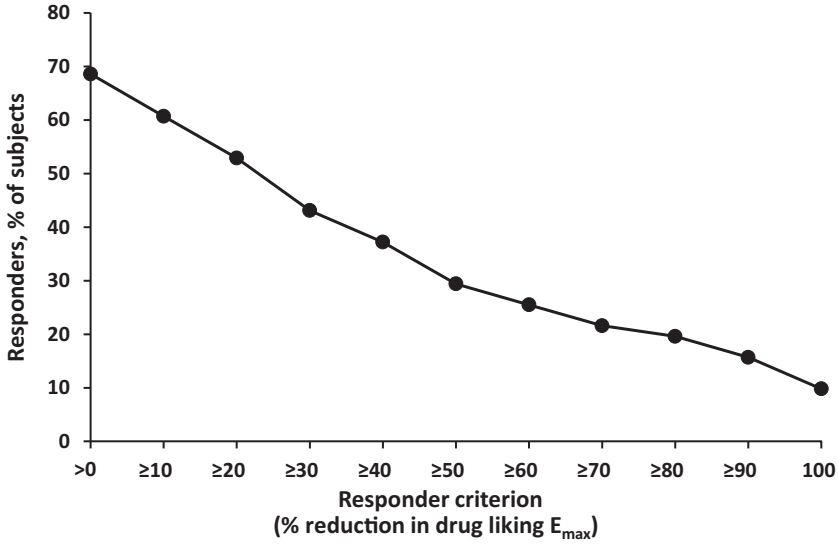

Figure 5 Responder analyses based on percent reduction in Drug Liking E_{max} for intranasal (IN) benzhydrocodone API relative to IN hydrocodone bitartrate API in the Completer population (N = 51).

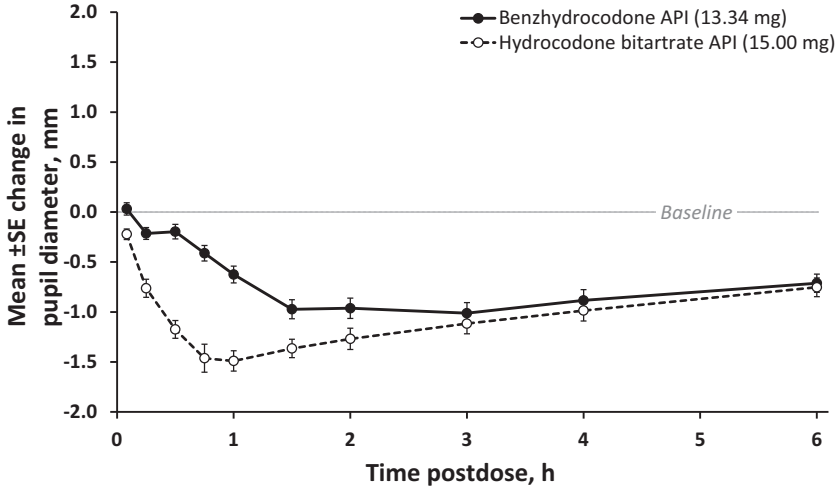

Figure 6 Mean (SE) pupil diameter over time for intranasal (IN) benzhydrocodone API and IN hydrocodone bitartrate API, Completer population (N = 51).

of ~4.6 mm at two hours postdose. IN administration of benzhydrocodone API resulted in a smaller mean change from baseline in pupil diameter (i.e., less constriction) than HB API (–1.4, SD = 0.7, vs –1.7, SD = 0.7, respectively, $P = 0.0002$). Return to near predose pupil diameter (~5.7 mm) occurred at 10 hours postdose for both treatments. Time-dependent alterations in mean pupil diameter corresponded to the time-dependent variations in mean hydrocodone plasma concentrations as well as mean Drug Liking findings.

Ease of Insufflation and Nasal Effects

The mean ease of insufflation score was significantly higher (indicating harder to insufflate) for IN benzhydrocodone API vs the score for IN HB API at 78.7 (SD = 20.0) vs 65.6 (SD = 26.3), respectively. The difference between LS mean values was 12.7 points (95% CI = 19.4 to 5.9, $P = 0.0004$).

