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

Relative Bioavailability, Intranasal Abuse Potential, and Safety of Benzhydrocodone/Acetaminophen, a Novel Immediate-Release Hydrocodone Prodrug Combination, Compared With Hydrocodone Bitartrate/Acetaminophen in Recreational Drug Abusers

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Background

Immediate-release (IR) hydrocodone combination products are the most commonly prescribed analgesics, with 90 million dispensed prescriptions in 2015. Recent survey data indicate that intranasal abuse of such products is highly prevalent, among both adult and adolescent opioid abusers with a reported frequency of 23% and 43%, respectively.[1] Benzhydrocodone, a hydrocodone prodrug designed to deter non-oral abuse, has been combined with acetaminophen (APAP) in a novel IR product, benzhydrocodone/APAP (KP201/APAP; APADAZ™).

Objectives

To compare the bioavailability, intranasal (IN) abuse potential, and safety of KP201/APAP, formulated as 6.67/325 mg tablets, relative to equimolar doses of hydrocodone bitartrate plus APAP (HB/APAP; NORCO®), formulated as 7.5/325 mg tablets, in non-dependent, recreational opioid abusers.

Methods

This was a single-center, randomized, double-dummy, double-blind, two-part study comprising a Dose Selection (Part A) and Main Study (Part B). Part A was designed to identify the maximum tolerated dose (MTD) of crushed IN KP201/APAP and HB/APAP to be used in the Main Study.

Study participants included experienced opioid users, male or female, 18 to 55 years of age, inclusive, who were not currently physically dependent on opioids. In Part A, subjects were screened and qualified to be enrolled into sequential parallel cohorts (4 subjects each). For Part B, approximately 50 subjects were to be randomized into the Main Study Treatment Phase, with 40 planned completers.

Qualification Phases (Part A and B). 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]) and a Drug Discrimination Test (to ensure that the subject could identify active-drug effects).

- **Naloxone Challenge.** Naloxone hydrochloride 0.2 mg was administered by intravenous bolus. If no evidence of withdrawal occurred within 30 seconds, an additional 0.6 mg was administered. Dependence was defined by a Clinical Opiate Withdrawal Scale (COWS) score ≥5.[3]
- **Drug Discrimination Test.** Subjects received double-blind IN doses of active drug and placebo, separated by at least 24 hours. For Part A, the active drug was hydrocodone powder (40 mg); for Part B, it was crushed HB/APAP (at the MTD).

Study Part A. The purpose of the Dose Selection Phase was to determine the dose of KP201/APAP and HB/APAP that is safe and can produce distinguishable effects on pharmacodynamic measures in the Main Study.

Part A was a randomized, double-blind dose escalation (or reduction) in cohorts of 4 subjects. Subjects were assigned to 1 of 2 dose escalation sequences testing either KP201/APAP or HB/APAP vs placebo administered on consecutive days, separated by approximately 24 hours. After completion of each cohort's dosing, the resulting data were unblinded to evaluate the need for further cohorts.

The following criteria were considered for the selection of the dose to be used in Part B:

- Dose must be safe and well-tolerated and can be completely insufflated by at least 2 of 4 subjects.
- A peak difference of at least 15 points on the bipolar visual analog scale (VAS) for Drug Liking in at least 2 of the 4 subjects.
- Absence of treatment-related, moderate-to-severe AEs that pose a significant safety/tolerability concern and/or absence of clinically significant respiratory depression.

Study Part B. All enrolled subjects received five in-clinic treatments (**Table 1**), separated from each other by a minimum 96-hour washout and administered in one of 10 crossover sequences, to which each subject was assigned by a computer-generated randomization scheme with a Williams-square design. Each treatment included a crushed IN dose and an oral intact capsule.

Table 1. Crushed IN and Intact Oral Doses for the Treatment Phase (Part B)

Treatment	Crushed IN Dose	Oral Intact Dose (Capsules)
A	Placebo powder	Placebo capsules
B	Placebo powder	KP201/APAP (at MTD)
C	KP201/APAP (at MTD)	Placebo capsules
D	HB/APAP (at MTD)	Placebo capsules
E	Placebo powder	HB/APAP (at MTD)

Pharmacokinetic (PK) Analyses. During study Part B, plasma hydrocodone concentration was assayed in blood samples obtained pre-dose and at 0.083, 0.25, 0.5, 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 interval (CI) were calculated.

