# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 208653Orig1s000

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# CLINICAL PHARMACOLOGY REVIEW

| | |
|---|---|
| NDA: 208653 | Submission Date: 12/09/2015 |
| Relevant IND(s): | 108038 |
| Submission Type; Code: | 505 (b) (2) |
| Brand Name: | Apadaz |
| Generic Name: | KP201/APAP (benzhydrocodone hydrochloride and acetaminophen) |
| Reference Drugs: | Vicoprofen, NDA 020716 and Ultracet, NDA 021123 |
| Formulation; Strength(s): | Tablets; 6.67 mg/325 mg |
| Clinical Pharmacology Reviewer: | Suresh B Naraharisetti, Ph.D. |
| Team Leader: | Yun Xu, Ph.D. |
| OCP Division: | Division of Clinical Pharmacology II |
| OND Division: | Division of Anesthesia and Analgesia Products |
| Sponsor: | Kempharm Inc. |
| Proposed Indication: | short-term (no more than 14 day) management of acute pain |
| Proposed Dosage Regimen: | (b) (4) every 4 to 6 hours as needed |

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## 1.0 Executive Summary

### 1.1 Recommendation

This submission is acceptable from a Clinical Pharmacology perspective provided that a mutually satisfactory agreement is reached between Agency and Sponsor regarding the labeling language.

### 1.2 Phase 4 Commitments

None

### 1.3. Summary of Clinical Pharmacology Findings

Kempharm Inc. submitted NDA 208653, as a 505 (b) (2) application for KP201/APAP (benzhydrocodone hydrochloride/acetaminophen) tablet, 6.67 mg/325 mg, for the short-term (no more than 14 days) management of acute pain. Chemically, benzhydrocodone (KP201) is an inactive prodrug of hydrocodone and is converted rapidly to active hydrocodone by enzymes in the intestinal tract. As it is rapidly converted to hydrocodone, in human PK studies following oral administration, plasma concentrations of KP201 were not detectable with the limit of quantitation 25 pg/mL.

According to the Sponsor, the KP201 is an abuse deterrent drug and its prodrug form KP201 is a stable molecule that cannot be crushed or manipulated to release hydrocodone. Sponsor claims that, the prodrug combination is resistant to intranasal and as well as physical and chemical tampering.

The proposed product, KP201/APAP tablet contains 6.67 mg benzhydrocodone (KP201) and 325 mg acetaminophen. Sponsor is relying on the FDA's findings for efficacy and safety of Vicoprofen (7.5 mg hydrocodone/200 mg ibuprofen oral tablet – NDA #020716) for the hydrocodone component and Ultracet (37.5 mg tramadol hydrochloride/325 mg APAP oral tablet – NDA #021123) for the acetaminophen (APAP) component of this combination product.

**Regulatory History:**

During the End of Phase 1, End of Phase 2 and pre-NDA meeting meetings held on 11/15/2012, 10/31/2013 and 05/19/2015, respectively, it was agreed with the Agency that:

1) Sponsor must rely on two NDAs to bridge to previous findings of safety and efficacy by conducting relative bioavailability studies with Vicoprofen for the hydrocodone component and Ultracet for the APAP component
2) To support that KP201/APAP is not a novel combination, Sponsor need to demonstrate bioequivalence to an approved combination of hydrocodone and APAP. In this case, Norco (7.5 mg hydrocodone bitartrate/325 mg APAP oral tablet), which is an ANDA is an acceptable comparator for this purpose, and
3) Norco would be an appropriate reference product for KP201/APAP combination to compare its food effect.

Accordingly, to establish the scientific bridge with reference listed drugs, two bioequivalence studies were conducted comparing KP201/APAP with Vicoprofen for hydrocodone component

and Ultracet for APAP component in the fasted state. In addition, KP201/APAP was compared to Norco in fasted and fed state to support that KP201/APAP is not a novel combination.

In support of this NDA, sponsor submitted data from the following studies.
Clinical Pharmacology Studies:

Studies comparing KP201/APAP tablet to NDA listed drugs:

- KP201.105: Relative bioavailability study of KP201/APAP tablet to Vicoprofen tablet with respect to hydrocodone under fasted condition
- KP201.106: Relative bioavailability study of KP201/APAP tablet to Ultracet tablet with respect to APAP under fasted condition

Studies comparing KP201/APAP tablet to ANDA listed drug, Norco

- KP201.102: Bioequivalence study of KP201/APAP tablet to Norco tablet, 7.5 mg/325 mg under fasted condition
- KP201.104: Effect of food on the bioavailability and PK of hydrocodone and APAP from KP201/APAP tablet, and the relative bioavailability of KP201/APAP to Norco tablets under fed condition

Single and multiple-dose PK:

- KP201.103: Single and multiple dose PK of KP201/APAP

Abuse Liability Studies:

- KP201.A01: Oral relative abuse potential study
- KP201.A02: Intranasal relative abuse potential study
- KP201.A03: Intranasal relative abuse potential study

**KP201:**
Prodrug KP201 is not measurable in humans after oral administration with the limit of quantitation 25 pg/mL. However, following crushed intranasal (IN) administration in human abuse liability studies, KP201 is measureable in plasma. The mean Cmax and AUC values for KP201 increased with an increase in dose. The mean Cmax and AUCinf for KP201 ranged from 9.4 ± 2.8 ng/mL and 7.6 ± 2.4 h·ng/mL (KP201/APAP 6.67/325 mg, crushed) to 27.0 ± 25.7 ng/mL and 26.1± 20.6 h·ng/mL (KP201/APAP 26.68/1300 mg, crushed). The median Tmax range of KP201 was 0.46 to 0.73 hours post-dose. The T1/2 of KP201 was short, ranging from 1 to 1.48 h.

**1.3.1 Relative bioavailability of KP201/APAP compared to listed drugs, Vicoprofen and Ultracet to establish scientific bridge:**
Sponsor established bioequivalence for hydrocodone and APAP components from KP201/APAP tablet to hydrocodone and APAP components of listed drugs, Vicoprofen (study KP201.105) and Ultracet (study KP201.106). The hydrocodone and APAP from KP201/APAP tablet has similar Tmax values compared to the reference drugs and no further issues were noted in the studies KP201.105 and KP201.106, respectively. The PK aspects of hydrocodone and APAP in comparison to reference drugs are shown in the QBR section 2.2 of the review.

**1.3.2 Relative bioavailability of KP201/APAP compared to Norco under fasted conditions:**
Sponsor has not conducted any clinical efficacy and safety studies for KP201/APAP tablet. To support that KP201/APAP is not a novel combination, sponsor established bioequivalence to hydrocodone and comparable exposure to APAP between KP201/APAP tablet and Norco tablet

under fasting conditions. KP201/APAP or Norco showed similar Tmax values for hydrocodone and APAP and no further issues were noted in the study KP201.102. The PK aspects of the study KP201.102 is shown in the QBR section 2.2 of the review.

**1.3.3 Relative bioavailability of KP201/APAP compared to Norco under fed Conditions and food effect on KP201/APAP:**

The effect of food on the bioavailability and pharmacokinetics of hydrocodone and APAP from KP201/APAP, and the relative bioavailability of KP201/APAP versus Norco under fed conditions in healthy volunteers is evaluated in the study KP201.104. Subjects received the single doses of KP201/APAP under fasted and fed and Norco under fed conditions in a cross over fashion.

**Hydrocodone:**

The pharmacokinetic parameters for hydrocodone after administration of KP201/APAP under fasted and fed conditions and Norco under fed conditions are summarized in Table 1.3.3a below.

**Table 1.3.3a:** PK parameters for hydrocodone after administration of KP201/APAP under fasted and fed conditions and Norco under fed conditions.

| **Parameter** [a] | **KP201/APAP, 6.67 mg/325 mg** | | **Norco, 7.5 mg/325 mg** |
|---|---|---|---|
| | **Fed** | **Fasted** | **Fed** |
| Cmax (ng/mL) | 16.04 ± 3.61 (40) | 19.18 ± 4.84 (38) | 20.95 ± 7.65 (40) |
| Tmax (h) | 2.50 (40) [0.50–4.00] | 1.25 (38) [0.50–3.00] | 1.90 (40) [0.50–4.00] |
| AUC0-t (h×ng/mL) | 125.80 ± 26.90 (40) | 121.40 ± 35.18 (38) | 135.37 ± 30.30 (40) |
| AUCinf (h×ng/mL) | 130.91 ± 29.45 (40) | 125.73 ± 36.78 (38) | 140.16 ± 31.66 (40) |
| t½ (h) | 4.53 ± 0.70 (40) | 4.33 ± 0.67 (38) | 4.36 ± 0.68 (40) |

[a] Arithmetic mean ± standard deviation (N) except Tmax for which the median (N) [Range] is reported.

**KP201/APAP Fed vs Fasted (Hydrocodone):**

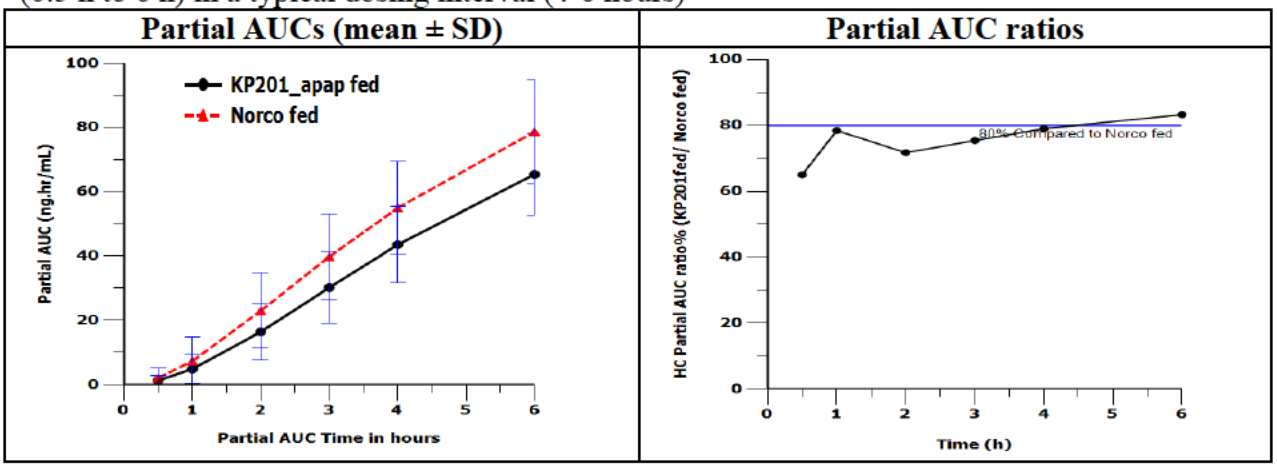
Administering KP201/APAP under fed conditions leads to 15% decrease in hydrocodone Cmax and comparable AUC compared to fasted conditions. The geometric means ratios (fed/fasted) for hydrocodone Cmax, AUC0-t, and AUCinf were 85.31%, 106.09% and 106.39%, respectively. The associated 90% CI for Cmax was 79.40% to 91.65%. The 90% CIs for AUC0-t, and AUCinf were contained within 80% to 125% limits. Although the median Tmax is slightly delayed from 1.25 h under fasted conditions to 2.5 h under fed conditions, it is still within minimum recommended dosing interval of 4 hours (proposed dosing regimen is 4-6 h).

