38

Presented at the
International Conference on Opioids (ICOO)
June 5–7, 2016
Boston, Massachusetts

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

Travis Mickle,[1] Sven Guenther,[1] Kathryn Roupe[2] Jing Zhou,[2] Daniel Dickerson,[3] Lynn Webster[3]
[1]KemPharm, Coralville, IA; [2]Worldwide Clinical Trials, Austin, TX; [3]PRA Health Sciences, Lenexa, KS

Background

Immediate-release opioids are commonly abused via alternative routes such as intranasal (IN) and intravenous administration.[1] Benzhydrocodone (also known as KP201) is a hydrocodone prodrug with inherent physicochemical and pharmacological properties designed to deter non-oral forms of abuse on a molecular level, rather than through formulation. Benzhydrocodone is the opioid active pharmaceutical ingredient in a novel, immediate-release hydrocodone combination product (Apadaz™; see also poster #17).

Objectives

To compare the pharmacokinetics (PK) and abuse potential of benzhydrocodone hydrochloride with those of hydrocodone bitartrate (HB) following IN administration to non-dependent, recreational opioid users.

Methods

This was a randomized, double-blind, two-way crossover study.

Study Participants. Study participants included experienced opioid users, male or female, 18 to 55 years of age, inclusive, who were not currently physically dependent on opioids.

Qualification Phases. Each part of the study began with an in-clinic Qualification Phase consisting of a Naloxone Challenge (to confirm the absence of physical opioid dependence).[2]

- In contrast to most human abuse potential studies, there was no drug discrimination test and therefore the study was not enriched in subjects that could differentiate active drug from placebo. As such, this design made it less likely to demonstrate differences in Drug Liking between the two treatments.

Study Design. Following the naloxone challenge, and a washout period of at least 12 hours:

- Eligible subjects were assigned in a 1:1 ratio to one of two in-clinic treatment sequences.
- The treatments were single, equimolar, IN doses. separated by a washout period of approximately 72 hours.
  - —Benzhydrocodone HCl, 13.34 mg
  - —Hydrocodone bitartrate, 15.0 mg

Pharmacokinetic Analyses. The primary objective of the study was to compare the rate and extent of absorption of hydrocodone from benzhydrocodone relative to HB.

- For each treatment, plasma hydrocodone concentration was assayed in blood samples obtained pre-dose and at 0.083, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post-dose.
- Descriptive statistics were calculated for parameters including peak plasma hydrocodone concentration (C_{max}) and area under the plasma hydrocodone concentration-time curve from time zero to 0.5 hours ($AUC_{0–0.5}$), 1 hour ($AUC_{0–1}$), 2 hours ($AUC_{0–2}$), 4 hours ($AUC_{0–4}$), 8 hours ($AUC_{0–8}$), and 24 hours ($AUC_{0–24}$).
- A linear mixed-effect model was used to analyze the natural log-transformed PK parameters (C_{max} and AUCs). The least square (LS) geometric mean ratio (test/control) along with the corresponding 90% confidence intervals (CI) were calculated.

Pharmacodynamic Analyses. At 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours post-dose, each subject was asked, "Do you like the drug effect you are feeling now?"

- Subjects responded on a 100-point, bipolar VAS anchored at 0 by "strong disliking," at 50 by "neither like nor dislike," and at 100 by "strong liking."
- At ≤5 minutes, each subject assessed the Ease of Insufflation ("snorting"). For this rating, a 100-point, unipolar VAS was utilized, anchored at 0 by "very easy" and at 100 by "very difficult."
- In addition to descriptive statistics, parameters derived for Drug Liking VAS and Ease of Insufflation VAS were analyzed using a standard mixed-effects model for all subjects in the Completers population.

Results

Study Participants. 66 subjects were enrolled.