For the nasal effects assessment, mean total scores were similar following IN benzhydrocodone API and HB API at each time point. Total scores were highest at 15 minutes postdose for both benzhydrocodone API (4.6, SD = 3.6) and HB API (3.7, SD = 2.6) and gradually declined to < 1 by 1.5 hours postdose.

Safety and Tolerability

In the Safety population (N = 54), treatment-emergent AEs (TEAEs) occurred in similar proportions of subjects

during treatment with benzhydrocodone API (30.8%) and HB API (27.8%). The most common TEAEs were generally reported at similar rates with benzhydrocodone API and HB API, and included headache (7.7% and 7.4%, respectively), pruritus generalized (5.8% and 5.6%, respectively), nausea (3.8% and 3.7%, respectively), nasal congestion, and vomiting (1.9% for both TEAEs and both treatments). Euphoric mood was reported as a TEAE in one subject treated with HB API. The majority of TEAEs were mild in severity and were generally reported within two hours of study drug administration. No severe AEs, deaths, or SAEs were reported. No subjects experienced clinically significant abnormalities in hematology or urinalysis. All vital signs and ECG interval values recorded were within the normal range.

Discussion

The results of this study showed that IN administration of benzhydrocodone API resulted in a significantly lower peak (C_{max}) and overall hydrocodone exposure (AUC), as well as a delayed time to peak hydrocodone concentration (T_{max}) compared with IN administration of HB API among nondependent recreational opioid users. These results were mirrored by the scores for Drug Liking on the DL-VAS, an FDA-recommended measure of abuse potential [18], indicating significantly lower E_{max}, consistently lower Drug Liking scores over time, and delays in reaching peak effects with benzhydrocodone API vs HB API. Benzhydrocodone API was also rated more difficult to insufflate than HB API, a property that is likely to contribute to its overall abuse-deterrent profile.

The difference in Drug Liking E_{max} between benzhydrocodone API and HB API, while statistically significant, was modest in magnitude. The modest difference may be due, in part, to the lack of a drug discrimination phase, which allowed enrollment of subjects who may have been less discerning than subjects in conventional human abuse potential studies. The finding that the HB API dose produced a mean Drug Liking E_{max} score of only 73.2 may also have hampered the ability to detect larger Drug Liking differences. This score is consistent with the relatively low dose of HB API (15 mg) and the inclusion of more experienced abusers, who in this study reported abusing drugs intranasally a mean of 55 times in the prior 12 months. In studies of putative abuse-deterrent ER opioids in which HB API has been used as a comparator, doses of 45 and 60 mg HB API engendered mean Drug Liking E_{max} scores of 80 and 90, respectively, on a 100-point bipolar VAS scale [19,20]. The abuse-related effects of higher doses of both HB API and benzhydrocodone API may be investigated in a future human abuse potential study.

Despite the lack of a placebo arm, the modest differences in Drug Liking VAS between HB API and benzhydrocodone API provide valid support for the design and use of prodrugs to deter certain forms of opioid abuse. It is well established that drug abusers commonly seek rapid absorption (fast T_{max}) of high concentrations of drug (large C_{max}) in order to achieve intense euphoria or "high" [17,21,22]. To modify the intended therapeutic pharmacokinetics of opioid products toward this more desirable profile, abusers manipulate solid oral dosage forms to facilitate snorting, injecting, and smoking, among other routes of abuse [23–25]. The prodrug benzhydrocodone is inactive in its native state and requires enzymatic conversion to active hydrocodone to deliver its analgesic and/or euphoric effects, a process that occurs most efficiently in the intestinal tract. Accordingly, nonoral administration of benzhydrocodone will result in slow and inefficient conversion to hydrocodone, thereby disincentivizing this form of abuse.

Pupillary constriction was observed to occur later and to a lesser extent with benzhydrocodone API relative to hydrocodone bitartrate API, and tended to correspond to mean hydrocodone plasma concentrations and Drug Liking scores over the dosing interval. Opioid-related pupillary constriction is a classic CNS-mediated effect that has long history of use in human abuse potential studies [e.g., 26,27]. The present pupillometry data provide an internal verification of the observed differences in subjective effects and support the overall finding of lower opioid-mediated effects with IN benzhydrocodone API relative to IN HB API.