**KP201/APAP Fed vs Norco Fed (Hydrocodone):**

Dosing KP201/APAP and Norco in the fed state led to median hydrocodone Tmax of 2.5 h and 1.9 h, respectively. The Tmax ranges were identical, within the minimum recommended dosing interval of 4 h (0.5 to 4 h for both products). While the hydrocodone Cmax for KP201/APAP under fed condition is 78% compared to Norco, the overall exposure to hydrocodone (AUClast and AUCinf) was within the 80% to 125% range. When hydrocodone partial AUCs in a typical dosing interval (4 to 6 hours) were compared between KP201/APAP fed and Norco fed, the data demonstrated a slight decrease in hydrocodone partial exposure for KP201/APAP compared to Norco. However, numerically it is not much lower and the standard deviations in hydrocodone

partial AUCs overlapped between two treatments. The partial AUC ratios for KP201/APAP under fed range from 65 to 83% compared to Norco under fed at different time points (0.5 h to 6 h) in a typical dosing interval (4-6 hours). The data are shown in Figure 1.3.3 below.

**Figure 1.3.3:** Hydrocodone partial AUCs (mean ± SD) for KP201/APAP Vs. Norco under fed conditions (left) and partial AUC ratios (KP201/APAP fed/ Norco fed) at different time points (0.5 h to 6 h) in a typical dosing interval (4-6 hours)




**APAP**

The pharmacokinetic parameters for APAP after administration of KP201/APAP or Norco are summarized in Table 1.3.3b below.

**Table 1.3.3b:** PK parameters for APAP after administration of KP201/APAP under fasted and fed conditions and Norco under fed conditions

| **Parameter** [a] | **KP201/APAP, 6.67 mg/325 mg** | | **Norco, 7.5 mg/325 mg** |
|---|---|---|---|
| | **Fed** | **Fasted** | **Fed** |
| Cmax (µg/mL) | 3.34 ± 1.01 (39) | 4.05 ± 1.30 (38) | 3.52 ± 1.20 (40) |
| Tmax (h) | 1.50 (39) [0.50–4.00] | 1.00 (38) [0.50–3.00] | 1.25 (40) [0.50–3.00] |
| AUC0-t (h×µg/mL) | 14.5 ± 3.41 (39) | 14.6 ± 4.42 (38) | 14.8 ± 3.34 (40) |
| AUCinf (h×µg/mL) | 15.0 ± 3.53 (36) | 14.7 ± 3.87 (36) | 15.3 ± 3.45 (40) |
| t½ (h) | 5.64 ± 1.58 (36) | 4.78 ± 1.30 (36) | 5.54 ± 1.47 (40) |

[a] Arithmetic mean ± standard deviation (N) except Tmax for which the median (N) [Range] is reported.

**KP201/APAP Fed vs Fasted (APAP):**

Administration of KP201/APAP under fed conditions resulted in 16% decrease in Cmax and identical AUC for APAP compared to the fasted conditions. The geometric means ratios (fed/fasted) for APAP Cmax, AUC0-t, and AUCinf were 84.43%, 102.35% and 105.36%, respectively. The associated 90% CI for Cmax was 76.64% to 93.01%. The 90% CIs for AUC0-t, and AUCinf were contained within 80% to 125% limits. There was slight delay in median Tmax of APAP for KP201/APAP under fed (1.5h) compared to fasted conditions (1.0 h).

**KP201/APAP Fed vs Norco Fed (APAP):**

KP201/APAP under fed conditions, results in equivalent Cmax and AUC compared to Norco fed. The geometric means ratios (KP201/APAP fed/ Norco fed) for APAP Cmax, AUC0-t, and

AUCinf were 96.77%, 99.12%, and 99.31%%, with associated 90% CIs within 80% to 125% limits. The median Tmax for APAP was 1.5 and 1.25 h for KP201/APAP fed and Norco fed, respectively with Tmax range within the minimum recommended dosing interval of 4 hours (0.5 to 3 h for Norco fed and 0.5 to 4 h for KP201/APAP fed).

**Conclusions on Food effect:**
Norco can be administered without regard to food. Although KP201/APAP showed slightly delay in Tmax for both hydrocodone and APAP under fed condition compared to fasted condition, its PK profiles and PK parameters under fed condition are similar to those of Norco under fed condition. In addition, by evaluating the individual PK profiles, no significant delay of absorption were identified for KP201/APAP under fed condition. Based on totality of the data, food effect study results support the conclusion that KP201/APAP may be administered without regard to food.

**1.3.4. Single and Multiple Dose PK of KP201/APAP:**
Single and multiple-dose PK of KP201/APAP tablets was evaluated in the study KP201.103 in 24 healthy volunteers under fasted conditions. Subjects received a single dose (Dose 1, Day 1) of KP201/APAP Tablets (2 × 6.67 mg/325 mg) to evaluate single-dose PK. Twenty-four hours after the first dose (Day 2), subjects entered the multi-dose portion of the study and received KP201/APAP Tablets [Dose 2 (at 24h) through Dose 14 (at 72h)] every 4 hours (13 doses). Subjects received a total of 14 doses (single and multiple dose portions) in a confined setting.

Median Tmax for hydrocodone after multiple dosing of KP201/APAP is 1.25 h (range 0.5–2 h), and is comparable to median Tmax after single dose of 1 h (range 0.5–4 h). After multiple dosing, the steady-state for hydrocodone reached at approximately 24 hours after the initiation of multiple dosing. The accumulation ratio for hydrocodone Cmax, AUC0-4 and AUC0-t values (Day 4/Day1 or $14^{th}$ dose/ $1^{st}$ dose of KP201/APAP) were 1.85-fold, 2.10-fold and 2.03-fold, respectively. The half-life (mean ± SD) of hydrocodone after multiple dosing (4.87 ± 0.63h) is comparable to the half-life after single dose (4.45 ± 0.59).

Median Tmax for APAP after multiple dosing of KP201/APAP is 1 h (range 0.5–1.5 h), and is comparable to the median Tmax after single dose of 0.5 h (range 0.5–3 h). The steady-state for APAP reached approximately at between 24-36 hours after the initiation of multiple dosing. The APAP accumulation ratio for Cmax, AUC0-4 and AUC0-t values (Day 4/Day1 or $14^{th}$ dose/ $1^{st}$ dose of KP201/APAP) were 1.38-fold, 1.69-fold and 1.80-fold, respectively. The mean ± SD half-life of APAP after KP201/APAP multiple dosing is slightly longer (6.84 ± 2.42 h) compared to the half-life after single dose (4.79 ± 1.21 h).

The plasma KP201 levels were not detectable after multiple oral dosing of KP201/APAP.

**1.3.5 Human abuse liability studies:**
Three human abuse liability studies were conducted for KP201/APAP. The KP201/APAP was administered orally in one study (study KP201.A01), and intra-nasally (IN) in the other two (studies KP201.A02 and study KP201.A03). For these studies, the PK endpoints of KP201/APAP versus Norco were reviewed. With regards to the PD endpoints, including Emax for drug liking and high and its statistical significance, refer to Control Substance Staff review.

The details of the PK results and the conclusions for human abuse liability studies is discussed in details in Section 2.5 the QBR

Overall, adequate information has been provided characterizing the clinical pharmacology aspects of KP201/APAP.

## 2.0 Question Based Review

### 2.1 General Attributes of the Drug

#### 2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

**Drug product** (Source 3.2.P.1.1)
The drug product, benzhydrocodone hydrochloride/acetaminophen Tablet is an abuse deterrent form of hydrocodone bitartrate/acetaminophen (APAP) immediate release combination product. Benzhydrocodone hydrochloride (KP201) is a prodrug of hydrocodone and benzoic acid in which the carboxyl group of benzoic acid is covalently bound to the 6-enol tautomer of hydrocodone. KP201/APAP tablets are a fixed-dose combination of 6.67 mg of KP201 HCl (equivalent to 4.54 mg of hydrocodone base and 7.5 mg of hydrocodone bitartrate) and 325 mg of acetaminophen. The KP201/APAP tablet, 6.67 mg/325 mg is a white, capsule-shaped tablet debossed with the "KP201" on one side.