- Cohort 1: (n=33) excluded from all PK analyses due to blood sample mishandling.
- Cohort 2: (n=33) 24 subjects had evaluable pharmacokinetic data (PK population).
- 54 subjects (28 from Cohort 1 and 26 from Cohort 2) were randomized and received at least one dose of study drug (safety population; 27 subjects per treatment sequence).
- 51 subjects (94.4%) completed both treatment periods (completer population).

Demographic and baseline characteristics of the safety population and the PK population are summarized in **Table 1.**

Table 1. **Subjects' Demographic and Baseline Characteristics**

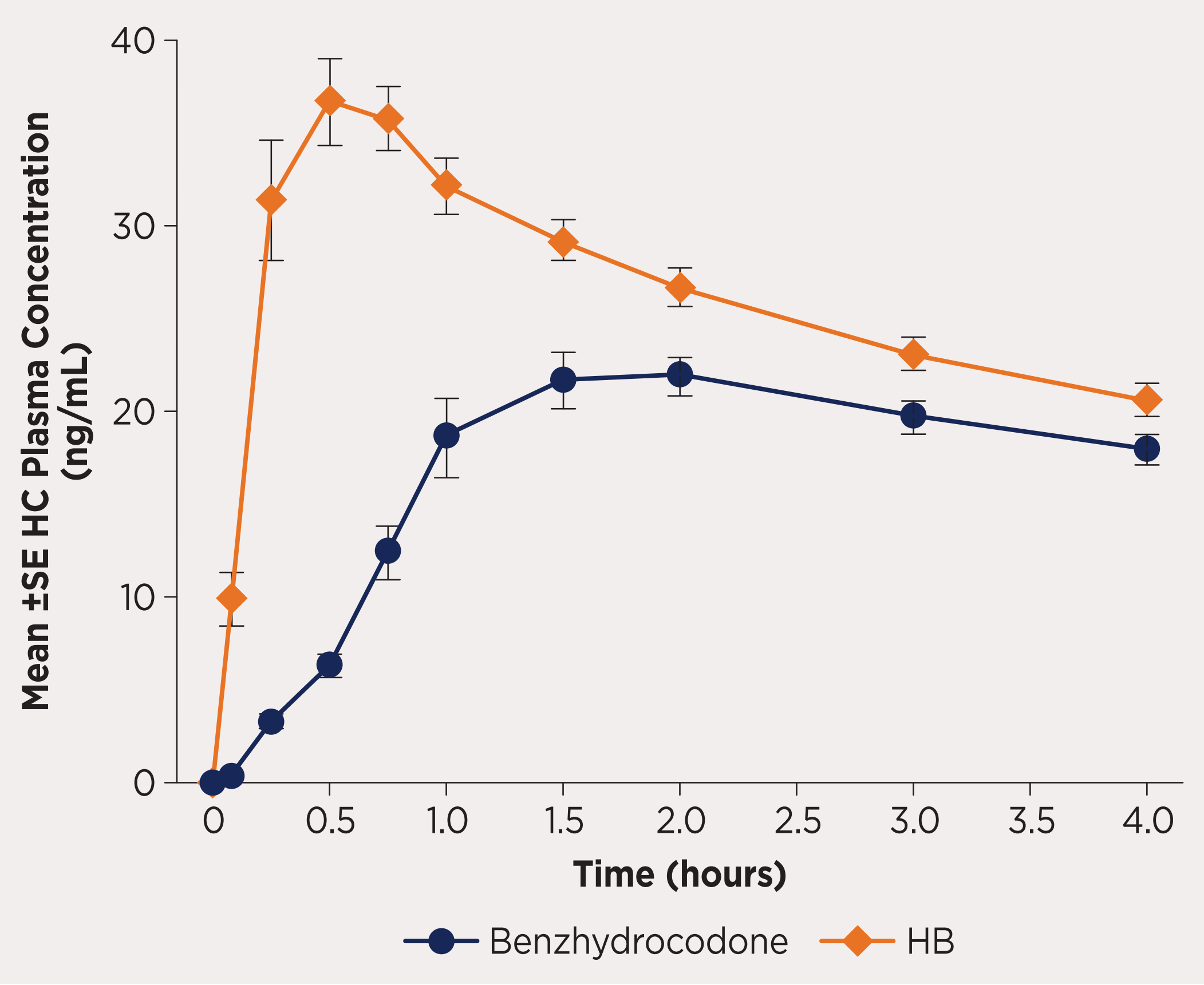
Characteristic		Safety Population (N=54)	PK Population (N=24)
Age (years)	Mean (SD)	27.7 (7.3)	27.5 (6.5)
	Median [range]	26 [18–49]	26.5 [18–46]
Sex, n (%)	Male	41 (75.9%)	18 (75.0%)
	Female	13 (2.1%)	6 (25.0%)
Race, n (%)	White	48 (88.9%)	20 (83.3%)
	Black/African American	4 (7.4%)	2 (8.3%)
	Other	2 (3.7%)	2 8.3%)
Weight (kg)	Mean (SD)	76.8 (14.6)	78.3 (15.4)
	Median [range]	71.2 [55.2–120.9]	72.6 [58.9–120.9]
BMI (kg/m²)	Mean (SD)	25.0 (3.6)	25.3 (3.6)
	Median [range]	24.4 [19.4–32.8]	25.0 [19.5–32.8]
Drug class most often abused during the past 12 weeks, n (%)			
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			
Total during the past 12 weeks			
	Mean (SD)	144.9 (219.0)	114.9 (219.2)
	Median [range]	91 [3–1,036]	45 [6–1,017]
IN during the past 12 months			
	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; SD, standard deviation.