Pharmacodynamic Analyses. During study Part B, post-dose Drug Liking was assessed at 0.083, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours. At each of these times, 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." Ease of Insufflation ("snorting") was assessed at ≤5 minutes. For this rating, subjects utilized a 100-point, unipolar VAS anchored at 0 by "very easy" and at 100 by "very difficult."

The study's primary pharmacodynamic endpoint was Drug Liking peak effect (E_{max}). Among secondary endpoints, area under the Drug Liking effect curve was calculated for time zero to 0.5 hours ($AUE_{0-0.5}$), 1 hour (AUE_{0-1}), 2 hours (AUE_{0-2}), 4 hours (AUE_{0-4}), 8 hours (AUE_{0-8}), and 24 hours (AUE_{0-24}). In subjects completing all treatments, results were tested by analysis of variance (ANOVA) for statistically significant differences between treatments ($P<0.05$). The primary comparison was between IN KP201/APAP and IN HB/APAP. Ease of Insufflation results were tested by the same methodology.

Results

Study Participants. Of 110 subjects admitted to the qualification phase of Part A, 51 were randomized and received study drug during the dose selection phase, and 49 completed Part A. Of 80 subjects admitted to the qualification phase of Part B (41 from Part A, including 4 not requiring naloxone re-challenge, and 39 newly recruited), 46 were randomized and received study drug during the treatment phase, and 42 completed Part B. Subject disposition during Part B is summarized in **Figure 1**. Subject characteristics in both parts of the study are summarized in **Table 2**.

Figure 1. Subject Disposition in Study Part B

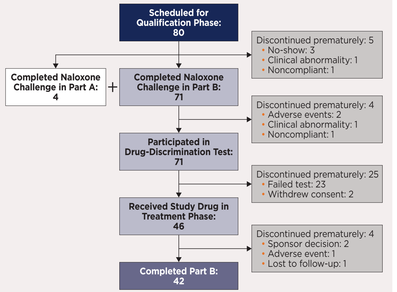


Table 2. Demographic and Baseline Characteristics (All Randomized, Treated Subjects)

Characteristic		Study Part A (N=51)	Study Part B (N=46)
Age (years)	Mean (SD)	39.3 (9.2)	37.6 (9.3)
	Median [range]	38 [21–55]	37 [19–54]
Sex, n (%)	Male	39 (76.5%)	35 (76.1%)
	Female	12 (23.5%)	11 (23.9%)
Race, n (%)	White	43 (84.3%)	31 (67.4%)
	Black/African American	6 (11.8%)	11 (23.9%)
	Asian	0	2 (4.3%)
	Other	2 (3.9%)	2 (4.3%)
Weight (kg)	Mean (SD)	78.8 (12.7)	79.5 (11.8)
	Median [range]	75.1 [56.0–116.7]	77.7 [61.6–105.0]
BMI (kg/m²)	Mean (SD)	25.5 (2.8)	25.9 (3.1)
	Median [range]	25.3 [19.9–31.9]	25.7 [20.9–32.0]
Drug class most often abused during the past 12 months, n (%)			
Opioids/morphine derivatives		12 (23.5%)	13 (28.3%)
Stimulants		39 (76.5%)	33 (71.7%)
Number of drug-abuse occasions during the past 12 weeks			
Total	Mean (SD)	41.1 (34.4)	45.1 (57.2)
	Median [range]	35 [8–215]	33 [5–330]
IN	Mean (SD)	11.5 (7.8)	11.8 (11.9)
	Median [range]	10 [2–30]	8 [1–70]

BMI, body mass index; IN, intranasal; SD, standard deviation.

Dose Selection. During Part A, seven cohorts received IN doses of KP201/APAP and placebo and six cohorts received IN doses of HB/APAP and placebo. Treatment doses included 1–4 crushed tablets. For KP201/APAP, two-tablet doses were the highest that could be reliably insufflated (**Table 3**). Accordingly, two-tablet doses (totaling 13.34/650 mg of KP201/APAP and 15/650 mg of HP/APAP) were administered in Part B.