**Table 2.1.1:** Composition KP201/APAP Tablet, 6.67 mg/325 mg

| Component | Quantity (mg/tablet) | % w/w | Function | Reference To Quality Standard |
|---|---|---|---|---|
| Benzhydrocodone hydrochloride | 6.67 | (b) (4) | Active | In-house |
| Acetaminophen | 325.0 | | Active | USP |
| Microcrystalline cellulose | | | (b) (4) | NF |
| Pregelatinized starch | | | | NF |
| Crospovidone | | | | NF |
| Povidone K30 | | | | NF |
| Stearic acid | | | | NF |
| | | | | (b) (4) |

### 2.1.2 What are the core studies submitted in this NDA?

The following studies submitted in this NDA:

Clinical Pharmacology Studies:

*Studies comparing KP201/APAP tablet to NDA listed drugs:*

- KP201.105: Relative bioavailability study of KP201/APAP tablet to Vicoprofen tablet with respect to hydrocodone and hydromorphone under fasted conditions
- KP201.106: Relative bioavailability study of KP201/APAP tablet to Ultracet tablet with respect to APAP under fasted conditions

*Study comparing KP201/APAP tablet to ANDA listed drug, Norco*

- KP201.102: Bioequivalence study of KP201/APAP tablet to Norco tablet, 7.5 mg/325 mg under fasted conditions

*Food effect on KP201/APAP and comparison to Norco:*

- KP201.104: Effect of food on the bioavailability and PK of hydrocodone and APAP from KP201/APAP tablet, and the relative bioavailability of KP201/APAP to Norco tablets under fed conditions

*Single and multiple-dose PK:*

- KP201.103: Single and multiple dose PK of KP201/APAP

Abuse Liability Studies:

- KP201.A01: Oral relative abuse potential study
- KP201.A02: Intranasal relative abuse potential study
- KP201.A03: Intranasal relative abuse potential study

## 2.2 General Clinical Pharmacology

### 2.2.1. Is hydrocodone component of KP201/APAP tablet bioequivalent to hydrocodone component of Vicoprofen?

*Under fasting conditions, the hydrocodone component from KP201/APAP tablet is bioequivalent to hydrocodone component of Vicoprofen tablet*

Study KP201.105 was an open-label, single-dose, randomized, 2-treatment, 2-period, 2-sequence crossover bioequivalence study in 28 subjects under fasted conditions. In a random fashion, subjects received 2 single-dose treatments of KP201/APAP (6.67 mg/325 mg) or Vicoprofen (7.5 mg hydrocodone/ 200 mg ibuprofen). Each treatment was separated by a 7-day washout period. All study doses were administered after a standard overnight fast (approximately 10 hours).

Lot and Formulation Identification:

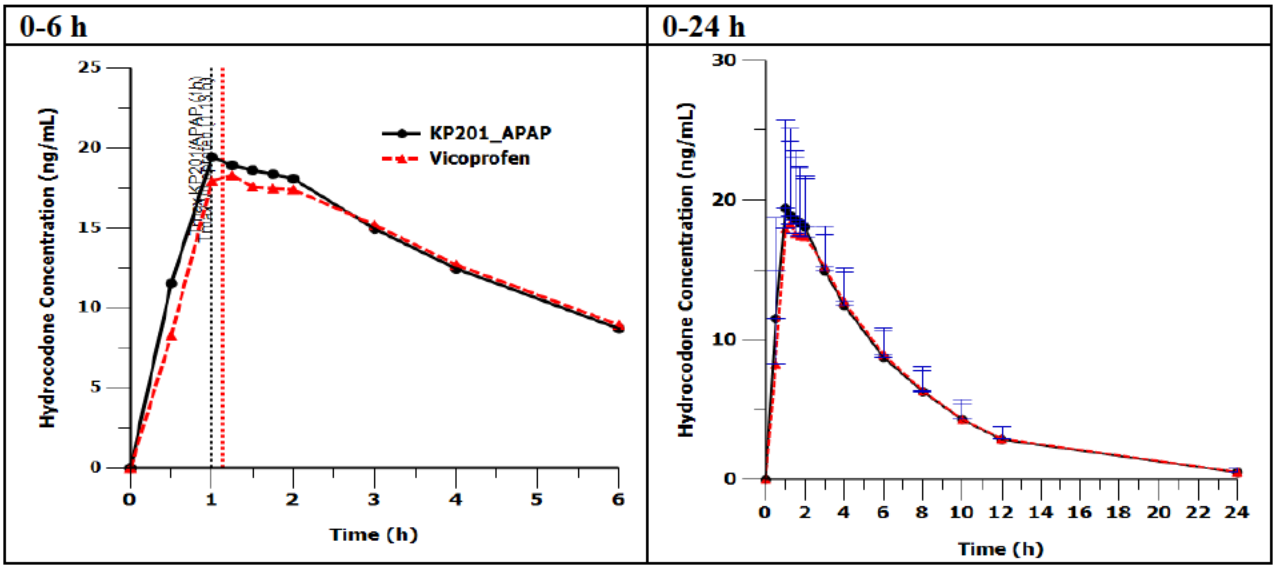
- KP201/APAP: Batch: 3111387, Expiration Date: June 2015
- Vicoprofen: Lot: 2803SGY Expiration Date: 04/2016

PK blood samples during each study period:

- At predose (time zero) and at 0.5, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, and 24.0 hours after dosing

The proposed dosing regimen for KP201/APAP is 4-6 h as needed for pain. The hydrocodone concentration time profile over the dosing regimen (6 h) and for 0-24 h overlaps following administration of KP201/APAP or Vicoprofen under fasted conditions as shown in the Figure 2.2.1a.

**Figure 2.2.1a:** Mean ± SD plasma hydrocodone concentration-time profile for 0-24h (right) and mean concentration-time profile 0-6h (left) following administration of single doses of KP201/APAP and Vicoprofen under fasted conditions to healthy subjects (Study KP201.105)




Plasma concentrations of KP201 were below LOQ (25 pg/mL) in this study.

The Cmax and total exposure (AUCt and AUCinf) met the bioequivalent criteria for the hydrocodone component between KP201/APAP and Vicoprofen under fasted conditions. The hydrocodone mean Cmax was 21.06 and 20.94 ng/mL, respectively for KP201/APAP and Vicoprofen, with a median Tmax of 1 h for KP201/APAP and 1.13 h for Vicoprofen. The mean elimination t1/2 of hydrocodone was 4.2 h for KP201/APAP or Vicoprofen. The descriptive statistics of hydrocodone PK parameters are listed in the Table 2.2.1a.

**Table 2.2.1a:** Descriptive statistics of hydrocodone PK parameters following administration of following administration of KP201/APAP tablet, 6.67 mg/325 mg and Vicoprofen tablet, 7.5 mg/200 mg under fasted conditions (Study KP201.105).

| PK Parameter * | KP201/APAP (6.67/325) (n=28) | | | | | Vicoprofen (7.25/200) (n=28) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | %CV | Min | Max | Mean | SD | %CV | Min | Max |
| AUCt (ng hr/mL) | 132.6 | 34.2 | 26 | 62.3 | 207.5 | 131.5 | 26.3 | 20 | 71.0 | 179.7 |
| AUCinf (ng hr/mL) | 136.6 | 34.9 | 26 | 66.4 | 215.9 | 135.4 | 27.3 | 20 | 73.9 | 185.2 |
| Cmax (ng/mL) | 21.1 | 4.4 | 21 | 13.4 | 31.2 | 20.9 | 3.8 | 18 | 14.9 | 27.0 |
| Halflife (h) | 4.2 | 0.6 | 15 | 2.8 | 5.7 | 4.2 | 0.6 | 15 | 2.6 | 5.4 |
| Tmax* | 1.0 (0.5 -3.0) | | | | | 1.13 (1.0-3.0) | | | | |

* Tmax -median (range)

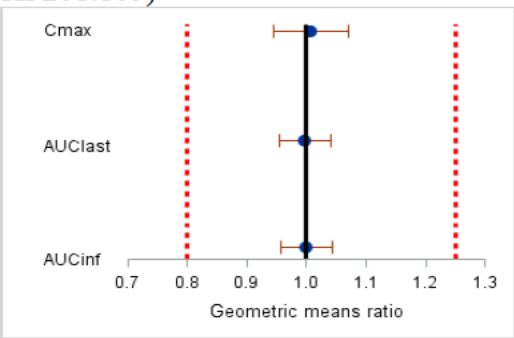
The statistical analysis show that Cmax, AUCt, AUCinf for hydrocodone from KP201/APAP tablets (6.67 mg/325 mg) was bioequivalent to Vicoprofen tablets (7.5 mg/200 mg) as shown in the Table 2.2.1b and Figure 2.2.1b below.

**Table 2.2.1b:** Statistical comparison of pharmacokinetic parameters for hydrocodone after oral administration of single doses of KP201/APAP (test) and Vicoprofen (reference) to healthy subjects under fasted conditions (Study KP201.105)

| Parameter | Geometric Mean [a] | | Geometric Mean Ratio [%] | |
|---|---|---|---|---|
| | Test | Reference | Estimate | 90% Confidence Interval (Lower, Upper) |
| KP201/APAP, 6.67 mg/325 mg vs. Vicoprofen, 7.5 mg/200 mg | | | | |
| Cmax | 20.58 | 20.46 | 100.55 | 94.50 , 106.99 |
| AUC0-t | 128.40 | 128.90 | 99.61 | 95.39 , 104.03 |
| AUCinf | 132.37 | 132.61 | 99.82 | 95.62 , 104.20 |

[a] Least squares geometric means, based on the analysis of natural log-transformed data.

**Figure 2.2.1b:** Ratios of geometric means and the 90% confidence intervals for hydrocodone AUC and Cmax for KP201/APAP versus Vicoprofen under fasted conditions (Study KP201.105)



### 2.2.2. Is APAP component of KP201/APAP tablet bioequivalent to APAP component of Ultracet Tablet?

*Under fasting conditions, the APAP component of KP201/APAP tablet is bioequivalent to APAP component of Ultracet tablet*

Study KP201.106 was an open-label, single-dose, randomized, 2-treatment, 2-period, 2-sequence crossover bioequivalence study in 27 subjects. In a random fashion, subjects received a single dose of KP201/APAP (6.67 mg/325 mg) or Ultracet, 37.5 mg tramadol/325 mg APAP, on 2 separate occasions separated by a 7-day washout period. All study doses were administered after a standard overnight fast (approximately 10 hours).