Pharmacokinetic Findings. For each treatment, hydrocodone plasma levels throughout the first four post-dose hours are displayed in **Figure 1.** Ratios between log-transformed geometric least-squares mean values of selected pharmacokinetic parameters are displayed in **Figure 2.** In these analyses, peak hydrocodone plasma concentration (C_{max}) was 36.0% lower for benzhydrocodone than for HB ($P<0.0001$), and total hydrocodone exposures (AUC_{last} and AUC_{inf}) were 20.3% and 19.5% lower, respectively ($P<0.0001$ for each ratio). All partial AUC values also were lower for benzhydrocodone than for HB ($P<0.0001$ for each ratio), with a ≥75% reduction in hydrocodone exposure for all time intervals up to 1 hour post-dose.

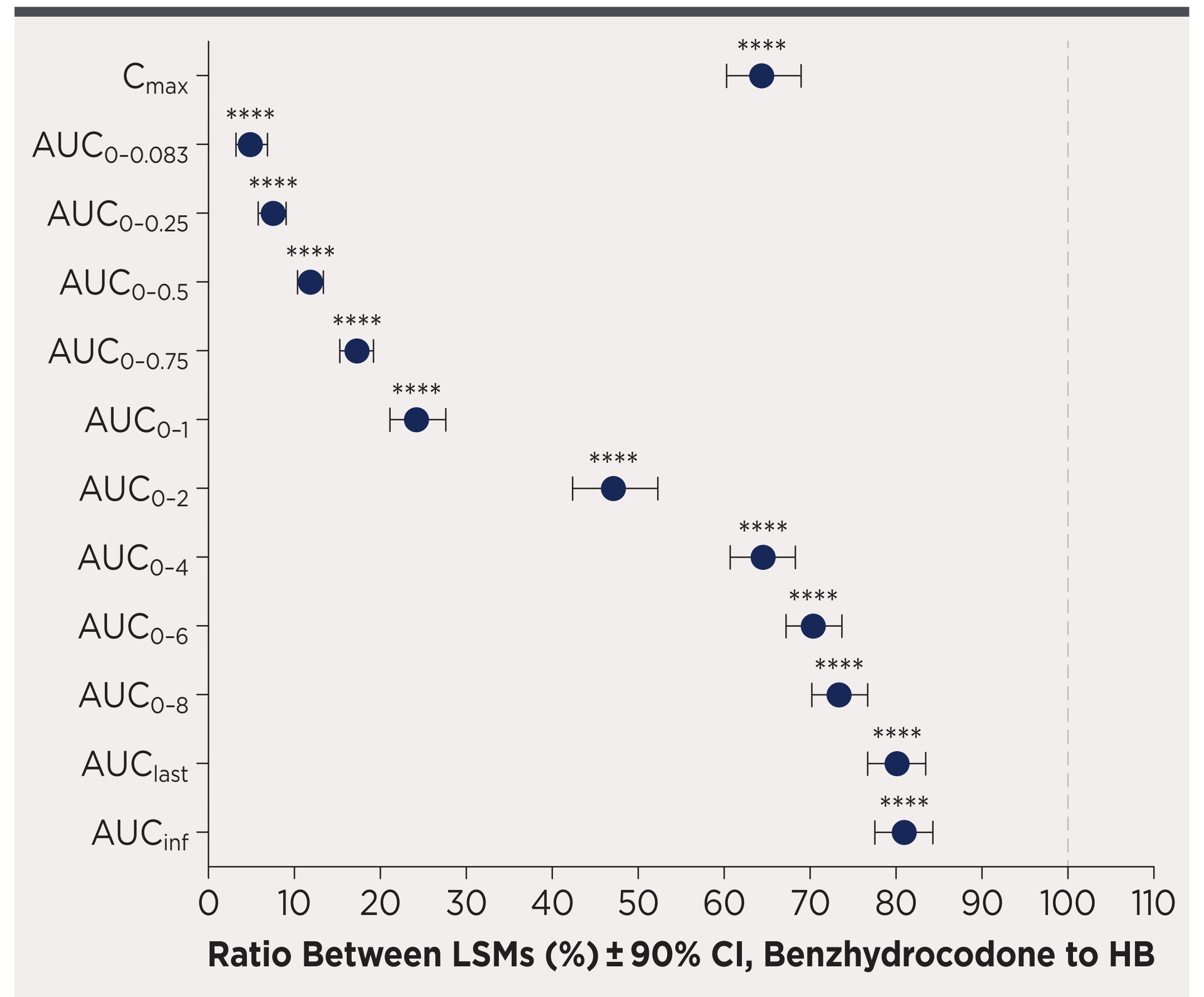
Pharmacodynamic Findings. Peak Drug Liking (E_{max}) was significantly lower for IN benzhydrocodone than for IN HB, at a mean (SD) value of 67.4 (13.3) vs 73.2 (12.7). The difference between least-squares mean values was 5.8 points (95% confidence interval: 1.9, 9.6; $P=0.004$). This significant difference was observed despite the study being underpowered compared with traditional human abuse potential studies that include a discrimination phase to qualify.

Figure 1. **Mean Hydrocodone Plasma Levels After Study-Drug Dosing (PK Population, N=24)**



HB, hydrocodone bitartrate; HC, hydrocodone; PK, pharmacokinetics; SE, standard error.

Figure 2. **Ratios of Log-Transformed Geometric Least-Squares Mean Values of Hydrocodone Parameters for IN Benzhydrocodone and IN HB (PK Population, N=24)**