Table 3. Study-Drug Insufflation During the Dose-Selection Phase of Study Part A

Dose (Number of Crushed Tablets)	KP201/APAP		HB/APAP	
	Total Number of Subjects	Completed Insufflation,[a] n (%)	Total Number of Subjects	Completed Insufflation,[a] n (%)
1	8	7 (88%)	8	8 (100%)
2	7	6 (86%)	8	6 (75%)
3	6	3 (50%)	4	4 (100%)
4	4	1 (25%)	4	1 (25%)

[a]Each treatment was to be "snorted" in ≤10 minutes.
APAP, acetaminophen.

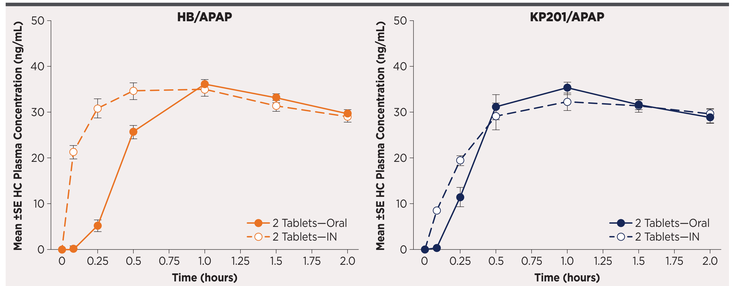
Relative Bioavailability. Hydrocodone plasma levels for active treatments post-dose up to 2 hours for oral and IN HB/APAP and KP201/APAP in Part B are shown in **Figure 2** and Drug Liking for the same times are shown in **Figure 3**.

- Peak concentration is reached fastest for IN HB/APAP.
- PK for oral and IN KP201/APAP are more similar than HB/APAP.
- The LS geometric mean ratios for C_{max} and AUCs up to 4 hours were significantly lower for IN KP201/APAP and IN HB/APAP (**Figure 4**).
- Trends in Drug Liking over the first two hours essentially mirrored the PK results (**Figures 2** and **3**).
- Drug Liking over time was essentially identical for oral and IN KP201/APAP.

IN Abuse Potential.

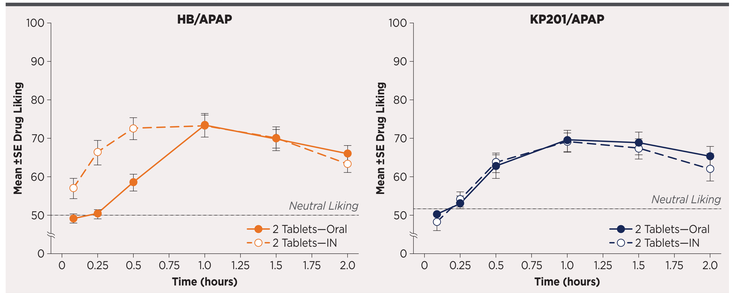
- Drug Liking scores at early time intervals ($AUE_{0-0.5}$, AUE_{0-1}, and AUE_{0-2}) were significantly lower for KP201/APAP than for HB/APAP ($P<0.0001$, $P<0.0001$, and $P=0.0079$).
- Peak Drug Liking scores (E_{max}) for IN KP201/APAP and HB/APAP were not significantly different ($P=0.2814$).

Figure 2. Mean Hydrocodone Plasma Levels After Active-Treatment Dosing During the Treatment Phase of Study Part B



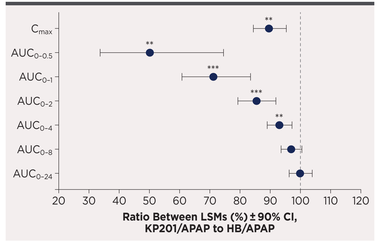
APAP, acetaminophen; HB, hydrocodone bitartrate; HC, hydrocodone; SE, standard error.

Figure 3. Mean Drug Liking Ratings[a] After Active-Treatment Dosing During the Treatment Phase of Study Part B



[a]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."
APAP, acetaminophen; HB, hydrocodone bitartrate; SE, standard error.

Figure 4. Ratios of Log-Transformed Geometric Least-Squares Mean Values of Pharmacokinetic Parameters for IN KP201/APAP and IN HB/APAP



**P<0.01; ***P<0.001, linear mixed-effect model.
APAP, acetaminophen; $AUC_{0-0.5}$, AUC_{0-1}, AUC_{0-2}, AUC_{0-4}, AUC_{0-8}, AUC_{0-24}, area under the plasma concentration-time curve from time zero to the specified time point, in hours; C_{max}, maximum observed concentration; CI, confidence interval; HB, hydrocodone bitartrate; LSM, least-squares mean.