Lot and Formulation Identification:

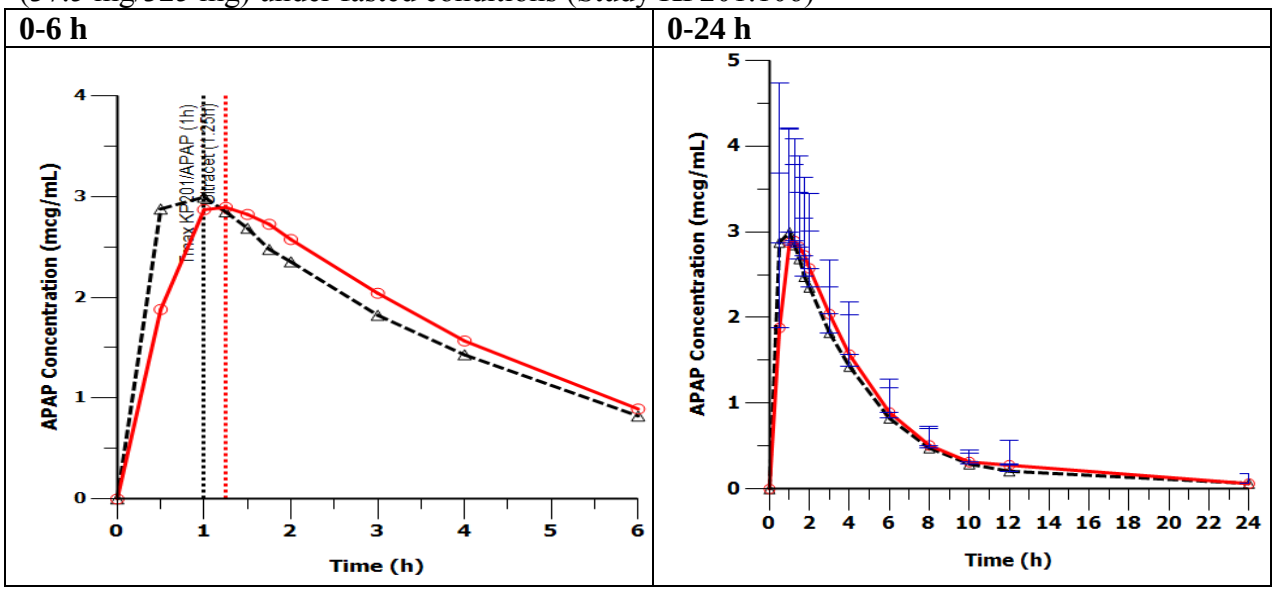
- KP201/APAP: Batch- 3111388, Expiration Date: June 2015
- Ultracet: Lot- 14EG080, Expiration Date: April 2017

PK blood samples during each study period:

- At predose (time zero) and at 0.5, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 24.0 and 36.0 hours after dosing

The APAP concentration time profile over the dosing regimen (6 h) and for 0-24 h following administration of KP201/APAP tablets, 6.67 mg/325 mg and Ultracet tablets, 37.5 mg/325 under fasted conditions is shown in the Figure 2.2.2.a.

**Figure 2.2.2a:** The plasma APAP concentration-time profiles for 0-6h (mean) and 0-24 h (mean ± SD) following administration of KP201/APAP tablet (6.67 mg/325 mg) and Ultracet tablet (37.5 mg/325 mg) under fasted conditions (Study KP201.106)




The Cmax and total exposure (AUCt and AUCinf) were similar for the APAP component between KP201/APAP and Ultracet tablet under fasted conditions. The APAP mean Cmax was

3.8 and 3.7 mcg/mL, respectively for KP201/APAP and Ultracet tablet, with a median Tmax of approximately 1 h for KP201/APAP and 1.25 h for Ultracet tablet. The mean elimination t1/2 of APAP was 5.3 and 4.5 hours for KP201/APAP and Ultracet, respectively. The descriptive statistics of APAP PK parameters are listed in the Table 2.2.2.a. below.

**Table 2.2.2.a.:** Descriptive statistics of APAP PK parameters following administration of KP201/APAP tablet and Ultracet under fasted conditions (Study KP201.106)

| | PK parameter | N | Mean | SD | %CV | Min | Max |
|---|---|---|---|---|---|---|---|
| **KP201/APAP Tablet (6.67/325)** | **AUCt (ng.hr/mL)** | **27** | 15.1 | 4.5 | 30 | 7.5 | 24.6 |
| | **AUCinf (ng.hr/mL)** | **25** | 15.5 | 4.6 | 30 | 7.9 | 24.9 |
| | **Cmax (ng/mL)** | **27** | 3.8 | 1.3 | 34 | 1.8 | 6.5 |
| | **Halflife (h)** | **25** | 5.3 | 1.9 | 35 | 2.6 | 11.3 |
| | **Tmax (h) Median (range)** | **27** | 1.0 (0.5-4.0) | | | | |
| | | | | | | | |
| **Ultracet Tablet (7.25/200)** | **AUCt (ng.hr/mL)** | **27** | 15.9 | 5.6 | 35 | 6.8 | 33.8 |
| | **AUCinf (ng.hr/mL)** | **25** | 15.7 | 4.5 | 29 | 7.1 | 24.6 |
| | **Cmax (ng/mL)** | **27** | 3.7 | 1.1 | 29 | 2.1 | 6.5 |
| | **Halflife (h)** | **25** | 4.5 | 1.1 | 24 | 2.6 | 6.9 |
| | **Tmax (h) Median (range)** | **27** | 1.25 (0.5-4.0) | | | | |

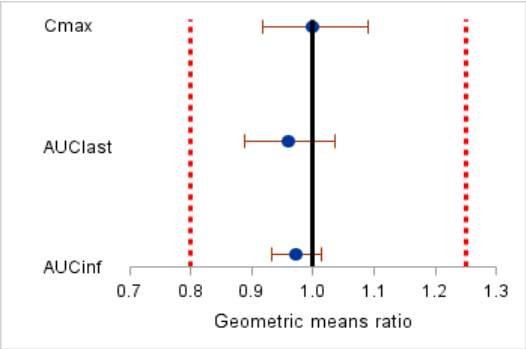
*Arithmetic mean ± standard deviation (N) except Tmax for which the median (range)

The statistical analysis show that Cmax, AUCt, AUCinf for APAP from KP201/APAP tablet, 6.67 mg/325 mg was bioequivalent to Ultracet tablet, 37.5 mg/325 mg as shown in the Table 2.2.2.b and Figure 2.2.2.b below.

**Table 2.2.2.b:** Statistical comparison of pharmacokinetic parameters for APAP after oral administration of single doses of KP201/APAP tablet, 6.67 mg/325 mg and Ultracet tablet, 37.5 mg/325 mg under fasted conditions (Study KP201.106)

| **Parameter** | **Geometric Mean** [a] | | **Geometric Mean Ratio [%]** | |
|---|---|---|---|---|
| | **Test** | **Reference** | **Estimate** | **90% Confidence Interval (Lower, Upper)** |
| **KP201/APAP, 6.67 mg/325 mg vs. Ultracet, 37.5 mg/325 mg** | | | | |
| Cmax | 3.60 | 3.60 | 99.99 | 91.73 , 108.98 |
| AUC0-t | 14.78 | 15.42 | 95.86 | 88.71 , 103.59 |
| AUCinf | 14.94 | 15.36 | 97.28 | 93.32 , 101.39 |

**Figure 2.2.2.b:** Ratios of geometric means and the 90% confidence intervals for APAP AUC and Cmax for KP201/APAP versus Ultracet under fasted conditions (Study KP201.106)




### 2.2.3. Are hydrocodone and APAP components of KP201/APAP tablet bioequivalent to hydrocodone and APAP components of Norco tablet (hydrocodone/APAP) under fasted conditions?

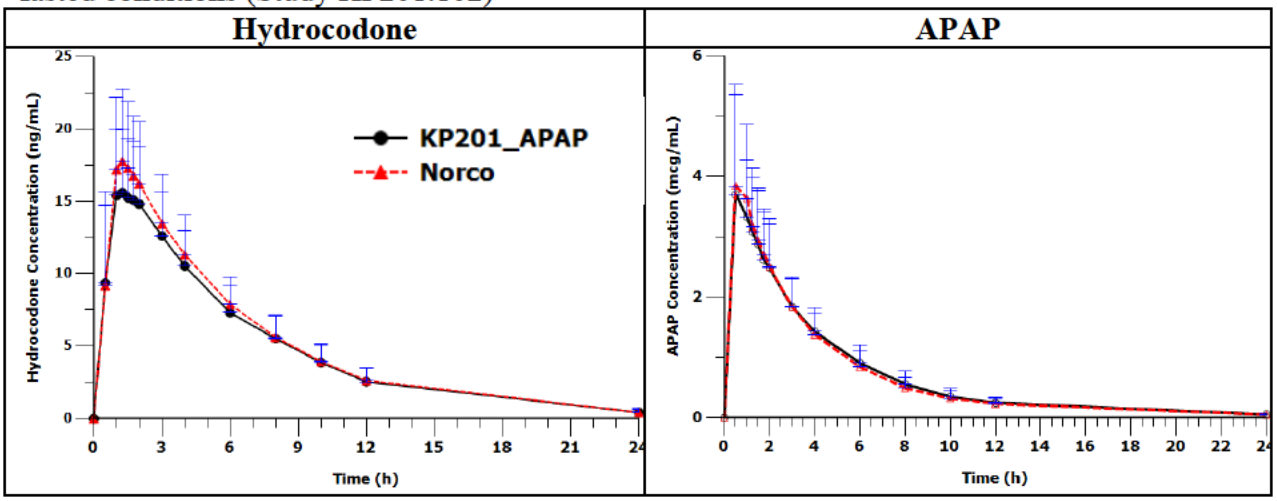
*Under fasting condition, the HC component of KP201/APAP tablet is bioequivalent to HC component of Norco and APAP component of KP201/APAP tablet has comparable PK to APAP component of Norco*

Sponsor has not conducted any clinical efficacy and safety studies with KP201/APAP tablet.
To support that KP201/APAP is not a novel combination, sponsor established bioequivalence of hydrocodone and APAP from the proposed KP201/APAP tablet, 6.67 mg/325 mg with the Norco tablet, 7.5 mg/325 mg (hydrocodone /APAP) under fasting condition in the study KP201.102.

