13

# Pharmacokinetics and Abuse Potential of KP511, a Novel Prodrug of Hydromorphone, after Intranasal Administration in Recreational Drug Users

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## Introduction

- Hydromorphone products are commonly prescribed for the management of moderate to severe pain and are available as immediate-release and extended-release products
- As a potent μ-opioid receptor agonist with low oral bioavailability, hydromorphone (HM) is attractive for non-oral routes of abuse (e.g., intranasal, intravenous) that avoid presystemic metabolism
- Surveillance data indicate that even among μ-opioid receptor agonists, HM is a particularly sought after drug of abuse, and non-oral routes of abuse (i.e., intranasal, intravenous) are commonly reported (Butler 2011)
- There are currently no marketed HM products with abuse-deterrent label claims in accordance with the FDA Guidance, Abuse-Deterrent Opioids — Evaluation and Labeling (FDA 2015)
- KP511 is a prodrug of HM being developed as a potentially less abusable hydromorphone product for the treatment of moderate to severe pain
  - In rats, HM bioavailability following intranasal and intravenous KP511 was reduced by 75% and 95%, respectively, when compared with HM HCl

## Objective

- The objective of this study was to assess the pharmacokinetics and abuse potential of equimolar doses of KP511 hydrochloride API (16.1 mg) compared with HM hydrochloride (HCl) API (8 mg) following intranasal administration in non-dependent, recreational opioid users

## Methods

### *Study participants*

- Recreational opioid users who were not currently physically dependent on opioids (based on DSM-IV-TR criteria), but who had used opioids for non-therapeutic purposes (i.e., for psychoactive effects) ≥5 times within the last year and ≥1 time in the last 8 weeks
- Experience with intranasal opioid use ≥3 times within the last year
- Adults, 18 to 55 years of age (inclusive), with a body mass index (BMI) between 18 and 34 kg/m$^2$ and weight between 50 and 100 kg

### *Study design*

- This was a Phase 1, double-blind, single-dose, 2-treatment, 2-period, randomized, crossover study to compare the pharmacokinetics, safety and exploratory abuse potential of 16.1 mg of KP511 API with 8 mg HM API after intranasal administration
- The study consisted of a Screening Period, a Naloxone Challenge Test, a Treatment Phase with 2 Treatment Periods and a Follow-Up Visit
- Following Screening and a Naloxone Challenge Test to confirm that subjects were not physically dependent on opioids, eligible subjects were randomized to receive a single intranasal dose of 16.1 mg KP511 API or 8 mg HM API according to a randomization schedule. The alternate treatment was administered after a minimum 48-hour washout period
- Unlike conventional human abuse potential studies, this study was not specifically enriched for subjects that could discriminate the opioid from placebo
- Safety assessments were performed at each study visit, including physical examinations, vital sign measurements, safety laboratory tests, 12-lead ECGs, adverse events, and nasal-specific safety parameters (Nasal Cavity Assessment)

### *Pharmacokinetic Assessments*

- The primary endpoint was pharmacokinetic evaluation of HM released from 16.1 mg KP511 API compared with 8 mg HM API, treatments that are equimolar with respect to the HM content
- During each treatment period, blood samples were collected pre-dose (0 hr); at 5 minutes post-dose; and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 10, 12, and 24 hours post-dose

### *Pharmacodynamic Assessments*

- Abuse potential measures, considered exploratory endpoints, included:
  - Drug Liking Visual Analog Scale (VAS) score (100-point bipolar scale), assessed at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, and 8 hours post-dose
  - High VAS score (100-point unipolar scale), assessed pre-dose (0 hour) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, and 8 hours post-dose
  - Take Drug Again and Overall Drug Liking (100-point bipolar scale), assessed at 8, 12, and 24 hours post-dose
  - Drug Preference Assessment: At 12 and 24 hours postdose, subjects were asked, "Which dose do you prefer taking?" with selection of either Dose 1 or Dose 2
  - Ease of Insufflation VAS score at 5 min post-dose
  - Subject-Rated Assessment of Intranasal Irritation (SRAII), assessed at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours post-dose

### *Statistical Analyses*

- The primary statistical comparison of interest was performed for hydromorphone pharmacokinetic parameters ($C_{max}$, $AUC_{last}$, $AUC_{inf}$, partial AUCs) using a mixed effect Analysis of Variance (ANOVA) model on the log-transformed data, with fixed effects for sequence, period, and treatment, and a random effect for subject nested within sequence
- The least squares geometric means (LSGM) of the pharmacokinetic parameters for each treatment were reported. Point estimates and 90% CIs for the Test (16.1 mg KP511 API) to Reference (8 mg HM HCl API) ratios of geometric means provided a measure of relative bioavailability
- All pharmacodynamic endpoints were analyzed using a linear mixed effect ANOVA model, with fixed effects for sequence, period, and treatment, and a random effect for subject nested in sequence. Least-squares (LS) means along with 95% CIs were provided for each treatment. When assumptions of ANOVA were violated, the Wilcoxon Signed-Rank Test (a non-parametric model) was used