Nasal Effects.

- Ease of Insufflation score was significantly higher (i.e., more difficult) for KP201/APAP than for IN HB/APAP, at a mean VAS rating of 57.0 vs 43.3 ($P=0.0100$).
- KP201/APAP was associated with significantly greater nasal effects than HB/APAP (**Table 4**).

Table 4. Nasal Effects of IN KP201/APAP and IN HB/APAP[a]

Parameter Mean (SD)	KP201/APAP, IN	HB/APAP, IN	*P* Value[b]
Average E_{max}	1.5 (0.8)	0.9 (0.8)	<0.0001
Burn E_{max}	1.6 (1.0)	0.7 (0.7)	<0.0001
Pain E_{max}	1.0 (1.0)	0.5 (0.8)	<0.0001
Blow E_{max}	1.5 (0.9)	1.0 (0.9)	<0.0001
Irritate E_{max}	1.5 (1.0)	0.7 (0.7)	<0.0001
Congestion E_{max}	1.5 (1.0)	1.0 (0.8)	0.0009
Discharge E_{max}	1.4 (1.0)	0.8 (0.9)	<0.0001

[a]Nasal effects were determined using a 4-point Likert scale, with 0=none, 1=mild, 2=moderate, and 3=severe; [b]Statistical significance of difference in LS means for the comparison of IN KP201/APAP vs IN HB/APAP.
APAP, acetaminophen; E_{max}, maximum effect rating; HB, hydrocodone bitartrate; IN, intranasal; LS, least-squares; SD, standard deviation.

Safety. Overall the most common TEAEs were typical of opioids and there were no differences between the two treatments. Respiratory, thoracic, and mediastinal adverse events reported after IN dosings in the treatment phase of Part B are summarized in **Table 5**. Events classified as nasal discomfort, nasal congestion, rhinorrhea, and throat irritation were more frequent for IN KP201/APAP than for IN HB/APAP.

Table 5. Respiratory, Thoracic, and Mediastinal Adverse Events During the Treatment Phase of Part B

TEAE Incidence, n (%)	IN KP201/APAP, 13.34/650 mg (N=44)	IN HB/APAP, 15/650 mg (N=43)	Placebo[a] (N=42)
Any respiratory, thoracic, or mediastinal TEAE	29 (65.9%)	9 (20.9%)	10 (23.8%)
Nasal discomfort	16 (36.4%)	2 (4.7%)	2 (4.8%)
Nasal congestion	7 (15.9%)	2 (4.7%)	6 (14.3%)
Rhinorrhoea	7 (15.9%)	4 (9.3%)	3 (7.1%)
Throat irritation	6 (13.6%)	3 (7.0%)	0
Oropharyngeal pain	1 (2.3%)	1 (2.3%)	1 (2.4%)
Dry throat	1 (2.3%)	0	0
Upper-airway cough syndrome	0	1 (2.3%)	0

[a]Placebo was administered both IN and orally. Each IN active treatment was co-administered with oral placebo.
APAP, acetaminophen; HB, hydrocodone bitartrate; IN, intranasal; TEAE, treatment-emergent adverse event.

Conclusions

- The maximum tolerated dose for crushed IN tablets of both KP201/APAP and HB/APAP was two tablets.
- Hydrocodone C_{max} and AUC up to 4 hours were significantly lower for IN KP201/APAP compared with IN HB/APAP.
- In recreational opioid abusers, IN KP201/APAP did not show a statistically significant difference in Drug Liking E_{max} compared with IN HB/APAP.
- Early Drug Liking through peak effect (2.0 hours) was significantly lower for IN KP201/APAP vs. IN HB/APAP.
- Crushed KP201/APAP was more difficult to snort and was associated with significantly greater nasal adverse effects compared to crushed HB/APAP.

Disclosures Sven Guenther and Travis Mickle are employees of KemPharm, Inc. Kathryn Roupe and Jing Zhou have no conflicts of interest to declare. Beatrice Setnik is an employee of INC Research and in her role consults with various pharmaceutical and biotech companies. Vincent Lam, Talar Hopyan, and Catherine Mills are employees of INC Research.

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.

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