This study was an open-label, single-dose, randomized, 2-treatment, 2-period, 2-sequence, crossover bioequivalence study in 23 subjects. In a random fashion, subjects received 2 single-dose treatments. Each treatment was separated by a 7-day washout period. All study doses were administered after a standard overnight fast (approximately 10 hours). The primary objective of this study was to compare the rate and extent of absorption of hydrocodone and APAP from a single dose of KP201/APAP relative to a single dose of Norco, 7.5 mg hydrocodone/325 mg acetaminophen, when administered orally under fasted conditions.

The mean ± SD hydrocodone and APAP plasma concentrations vs time by treatment is presented in Figure 2.2.3.a.

**Figure 2.2.3.a.** Mean ± SD plasma hydrocodone and APAP concentration-time profile (0-24 h) following administration of single doses of KP201/APAP and Norco to healthy subjects under fasted conditions (Study KP201.102)




**Hydrocodone**

Pharmacokinetic parameters for hydrocodone after administration of KP201/APAP or Norco are summarized in Table 2.2.3.a.

**Table 2.2.3.a:** Summary of pharmacokinetic parameters for hydrocodone after oral administration of single doses of KP201/APAP and Norco to healthy subjects under fasted conditions (Study KP201.102)

| **Parameter** [a] | **KP201/APAP, 6.67 mg/325 mg** | **Norco, 7.5 mg/325 mg** |
|---|---|---|
| Cmax (ng/mL) | 16.86 ± 4.15 (23) | 19.38 ± 4.89 (23) |
| Tmax (h) | 1.25 (23) [0.50–3.00] | 1.25 (23) [0.50–2.00] |
| AUC0-t (h×ng/mL) | 112.09 ± 28.77 (23) | 119.01 ± 31.37 (23) |
| AUCinf (h×ng/mL) | 115.77 ± 29.10 (23) | 122.91 ± 31.32 (23) |
| t½ (h) | 4.21 ± 0.57 (23) | 4.14 ± 0.61 (23) |

a Arithmetic mean ± standard deviation (N) except Tmax for which the median (N) [Range] is reported.

A statistical comparison of pharmacokinetic parameters for hydrocodone after administration of KP201/APAP or Norco is presented in Table 2.2.3.b. Geometric means ratios for Cmax, AUC0-t, and AUCinf were 86.79%, 94.17%, and 94.05%, respectively. The associated 90% confidence intervals (CI) for all 3 parameters were contained within 80% to 125%, meeting bioequivalence criteria with respect to hydrocodone.

**Table 2.2.3.b:** Statistical comparison of pharmacokinetic parameters for hydrocodone after oral administration of single doses of KP201/APAP and Norco to healthy subjects under fasted conditions (Study KP201.102)

| **Parameter** | **Geometric Mean [a]** | | **Geometric Mean Ratio [%]** | |
|---|---|---|---|---|
| | **Test** | **Reference** | **Estimate** | **90% Confidence Interval (Lower, Upper)** |
| **KP201/APAP, 6.67 mg/325 mg vs. Norco, 7.5 mg/325 mg** | | | | |
| Cmax | 16.27 | 18.75 | 86.79 | 81.38 , 92.56 |
| AUC0-t | 108.01 | 114.70 | 94.17 | 89.99 , 98.54 |
| AUCinf | 111.76 | 118.83 | 94.05 | 90.32 , 97.94 |

[a]Least squares geometric means, based on the analysis of natural log-transformed data.

**APAP**

Pharmacokinetic parameters for APAP after administration of KP201/APAP or Norco are summarized in Table 2.2.3.c.

**Table 2.2.3.c:** Summary of pharmacokinetic parameters for APAP after oral administration of single doses of KP201/APAP and Norco to healthy subjects under fasted conditions (Study KP201.102)

| **Parameter [a]** | **KP201/APAP, 6.67 mg/325 mg** | **Norco, 7.5 mg/325 mg** |
|---|---|---|
| Cmax (µg/mL) | 4.07 ± 1.32 (23) | 4.43 ± 1.41 (23) |
| Tmax (h) | 0.50 (23) [0.50–2.00] | 0.50 (23) [0.50–2.00] |
| AUC0-t (h×µg/mL) | 16.4 ± 3.99 (23) | 16.1 ± 3.68 (23) |
| AUCinf (h×µg/mL) | 17.2 ± 3.70 (22) | 17.3 ± 3.06 (21) |
| t½ (h) | 4.93 ± 0.98 (22) | 5.11 ± 1.19 (21) |

[a]Arithmetic mean ± standard deviation (N) except Tmax for which the median (N) [Range] is reported.

A statistical comparison of pharmacokinetic parameters for APAP after administration of KP201/APAP or Norco is presented in Table 2.2.3.d below. Geometric means ratios for APAP Cmax, AUC0-t, and AUCinf were 90.76%, 101.15%, and 100.76%, respectively. The associated 90% CIs for both AUCs were contained within 80% to 125%. For Cmax, the lower limit of the 90% CI was 79.81%, slightly under the 80% limit. Given that the purpose of the relative bioavailability study with Norco was to demonstrate that KP201/APAP is not a novel drug-drug combination, this is unlikely to have clinical impact on efficacy and safety of KP201/APAP.

**Table 2.2.3.d.:** Statistical comparison of pharmacokinetic parameters for APAP after oral administration of single doses of KP201/APAP and Norco to healthy subjects under fasted conditions (Study KP201.102)

| Parameter | Geometric Mean [a] | | Geometric Mean Ratio [%] | |
|---|---|---|---|---|
| | Test | Reference | Estimate | 90% Confidence Interval (Lower, Upper) |
| **KP201/APAP, 6.67 mg/325 mg vs. Norco, 7.5 mg/325 mg** | | | | |
| Cmax | 3.79 | 4.18 | 90.76 | 79.81 , 103.20 |
| AUC0-t | 15.82 | 15.64 | 101.15 | 98.08 , 104.32 |
| AUCinf | 16.76 | 16.63 | 100.76 | 97.66 , 103.96 |

[a] Least squares geometric means, based on the analysis of natural log-transformed data.

## 2.3. EXTRINSIC FACTORS

**What is relative bioavailability of KP201/APAP Compared to Norco under Fed Conditions and effect of food on the bioavailability of KP201/APAP?**

Study KP201.104 evaluated the effect of food on the bioavailability and pharmacokinetics of hydrocodone and APAP from KP201/APAP, and the relative bioavailability of KP201/APAP and Norco under fed conditions in healthy volunteer. Eligible subjects received the following 3 treatments:

| | |
|---|---|
| Treatment A: | KP201/APAP, 1 x 6.67 mg/325 mg tablet with 240 mL of water under fed conditions* |
| Treatment B: | KP201/APAP, 1 x 6.67 mg/325 mg tablet with 240 mL of water under fasted conditions [$]. |
| Treatment C: | Norco Tablets, 1 x 7.5 mg/325 mg tablet under fed conditions* |

*Treatments A and C were administered after subjects had completed an overnight fast for at least 10 hours, followed by an FDA standard high-calorie, high-fat breakfast meal. The FDA standard high-calorie, high-fat breakfast meal was to be consumed in its entirety within 30 minutes of being served. Treatments A and C were administered within 5 minutes of completing the standard high-calorie, high-fat breakfast meal

[$]Fasted doses were administered after a standard overnight fast (approximately 10 hours)

**Analysis population:**

- Total of 42 subjects were enrolled. 38 subjects completed all 3 periods, 2 subjects, (b) (6) completed 2 of the 3 periods, and 2 subjects, (b) (6) completed only 1 period. Subjects completing only 1 period (b) (6) were excluded from the descriptive statistics and statistical analyses.
- One (1) subject, (b) (6) was excluded from the descriptive statistics and statistical analyses for APAP for Treatment A (KP201/APAP fed) due to a pre-dose plasma concentration that was greater than the lower limit of quantitation (LOQ) and greater than 5% of the associated Cmax.
- The pharmacokinetic (PK) analysis population was comprised of 40 subjects for Treatment A (39 for APAP), 38 subjects for Treatment B, and 40 subjects for Treatment C.

**Lot and Formulation Identification:**

- KP201/APAP: Batch: 3111387 Manufacture Date: 06/2013
- Norco: Lot: 646877A Expiration Date: 12/2014

**PK blood samples during each study period:**

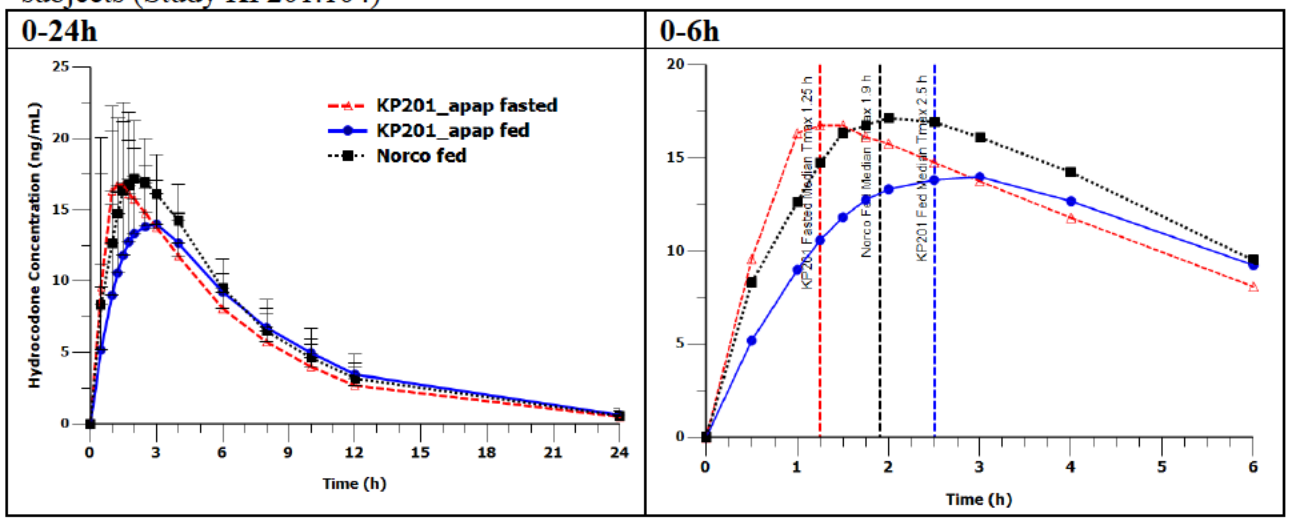
- At predose (time zero) and at 0.5, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, and 24.0 hours after dosing

KP201: The plasma concentrations of the prodrug, KP201 were below LOQ (25 pg/mL)

**Hydrocodone:**

The proposed dosing regimen for KP201/APAP is 4-6 h as needed for pain, which is similar to the approved dosing regimen for Norco, every 4 to 6 hours as needed for pain. The mean ± SD plasma hydrocodone concentration-time profile for 0-24h and mean plasma hydrocodone concentration-time profile over the typical dosing regimen (6 h), with median Tmax for KP201/APAP or Norco is presented in Figure 2.3a below.