## Results

### *Study participants*

- A total of 26 subjects were randomized, all of whom completed the study
- Mean (SD) age was 31.2 (6.2) years, mean (SD) weight was 77.4 (11.1) kg, and 92.3% were males. Mean BMI (SD) at screening was 24.8 (3.6) kg/m$^2$
- Subjects reported having taken recreational opioids with a mean (SD) of 9.3 (11.1) times in the prior 8 weeks, and a mean (SD) of 62.6 (79.2) times in the prior 12 months

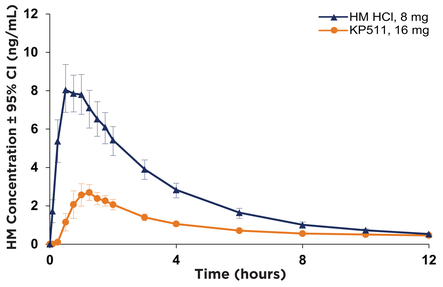
### *Pharmacokinetic findings*

- **Figure 1** shows mean plasma concentrations over time for HM following IN administration of KP511 API and HM HCl API
- Pharmacokinetic parameters for both treatments are shown in **Table 1**.
- When expressed according to geometric LS mean ratios, exposure to HM was reduced by ≥60% following intranasal KP511 API vs. HM HCl API, for parameters of $C_{max}$, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ (**Table 2**)

### *Pharmacodynamic findings*

- **Figure 2** shows Drug Liking and High VAS scores over time for KP511 API and HM HCl API
- Consistent with PK data, Drug Liking and High scores were significantly reduced following KP511 API administration
- **Table 3** shows analyses for all abuse-related pharmacodynamic endpoints, including both at-the-moment assessments (Drug Liking, High) and retrospective assessments (Take Drug Again, Overall Drug Liking)

**Figure 1. Mean (SD) Plasma Hydromorphone Concentrations After Intranasal Administration of KP511 API, 16.1 mg and HM HCl API, 8 mg**




CI = Confidence Interval

**Table 1. Pharmacokinetic Parameters – Hydromorphone**

| Parameter | 16.1 mg KP511 | 8 mg HM HCl |
|---|---|---|
| $C_{max}$ (ng/mL), mean (SD) | 3.45 (1.6) | 9.3 (3.0) |
| $AUC_{0\text{-}last}$ (h*ng/mL), mean (SD) | 14.5 (5.0) | 34.7 (9.3) |
| $AUC_{0\text{-}inf}$ (h*ng/mL), mean (SD) | 20.0 (7.9) | 38.8 (9.4) |
| $T_{1/2}$ (h), mean (SD) | 10.9 (8.0) | 8.5 (6.8) |
| $T_{max}$ (h), median (IQR) | 1.2 (0.50 – 2.0) | 0.75 (0.2-1.3) |

IQR: interquartile range

**Table 2. Relative Bioavailability of HM Following Intranasal Administration of KP511 API vs. HM HCl API**

| Parameter | Geometric LS Means[a] | | | 90% Confidence Limits | |
|---|---|---|---|---|---|
| | KP511 API (N=26) | Reference (N=26) | Ratio | Lower | Upper |
| $C_{max}$ | 3.21 | 8.94 | 0.36 | 0.30 | 0.43 |
| $AUC_{0\text{-}last}$ | 13.87 | 34.36 | 0.40 | 0.35 | 0.47 |
| $AUC_{0\text{-}inf}$ | 15.20 | 41.59 | 0.37 | 0.31 | 0.44 |

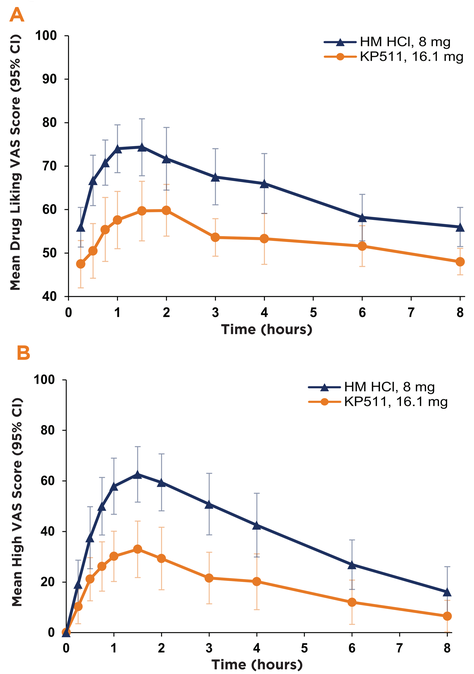
[a]units are ng/mL for $C_{max}$ and ng·h/mL for $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$