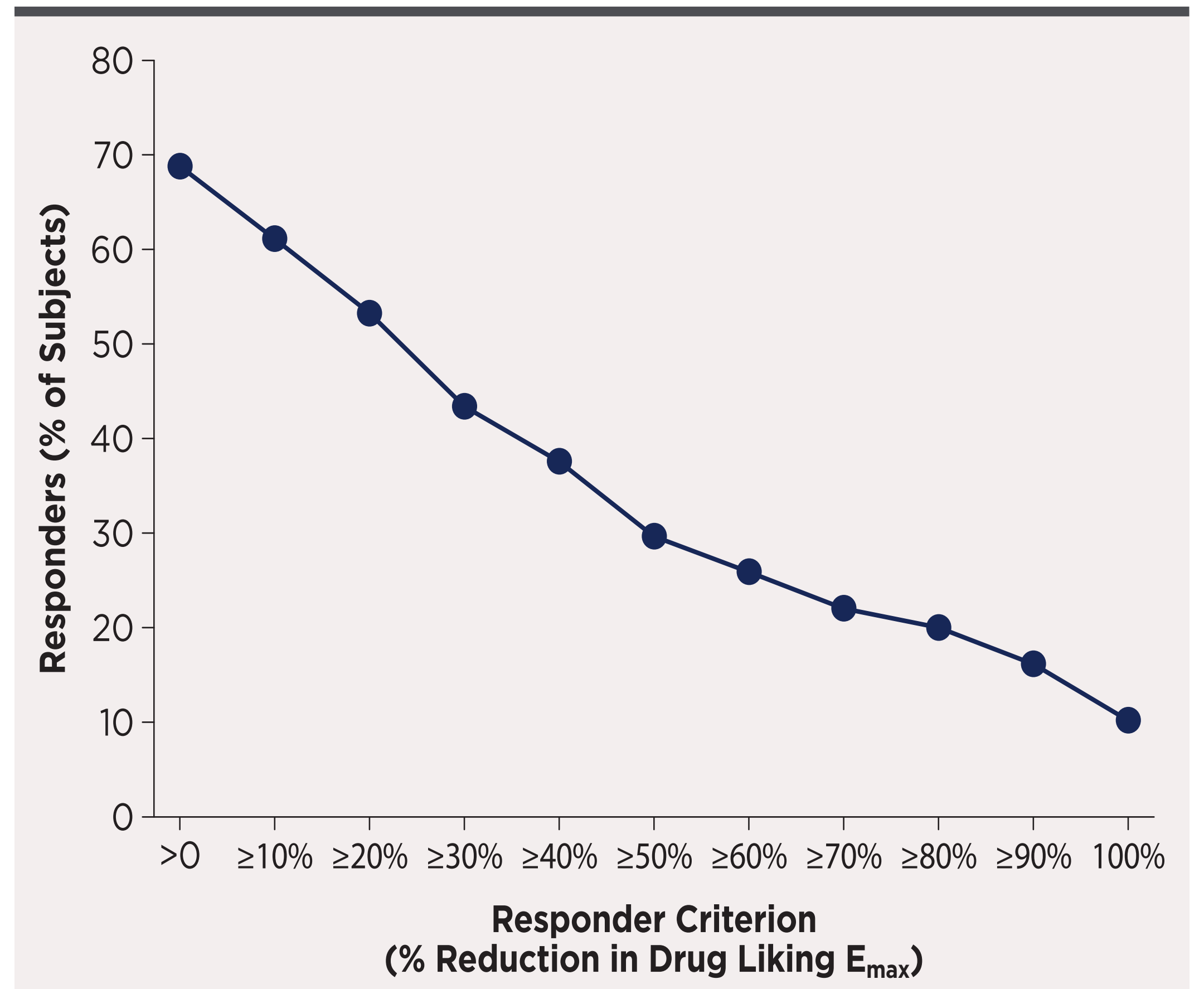


****$P<0.0001$, linear mixed-effect model.

$AUC_{0–0.083}$, $AUC_{0–0.25}$, $AUC_{0–0.5}$...$AUC_{0–8}$, area under the plasma concentration-time curve from time zero to the specified time point, in hours; AUC_{inf}, area under the plasma concentration-time curve from time zero extrapolated to infinity; AUC_{last}, area under the plasma concentration-time curve from time zero to the last measurable concentration; C_{max}, maximum observed concentration; CI, confidence interval; HB, hydrocodone bitartrate; LSM, least-squares mean; PK, pharmacokinetics.