**Figure 2.3a:** Mean ± SD plasma hydrocodone concentration-time profile for 0-24h (left) and mean concentration-time profile 0-6h (right) following administration of single doses of KP201/APAP under fasted and fed conditions and Norco under fed conditions to healthy subjects (Study KP201.104)




The pharmacokinetic parameters for hydrocodone after administration of KP201/APAP or Norco are summarized in Table 2.3a below.

**Table 2.3a:** Summary of pharmacokinetic parameters for hydrocodone after oral administration of single doses of KP201/APAP under fed and fasted conditions and Norco under fed conditions to healthy subjects (Study KP201.104)

| **Parameter** [a] | **KP201/APAP, 6.67 mg/325 mg** | | **Norco, 7.5 mg/325 mg** |
|---|---|---|---|
| | **Fed** | **Fasted** | **Fed** |
| Cmax (ng/mL) | 16.04 ± 3.60 (40) | 19.18 ± 4.84 (38) | 20.95 ± 7.65 (40) |
| Tmax (h) | 2.50 (40) [0.50–4.00] | 1.25 (38) [0.50–3.00] | 1.90 (40) [0.50–4.00] |
| AUC0-t (h×ng/mL) | 125.80 ± 26.90 (40) | 121.40 ± 35.18 (38) | 135.37 ± 30.30 (40) |
| AUCinf (h×ng/mL) | 130.91 ± 29.45 (40) | 125.73 ± 36.78 (38) | 140.17 ± 31.66 (40) |
| t½ (h) | 4.53 ± 0.70 (40) | 4.33 ± 0.67 (38) | 4.36 ± 0.68 (40) |

[a] Arithmetic mean ± standard deviation (N) except Tmax for which the median (N) [Range] is reported.

A statistical comparison of pharmacokinetic parameters for hydrocodone is presented in Table 2.3b below.

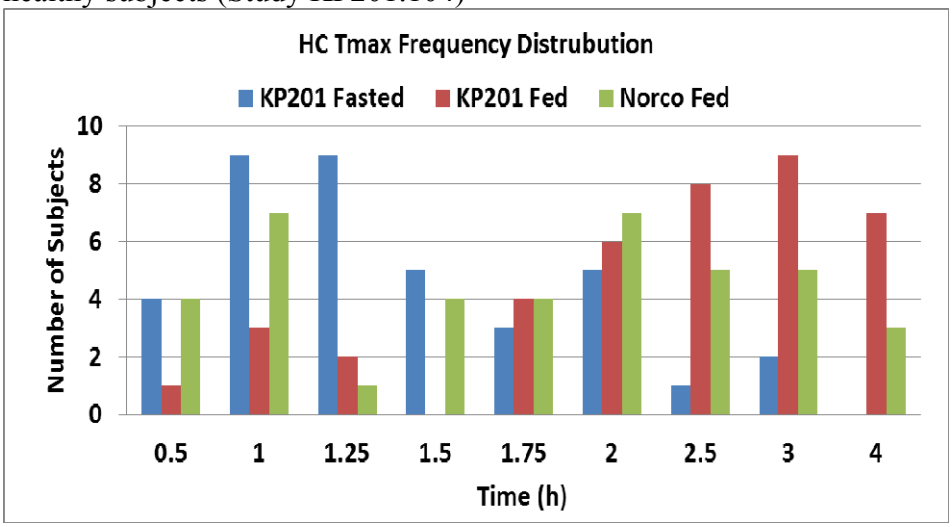
**Table 2.3b:** Statistical comparison of pharmacokinetic parameters for hydrocodone after oral administration of single doses of KP201/APAP under fed and fasted conditions and Norco under fed conditions to healthy subjects (Study KP201.104)

| **Parameter** | **Geometric Mean [a]** | | **Geometric Mean Ratio [%]** | |
|---|---|---|---|---|
| | **Test** | **Reference** | **Estimate** | **90% Confidence Interval (Lower, Upper)** |
| **KP201/APAP, 6.67 mg/325 mg, Fed (test) vs. Fasted (reference)** | | | | |
| Cmax | 15.70 | 18.40 | 85.31 | 79.40, 91.65 |
| AUC0-t | 122.85 | 115.80 | 106.09 | 101.00 , 111.42 |
| AUCinf | 127.66 | 120.00 | 106.39 | 101.62 , 111.38 |
| **KP201/APAP, 6.67 mg/325 mg, Fed (test) vs. Norco, 7.5 mg/325 mg, Fed (reference)** | | | | |
| Cmax | 15.70 | 20.03 | 78.36 | 73.04 , 84.06 |
| AUC0-t | 122.85 | 132.14 | 92.97 | 88.60 , 97.56 |
| AUCinf | 127.66 | 136.88 | 93.27 | 89.16 , 97.56 |

[a] Least squares geometric means, based on the analysis of natural log-transformed data.

The frequency histogram for Tmax of hydrocodone for KP201/APAP or Norco is presented in Figure 2.3b below.

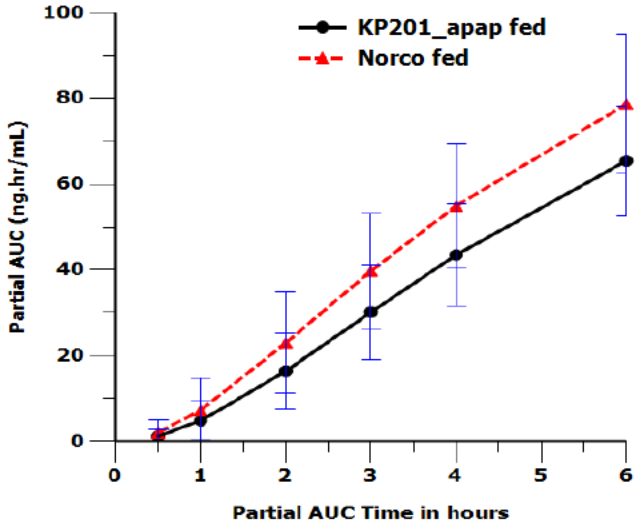
**Figure 2.3b:** Frequency histogram for hydrocodone Tmax following administration of single doses of KP201/APAP under fasted and fed conditions and Norco under fed conditions to healthy subjects (Study KP201.104)



**KP201/APAP Fed vs Fasted (hydrocodone):**
Administration of KP201/APAP under fed conditions resulted in 6% increase in AUC (geometric mean) and ~15% decrease in Cmax (geometric mean) compared to fasted conditions. The geometric means ratios for hydrocodone under fed conditions compared to fasted conditions for Cmax, AUC0-t, and AUCinf were 85.31%, 106.09% and 106.39%, respectively. The associated 90% CI for Cmax was 79.40% to 91.65%. The 90% CIs for AUC0-t, and AUCinf were contained within 80% to 125% range. Although the median Tmax is slightly delayed from 1.25 h to 2.5 under fed condition, it is still earlier compared to the 4-6 h dosing interval. In addition, the Tmax range under fed condition is within the minimum recommended dosing interval of 4 hours.

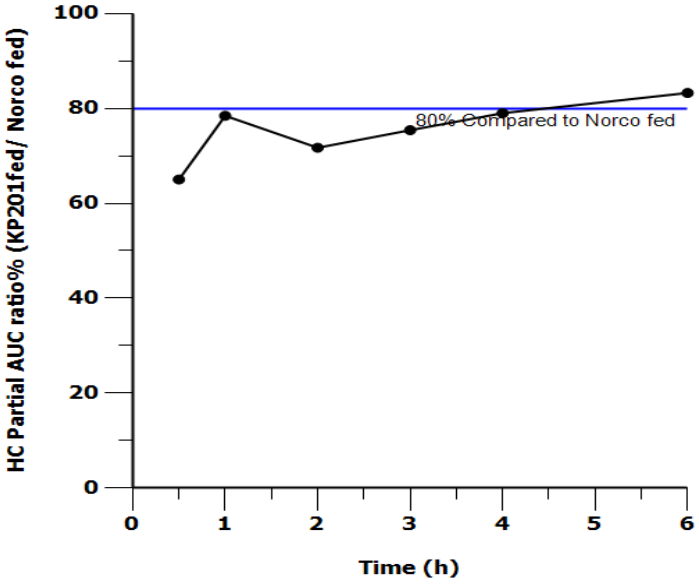
**KP201/APAP Fed vs Norco Fed (hydrocodone):**
Dosing KP201/APAP and Norco in the fed state led to median hydrocodone Tmax of 2.5 and 1.9 hours, respectively. The Tmax ranges were identical, within the minimum recommended dosing interval of 4 hours (0.5 to 4 hours for both products). While the hydrocodone Cmax for KP201/APAP under fed condition is 78% compared to Norco, the overall exposure to hydrocodone (AUClast and AUCinf) was within the 80% to 125% range. When hydrocodone partial AUCs in a typical dosing interval (4 to 6 hours) are compared for KP201/APAP fed and Norco fed, the data demonstrated a slight decrease in hydrocodone partial exposure for KP201/APAP compared to Norco. However, numerically it is not much lower and the standard deviations in hydrocodone partial AUCs overlapped between two treatments. The data are shown in Figure 2.3c below.