The unmet need for an APAP-free, IR hydrocodone product should be considered in the context of the prescribing patterns and abuse profile of currently available IR opioids. IR opioids account for approximately 90% of all opioid prescriptions in the United States and are abused at markedly higher rates than ER opioids, even when controlling for population differences in the geographical regions studied [28]. Nonoral routes of abuse appear to be at least as common as the oral route of abuse for single-entity IR opioids [10]. Additionally, IR opioids are nearly always the first type of opioid prescribed for individuals with acute pain initiating first-time opioid therapy, some of whom have risk factors for abuse. With the FDA approval of nine abuse-deterrent ER opioids to date, and only one abuse-deterrent IR opioid, it is possible that patterns of abuse and diversion will shift even more heavily to IR opioids. The current data suggest that benzhydrocodone has the potential to mitigate the risk of certain forms of abuse while also providing analgesia without the potential negative effects of APAP, and therefore would not be expected to introduce new or added risks to the opioid landscape.

This study has a number of limitations. First, because the primary objective of the study was to assess the pharmacokinetics of intranasally administered benzhydrocodone API, Drug Liking data were generated without the inclusion of a drug discrimination phase, an experimental design element that is customarily included in formal human abuse potential studies to ensure that subjects can reliably discriminate an opioid from placebo. It is possible, therefore, that some subjects were included who could not discriminate 15 mg of IN

hydrocodone from placebo. In spite of this possibility, significant differences in Drug Liking were observed between IN benzhydrocodone API and IN hydrocodone bitartrate API. Second, a placebo control arm was not included in the treatment phase, and therefore the abuse potential of 15 mg intranasal hydrocodone bitartrate API could not be formally validated in this study. Third, only one relatively low dose of benzhydrocodone API and hydrocodone bitartrate API was assessed. Additional information on the extent to which these two opioids differ in abuse potential could be gleaned from testing higher doses and with additional subjective end points. Finally, this study was conducted in recreational drug abusers, and the results may not be generalizable to other populations, such as novice abusers and experienced abusers.

In summary, among nondependent, recreational opioid abusers, IN benzhydocodone API produced reductions in early, peak, and overall hydrocodone exposure, compared with an equimolar dose IN HB API. The Drug Liking data mirrored PK findings, as lower early and peak exposures with benzhydrocodone API were associated with lower Drug Liking VAS at early time intervals after dosing and with a lower Drug Liking E_{max}. Benzhydrocodone API was also more difficult to insufflate than HB ABI. These findings suggest that the prodrug benzhydrocodone has the potential to provide APAP-free analgesia while also disincentivizing intranasal abuse. Prodrugs may afford a rational approach to abuse-deterrent opioid development.

References

1 IMS Institute for Healthcare Informatics. Medicine use and spending in the U.S.: A review of 2015 and outlook to 2020. Available at: http://www.imshealth.com/en/thought-leadership/ims-institute/reports/medicines-use-and-spending-in-the-us-a-review-of-2015-and-outlook-to-2020#form (accessed July 2017).

2 Raffa RB. Pharmacology of oral combination analgesics: Rational therapy for pain. J Clin Pharmacol Ther 2001;26:257–64.

3 Raffa RB, Clark-Vetri R, Tallarida RJ, Wertheimer AI. Combination strategies for pain management. Expert Opin Pharmacother 2003;4(10) 1697–708.

4 Wong I, St John-Green C, Walker SM. Opioid-sparing effects of perioperative paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) in children. Paediatr Anaesth 2013;23(6):475–95.

5 US Food and Drug Administration. FDA Drug Safety Communication: Prescription acetaminophen products to be limited to 325 mg per dosage unit; boxed warning will highlight potential for severe liver failure. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm239821.htm (accessed August 2017).

6 US Food and Drug Administration. FDA Drug Safety Communication: FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm451800.htm (accessed August 2017).