**Table 3. Pharmacodynamic Endpoints for KP511 API and HM HCl API**

| Parameter | KP511 API | HM HCl API | Mean/ Median Difference | *P*-Value |
|---|---|---|---|---|
| Drug Liking $E_{max}$, mean (SD) | 68.1 (12.4) | 78.7 (13.8) | -10.5 | 0.0017 |
| Feeling High $E_{max}$, median (IQR) | 44.5 (26-66) | 76.5 (50-87) | -25.0 | <0.001 |
| Take Drug Again (12 hr), median (IQR) | 57.5 (50-78) | 74.0 (61-92) | -13.0 | 0.0040 |
| Overall Drug Liking (12 hr), median (IQR) | 57.0 (49-77) | 79.0 (60-92) | -14.0 | 0.0052 |

Note: For Drug Liking $E_{max}$, mean and LS mean differences are reported; for High, Take Drug Again, and Overall Drug Liking, median and median differences (Wilcoxon Signed-Rank Test) are reported, as these distributions departed from normality. Median differences were estimated using the method of Hodges-Lehmann.

**Figure 2. Pharmacodynamic Endpoints of Drug Liking (A) and High (B) Following IN Administration of KP511 API and HM HCl API**




- In a retrospective assessment of Drug Preference, 17 of 26 subjects selected HM HCl API as the preferred drug of abuse

### *Nasal-Related Effects*

- Mean scores for subject rated Ease of Insufflation were low for both treatments (KP511: 12.0, HM: 8.4), indicating that both treatments were relatively easy to insufflate
- While mean SRAII subscale scores were relatively low overall, insufflation of KP511 API vs. HM HCl API was associated with small but statistically significant increases for:
  - Facial Pain ($p$=0.007), Nasal Burning ($p$<0.001), Need to Blow Nose ($p$=0.011) and Runny Nose ($p$<0.001), but not Nasal Congestion ($p$=0.203)

### *Safety*

- **Table 4** shows the most commonly reported AEs
- KP511 was associated with a greater number of nasal-related AEs while HM HCl API was associated with a greater number of typical opioid-related AEs

**Table 4. Most Common Adverse Events**

| MedDRA System Organ Class<br>Preferred Term | 16.1 mg KP511 API N=26 | 8 mg HM HCl API N=26 |
|---|---|---|
| **Respiratory, thoracic and mediastinal disorders** | **23 (88.5)** | **12 (46.2)** |
| Rhinorrhoea | 14 (53.8) | 4 (15.4) |
| Nasal congestion | 6 (23.1) | 4 (15.4) |
| Nasal discomfort | 6 (23.1) | 0 |
| **Psychiatric disorders** | **10 (38.5)** | **21 (80.8)** |
| Euphoric mood | 10 (38.5) | 20 (76.9) |
| **Nervous system disorders** | **8 (30.8)** | **13 (50.0)** |
| Somnolence | 5 (19.2) | 9 (34.6) |
| **Skin and subcutaneous tissue disorders** | **4 (15.4)** | **12 (46.2)** |
| Pruritus | 3 (11.5) | 12 (46.2) |
| **Gastrointestinal disorders** | **3 (11.5)** | **11 (42.3)** |
| Nausea | 3 (11.5) | 8 (30.8) |
| Vomiting | 0 | 7 (26.0) |
| **General disorders and administration site conditions** | **2 (7.7)** | **7 (26.9)** |
| Feeling hot | 2 (7.7) | 6 (23.1) |
| **Eye disorders** | **6 (23.1)** | **0** |
| Lacrimation increased | 6 (23.1) | 0 |

Note: Coded using MedDRA version 19.0.

## Conclusions

- The rate and extent of HM exposure was significantly lower following intranasal administration of KP511 API vs. HM HCl API
- Abuse-related pharmacodynamic endpoints were significantly lower, and nasal-related effects were significantly higher, for intranasal administration of KP511 API vs. HM HCl API
- These collective findings suggest that KP511 API may have reduced intranasal abuse potential relative to HM HCl API

## References

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

**2.** Food and Drug Administration (2015). FDA Center for Drug Evaluation and Research (CDER). Guidance: Abuse-Deterrent Opioids — Evaluation and Labeling.

## Disclosures

Sven Guenther, Travis Mickle, Andrew C. Barrett, Adam Smith, and Rene Braeckman are employees of KemPharm, Inc. Debra Kelsh and Bradley Vince are employees of Vince and Associates Clinical Research.

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