**Figure 2.3c:** Hydrocodone partial AUC (SD) for KP201/APAP Vs. Norco under fed conditions at different time points.




The partial AUC ratios of KP201/APAP under fed conditions range from 65 to 83% compared to Norco fed at different time points (0.5 h to 6 h) in a typical dosing interval (6 hours), which is shown in Figure 2.3d below.

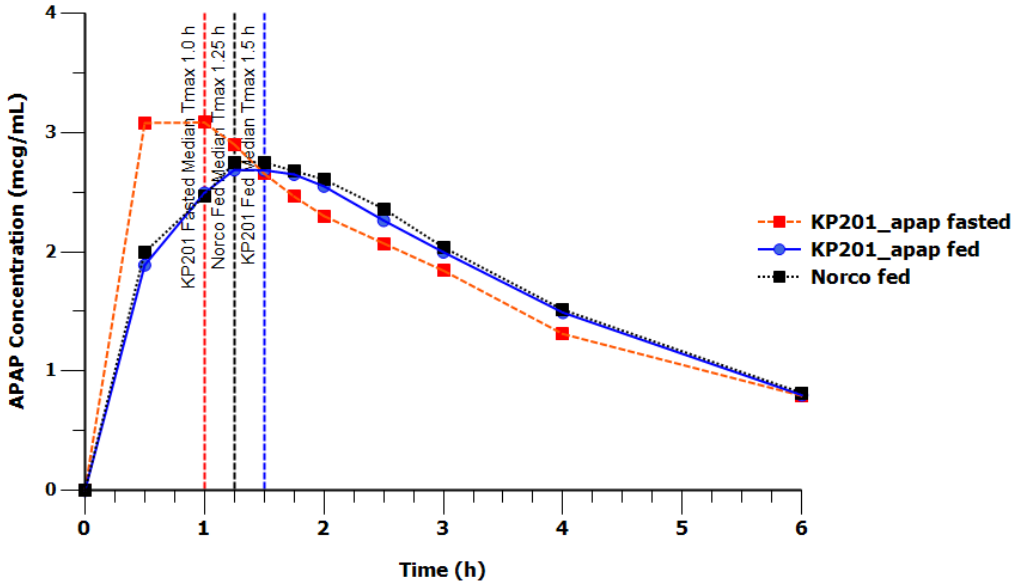
**Figure 2.3d:** Hydrocodone partial AUC ratios (KP201/APAP fed/ Norco fed) at different time points (0.5 h to 6 h) in a typical dosing interval (6 hours)




**APAP**

The mean plasma APAP concentration-time profile over the typical dosing regimen, (6 h) with median Tmax representation for KP201/APAP under fasted and fed conditions and Norco under fed conditions is presented in Figure 2.3e below.

**Figure 2.3e:** Mean plasma APAP concentration-time profile (0-6h) following administration of single dose of KP201/APAP under fasted and fed conditions and Norco under fed conditions to healthy subjects (Study KP201.104)



The pharmacokinetic parameters for APAP after administration of KP201/APAP or Norco are summarized in Table 2.3cbelow.

**Table 2.3c:** Summary of pharmacokinetic parameters for APAP after oral administration of single dose of KP201/APAP under fed and fasted conditions and Norco under fed conditions to healthy subjects (Study KP201.104)

| **Parameter** [a] | **KP201/APAP, 6.67 mg/325 mg** | | **Norco, 7.5 mg/325 mg** |
|---|---|---|---|
| | **Fed** | **Fasted** | **Fed** |
| Cmax (µg/mL) | 3.34 ± 1.01 (39) | 4.05 ± 1.30 (38) | 3.52 ± 1.20 (40) |
| Tmax (h) | 1.50 (39) [0.50–4.00] | 1.00 (38) [0.50–3.00] | 1.25 (40) [0.50–3.00] |
| AUC0-t (h×µg/mL) | 14.5 ± 3.41 (39) | 14.6 ± 4.42 (38) | 14.8 ± 3.34 (40) |
| AUCinf (h×µg/mL) | 15.0 ± 3.53 (36) | 14.7 ± 3.87 (36) | 15.3 ± 3.45 (40) |
| t½ (h) | 5.64 ± 1.58 (36) | 4.78 ± 1.30 (36) | 5.54 ± 1.47 (40) |

[a] Arithmetic mean ± standard deviation (N) except Tmax for which the median (N) [Range] is reported.

A statistical comparison of pharmacokinetic parameters for hydrocodone after administration of KP201/APAP under fed or fasted conditions or Norco under fed condition is presented in Table 2.3d below.

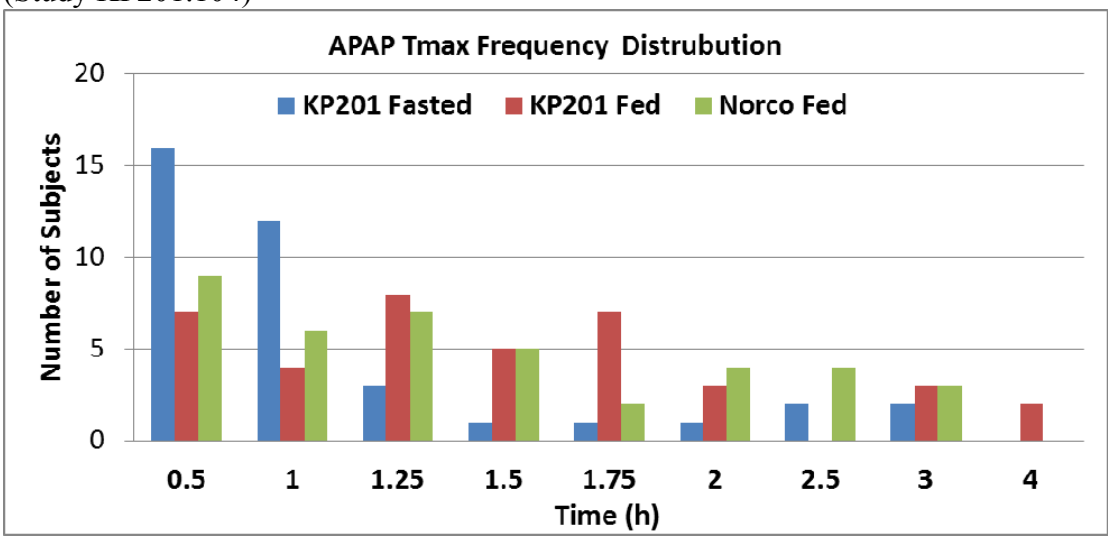
**Table 2.3d:** Statistical comparison of pharmacokinetic parameters for APAP after oral administration of single doses of KP201/APAP under fed and fasted conditions and Norco under fed condition to healthy subjects (Study KP201.104)

| **Parameter** | **Geometric Mean** [a] | | **Geometric Mean Ratio [%]** | |
|---|---|---|---|---|
| | **Test** | **Reference** | **Estimate** | **90% Confidence Interval (Lower, Upper)** |
| **KP201/APAP, 6.67 mg/325 mg, Fed vs. Fasted** | | | | |
| Cmax | 3.23 | 3.83 | 84.43 | 76.64 , 93.01 |
| AUC0-t | 14.33 | 14.00 | 102.35 | 97.46 , 107.49 |
| AUCinf | 14.84 | 14.09 | 105.36 | 101.30, 109.58 |
| **KP201/APAP, 6.67 mg/325 mg, Fed vs. Norco, 7.5 mg/325 mg, Fed** | | | | |
| Cmax | 3.23 | 3.34 | 96.77 | 88.00 , 106.40 |
| AUC0-t | 14.33 | 14.46 | 99.12 | 94.47 , 103.99 |
| AUCinf | 14.84 | 14.95 | 99.31 | 95.60 , 103.17 |

[a] Least squares geometric means, based on the analysis of natural log-transformed data.

The frequency histogram for Tmax for KP201/APAP under fasted and fed conditions and Norco under fed conditions is presented Figure 2.3f below.

**Figure 2.3f** Frequency histogram for APAP Tmax following administration of single dose of KP201/APAP under fasted and fed conditions and Norco under fed condition to healthy subjects (Study KP201.104)




Administration of KP201/APAP under fed condition resulted in slight delay in Tmax of APAP compared to KP201/APAP under fasted condition. However, KP201/APAP under fed condition demonstrated comparable Tmax, and equivalent AUC and Cmax for APAP compared to Norco under fed condition.

**Conclusions on Food effect:**
Norco can be administered without regard to food. Although KP201/APAP showed slightly delay in Tmax for both hydrocodone and APAP under fed condition compared to fasted condition, its PK profiles and parameters under fed condition are similar to those of Norco under fed condition. In addition, by evaluating the individual PK profiles, no significant delay of absorption were identified for KP201/APAP under fed condition. Based on totality of the data, food effect study results support the conclusion that KP201/APAP may be administered without regard to food.

**2.4. What are the single dose and multiple dose PK parameters of KP201/APAP?**

Single and multiple-dose PK of KP201/APAP tablets was evaluated in the study KP201.103 in 24 healthy volunteers under fasted conditions. Subjects received a single dose (Dose 1, Day 1) of KP201/APAP Tablets (2 × 6.67 mg/325 mg) to evaluate single-dose PK. Twenty-four hours after the first dose (Day 2), subjects entered the multi-dose portion of the study and received KP201/APAP Tablets [Dose 2 (at 24h) through Dose 14 (at 72h)] every 4 hours (13 doses). Subjects received a total of 14 doses (single and multiple dose portions) in a confined setting.

**Lot and Formulation Identification:**

- KP201/APAP: Batch: 3111386 Manufacture Date: 03.25//2013
- Norco: Lot: 646877A Expiration Date: 12/2014

**PK blood samples during each study period:**

- Day 1 PK after Dose 1: At predose (time zero) and at 0.5, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, and 24.0 hours after dosing
- Blood samples were collected prior to study drug administration on Day 2 (Dose 4 and Dose 6), and Day 3 (Dose 8, Dose 10, and Dose 12) for the determination of trough concentrations for each analyte.
- Day 4 PK after Dose 14: Postdose at 0.5, 1.0, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 10, 12, and 24 hours.