7 Riley J, Ross JR, Rutter D, et al. No pain relief from morphine? Individual variation in sensitivity to morphine and the need to switch to an alternative opioid in cancer patients. Support Care Cancer 2006;14(1):56–64.

8 Cherny N, Ripamonti C, Pereira J, et al. Strategies to manage the adverse effects of oral morphine: An evidence-based report. J Clin Oncol 2001;19 (9):2542–54.

9 Califf RM, Woodcock J, Ostroff S. A proactive response to prescription opioid abuse. N Engl J Med 2016;374(15):1480–5.

10 Cassidy TA, Oyedele N, Mickle TC, Guenther S, Budman SH. Patterns of abuse and routes of administration for immediate-release hydrocodone combination products. Pharmacoepidemiol Drug Saf. In press.

11 Green JL, Bucher Bartelson B, Le Lait MC, et al. Medical outcomes associated with prescription opioid abuse via oral and non-oral routes of administration. Drug Alcohol Depend 2017;175:140–5.

12 Walsh SL, Nuzzo PA, Lofwall MR, Holtman JR Jr. The relative abuse liability of oral oxycodone, hydrocodone and hydromorphone assessed in prescription opioid abusers. Drug Alcohol Depend 2008;98: 191–202.

13 Stoops WW, Hatton KW, Lofwall MR, Nuzzo PA, Walsh SL. Intravenous oxycodone, hydrocodone, and morphine in recreational opioid users: Abuse potential and relative potencies. Psychopharmacology (Berl) 2010;212(2):193–203.

14 Joint Meeting of Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee. FDA Briefing Materials for Apadaz. Silver Spring, MD: US Food and Drug Administration; 2016.

15 Guenther S, Mickle TC, Guochen C, Kanski J, Martin AK, Bera B. KP201. A novel opioid pain therapy with reduced abuse potential and improved safety. Poster presented at: International Conference on Opioids; Boston, MA; 2013.

16 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th edition. Washington, DC: American Psychiatric Association; 2000.

17 Moorman-Li R, Motycka CA, Inge LD, et al. A review of abuse-deterrent opioids for chronic nonmalignant pain. P T 2012;37(7):412–8.

18 US Food and Drug Administration. Abuse-Deterrent Opioids—Evaluation and Labeling: Guidance for Industry. Silver Spring, MD: Center for Drug Evaluation and Research; 2015. Available at: http://www.fda.gov/downloads/drugs/guidancecompliance%20regulatoryinformation/guidances/ucm334743.pdf (accessed August 2017).

19 HYSINGLA Full Prescribing Information. Stamford, CT: Purdue Pharma LP; 2015.

20 VANTRELA ER Full Prescribing Information. North Wales, PA: Teva Pharmaceuticals USA, Inc; 2017.

21 Cicero TJ, Ellis MS, Kasper ZA. Relative preferences in the abuse of immediate-release versus extended-release opioids in a sample of treatment-seeking opioid abusers. Pharmacoepidemiol Drug Saf 2017;26(1):56–62.

22 Comer S, Ashworth JB, Sullivan MA, et al. Relationship between rate of infusion and reinforcing strength of oxycodone in humans. J Opioid Manag 2009;5(4):203–12.

23 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.

24 Webster LR, Bath B, Medve RA. Opioid formulations in development designed to curtail abuse: Who is the target? Expert Opin Investig Drugs 2009;18(3):255–63.

25 Carise D, Dugosh KL, McLellan AT, et al. Prescription OxyContin abuse among patients entering addiction treatment. Am J Psychiatry 2007;164(11):1750–6.

26 Jasinski DR, Pevnick JS, Griffith JD. Human pharmacology and abuse potential of the analgesic buprenorphine: A potential agent for treating narcotic addiction. Arch Gen Psychiatry 1978;35(4):501–16.

27 Jaffe JH, Kanzler M, Green J. Abuse potential of loperamide. Clin Pharmacol Ther 1980;28(6):812–9.

28 Iwanicki JL, Severtson SG, McDaniel H, et al. Abuse and diversion of immediate release opioid analgesics as compared to extended release formulations in the United States. PLoS One 2016;11(12):e0167499.