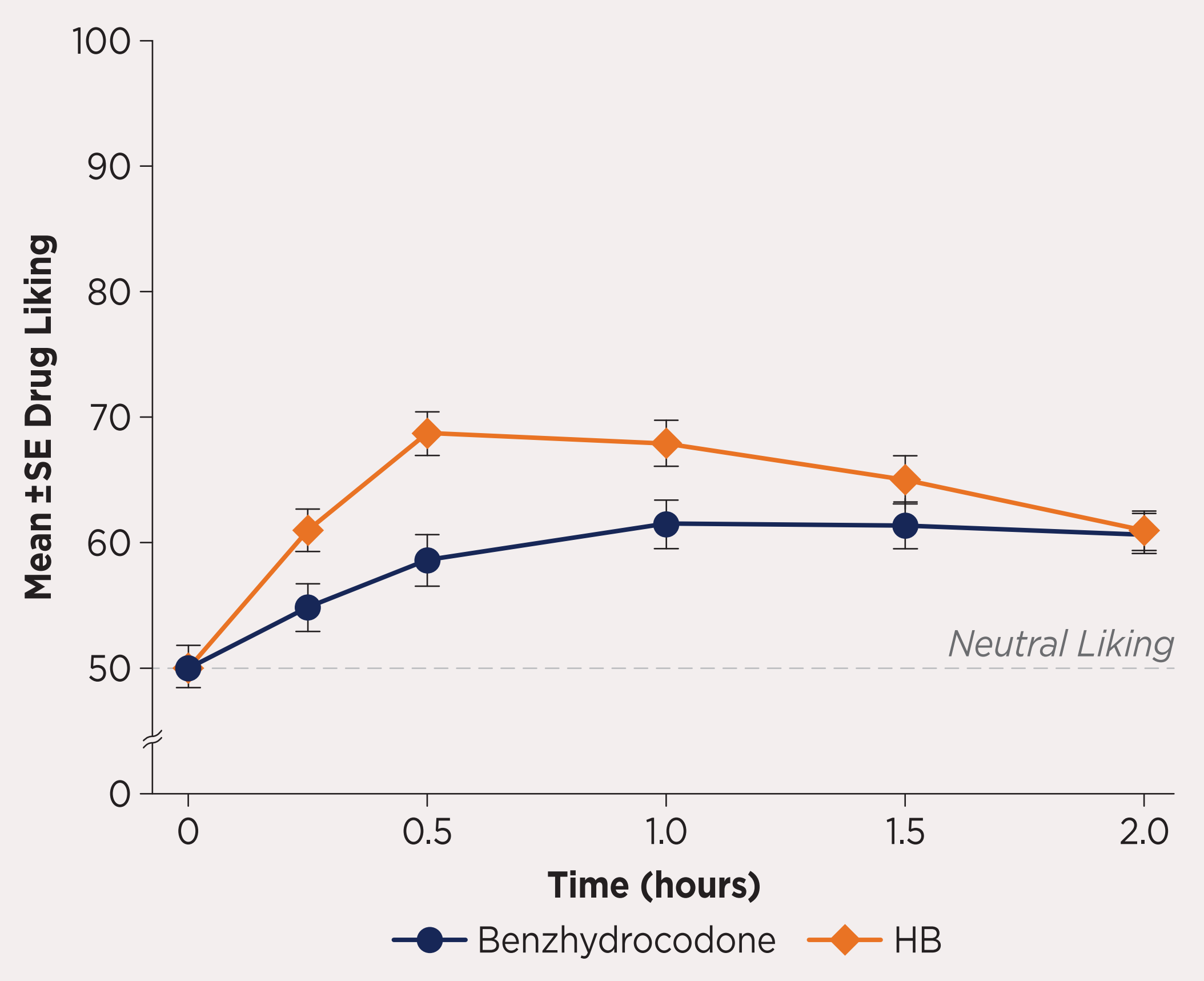
The proportions of subjects with various levels of E_{max} reduction (expressed as percent reduction from their E_{max} for HB) are displayed in **Figure 3**. Approximately 69% of subjects showed some degree of reduction, approximately 43% showed a ≥30% reduction, approximately 29% showed a ≥50% reduction. **Figure 4** shows Drug Liking over time for IN benzhydrocodone and IN HB.

Figure 3. **Responder Analyses Based on Percent Reduction in Drug Liking E_{max} for IN Benzhydrocodone Relative to IN HB (Completers Population, N=51)**



E_{max}, maximum Drug Liking, as rated by subjects on a 100-point, bipolar visual analogue scale anchored at 0 by "strong disliking," at 50 by "neither like nor dislike," and at 100 by "strong liking"; HB, hydrocodone bitartrate; IN, intranasal.

Figure 4. **Drug Liking Over Time for IN Benzhydrocodone and IN HB (N=51)**



HB, hydrocodone bitartrate; IN, intranasal; SE, standard error.

Ease of Insufflation score was significantly higher (i.e., more difficult) for IN benzhydrocodone than for IN HB, at a mean (SD) VAS rating of 78.7 (20.0) vs 65.6 (26.3). The difference between least-squares mean values was 12.7 points (95% confidence interval: 19.4, 5.9; $P=0.0004$).

Safety. The overall incidence of treatment-emergent adverse events (TEAEs) was similar across treatments, at 30.8% after administration of benzhydrocodone and 27.8% after administration of HB. For both treatments, the most commonly reported TEAEs were headache, generalized pruritus, and nausea (**Table 2**). No reported TEAEs were classified as serious or severe.

Table 2. **Treatment-Emergent Adverse Events (Safety Population)[a]**

Adverse Event, n (%)	Benzhydrocodone Hydrochloride 13.34 mg (N=52)	Hydrocodone Bitartrate 15.00 mg (N=54)
Any	16 (30.8%)	15 (27.8%)
Headache	4 (7.7%)	4 (7.4%)
Pruritus generalized	3 (5.8%)	3 (5.6%)
Nausea	2 (3.8%)	2 (3.7%)
Nasal congestion	1 (1.9%)	1 (1.9%)
Vomiting	1 (1.9%)	1 (1.9%)
Dizziness	0	2 (3.7%)

[a]The listing includes all events reported in ≥3% of all subjects.

Conclusions

- In recreational opioid abusers, IN benzhydrocodone produced reductions in peak and cumulative hydrocodone exposure compared with IN HB.
- Drug Liking data mirrored the PK findings, where lower early and peak exposure with benzhydrocodone was associated with lower Drug Liking early in the time course and with a lower Drug Liking E_{max}.
- These differences in Drug Liking were observed despite lack of a Drug Discrimination Test typically included to enrich the population with subjects that can differentiate active drug from placebo.
- Benzhydrocodone was more difficult to insufflate than HB.
- The findings suggest that the prodrug benzhydrocodone may provide a deterrent to intranasal opioid abuse.

Disclosures Travis Mickle and Sven Guenther are employees of KemPharm, Inc. Kathryn Roupe, Jing Zhou and Daniel Dickerson have no conflicts of interest to declare. Lynn Webster has received consulting fees, honorarium, and/or travel fees from AstraZeneca, Cara Therapeutics, Charleston Labs, Depomed, Egalet, Insys Therapeutics, Jazz Pharmaceuticals, Kaleo Pharmaceuticals, KemPharm, Inc., Marathon Pharmaceuticals, Merck, Pain Therapeutics, Pfizer, Proove Biosciences, Teva, Trevena, Scilex, and Shionogi.

Support Funding for editorial, design, and production support was provided by KemPharm, Inc., Coralville, IA, USA, to The Curry Rockefeller Group, LLC, Tarrytown, New York, USA.

References **1.** Butler et al. Abuse risks and routes of administration of different prescription opioid compounds and formulations. *Harm Reduct J.* 2011;8:29. **2.** NAVIPPRO® National Addictions Vigilance Intervention and Prevention Program Drug Abuse Surveillance Baseline Report. Analysis of Data for Hydrocodone Combination Products: 1/1/2012 through 6/30/2015. Final report issued 2 November 2015.