The mean ± SD plasma concentration-time profiles on Day 1 (single dose) and Day 4 (multiple-dose) for hydrocodone and APAP are shown in Figures 2.4a and 2.4b, respectively below.

**Figure 2.4a:** Mean ± SD plasma hydrocodone concentration-time profile following administration of of two KP201/APAP tablets on Day 1 followed by two KP201/APAP tablets Q4H × 13 doses (Days 2 to 4) to healthy subjects under fasted conditions (Study KP201.103)

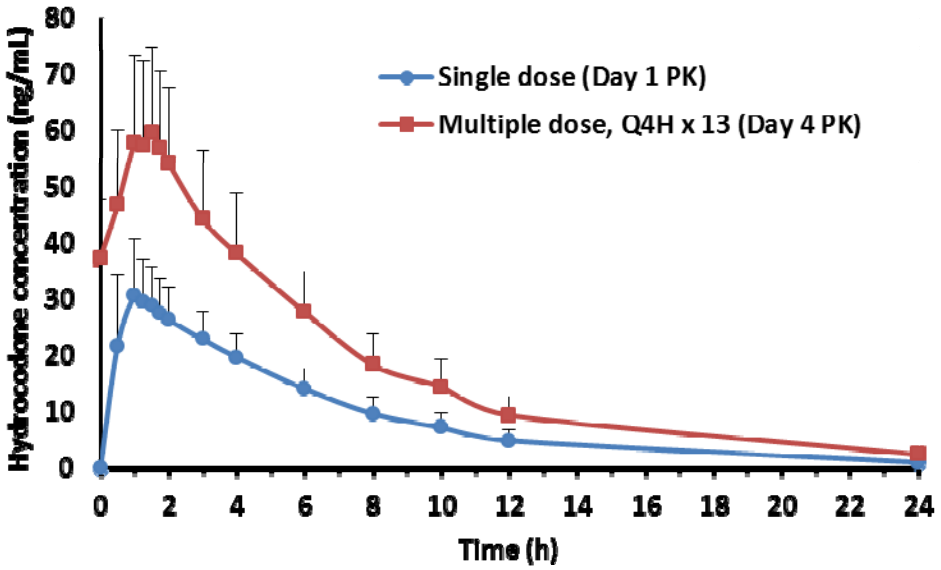
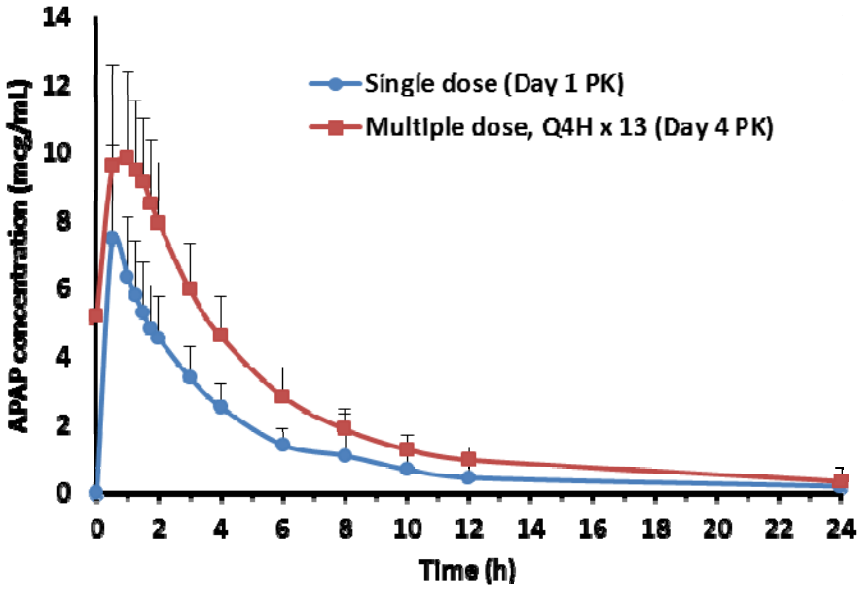


**Figure 2.4b:** Mean ± SD plasma APAP concentration-time profile following administration of two KP201/APAP tablets on Day 1 followed by two KP201/APAP tablets Q4H × 13 doses (Days 2 to 4) to healthy subjects under fasted conditions (Study KP201.103)




Pharmacokinetic parameters after administration of single and multiple doses of KP201/APAP are summarized for hydrocodone in Tables **2.4a** and for APAP in Table **2.4b**.

**Table 2.4a:** Summary of pharmacokinetic parameters for hydrocodone during oral administration of two KP201/APAP tablets on Day 1 followed by two KP201/APAP tablets Q4H × 13 doses (Days 2 to 4) to healthy subjects under fasted conditions (Study KP201.103)

| **Parameter** [a] | **Single dose, Day 1 PK** | **Multiple dose, Q4H × 13 doses (Days 2 to 4), Day 4 PK** |
|---|---|---|
| Cmax (ng/mL) | 33.95 ± 8.41 (24) | 62.79 ± 14.75 (24) |
| Tmax (h) | 1.00 (24) [0.50–4.00] | 1.25 (24) [0.50–2.00] |
| AUC0-4h (h×ng/mL) | 92.94 ± 20.16 (24) | 195.07 ± 47.66 (24) |
| AUCinf (h×ng/mL) | 219.36 ± 57.28 (24) | - |
| t½ (h) | 4.45 ± 0.59 (24) | 4.87 ± 0.63 (24) |

aArithmetic mean ± standard deviation (N) except Tmax for which the median (N) [Range] is reported.

**Table 2.4b:** Summary of pharmacokinetic parameters for APAP during oral administration of two KP201/APAP tablets on Day 1 followed by two KP201/APAP tablets Q4H × 13 doses (Days 2 to 4) to healthy subjects under fasted conditions (Study KP201.103)

| **Parameter** [a] | **Single dose, Day 1 PK** | **Multiple dose, Q4H × 13 doses (Days 2 to 4), Day 4 PK** |
|---|---|---|
| Cmax (µg/mL) | 7.95 ± 2.16 (24) | 11.0 ± 2.34 (24) |
| Tmax (h) | 0.50 (24) [0.50–3.00] | 1.00 (24) [0.50–1.50] |
| AUC0-4h (h×µg/mL) | 17.6 ± 4.25 (24) | 29.8 ± 6.19 (24) |
| AUCinf (h×µg/mL) | 28.9 ± 7.07 (23) | - |
| t½ (h) | 4.79 ± 1.21 (23) | 6.84 ± 2.42 (23) |

aArithmetic mean ± standard deviation (N) except Tmax for which the median (N) [Range] is reported.

Median Tmax for hydrocodone after multiple dosing of KP201/APAP is 1.25 h (range 0.5–2 h), and is comparable to median Tmax after single dose of 1 h (range 0.5–4 h). After multiple dosing, the steady-state for hydrocodone reached at approximately 24 hours after the initiation of multiple dosing. The accumulation ratio for hydrocodone Cmax, AUC0-4 and AUC0-t values (Day 4/Day1 or 14$^{th}$ dose/ 1$^{st}$ dose of KP201/APAP) were 1.85-fold, 2.10-fold and 2.03-fold, respectively. The half-life (mean ± SD) of hydrocodone after multiple dosing (4.87 ± 0.63h) is comparable to the half-life after single dose (4.45 ± 0.59).

Median Tmax for APAP after multiple dosing of KP201/APAP is 1 h (range 0.5–1.5 h), and is comparable to the median Tmax after single dose of 0.5 h (range 0.5–3 h). The steady-state for APAP reached approximately at 24-36 after the initiation of multiple dosing. The APAP accumulation ratio for Cmax, AUC0-4 and AUC0-t values (Day 4/Day1 or 14$^{th}$ dose/ 1$^{st}$ dose of KP201/APAP) were 1.38-fold, 1.69-fold and 1.80-fold, respectively. The mean ± SD half-life of APAP after KP201/APAP multiple dosing is slightly longer (6.84 ± 2.42 h) compared to the half-life after single dose (4.79 ± 1.21 h).

The plasma KP201 levels were not detectable after multiple dosing of KP201/APAP.

**2.5. What are the pharmacokinetics characteristics of KP201/APAP ER under abuse?**

Three human abuse liability studies were conducted for KP201/APAP. The KP201/APAP was administered orally in one study (study KP201.A01), and intra-nasally (IN) in the other two (study KP201.A02 and study KP201.A03). For these studies, the PK endpoints of KP201/APAP versus Norco were reviewed. With regards to the PD endpoints, including Emax for drug liking and high and its statistical significance, refer to Control Substance Staff review.

**2.5.1. Study KP201.A01 – Abuse liability study with oral administration**

This was a randomized, double-blind, placebo-controlled, single-dose, seven-way crossover study to determine the relative bioavailability, abuse potential, and safety of equivalent oral doses of KP201/APAP compared with hydrocodone/APAP (Norco) in opioid-experienced, non-dependent subjects.

- Treatment A: 12 placebo capsules

- Treatment B: 12 KP201/APAP 6.67 mg/325 mg tablets (over-encapsulated) (80.04 mg KP201/3,900 mg APAP)
- Treatment C: 4 placebo capsules + 8 KP201/APAP 6.67 mg/325 mg tablets (over-encapsulated) (53.36 mg/2,600 mg APAP)
- Treatment D: 8 placebo capsules + 4 KP201/APAP 6.67 mg/325 mg tablets (over-encapsulated) (26.68 mg/1,300 mg APAP)
- Treatment E: 12 hydrocodone/APAP 7.5 mg/325 mg tablets (over-encapsulated) (90 mg hydrocodone/3,900 mg APAP)
- Treatment F: 4 placebo capsules + 8 hydrocodone/APAP 7.5 mg/325 mg tablets (overencapsulated) (60 mg hydrocodone/2,600 mg APAP)
- Treatment G: 8 placebo capsules + 4 hydrocodone/APAP 7.5 mg/325 mg tablets (overencapsulated) (30 mg hydrocodone/1,300 mg APAP)

A summary of pharmacokinetic parameters of hydrocodone after administration of the highest doses of KP201/APAP or hydrocodone/APAP are presented in the Table 2.5.1 below.

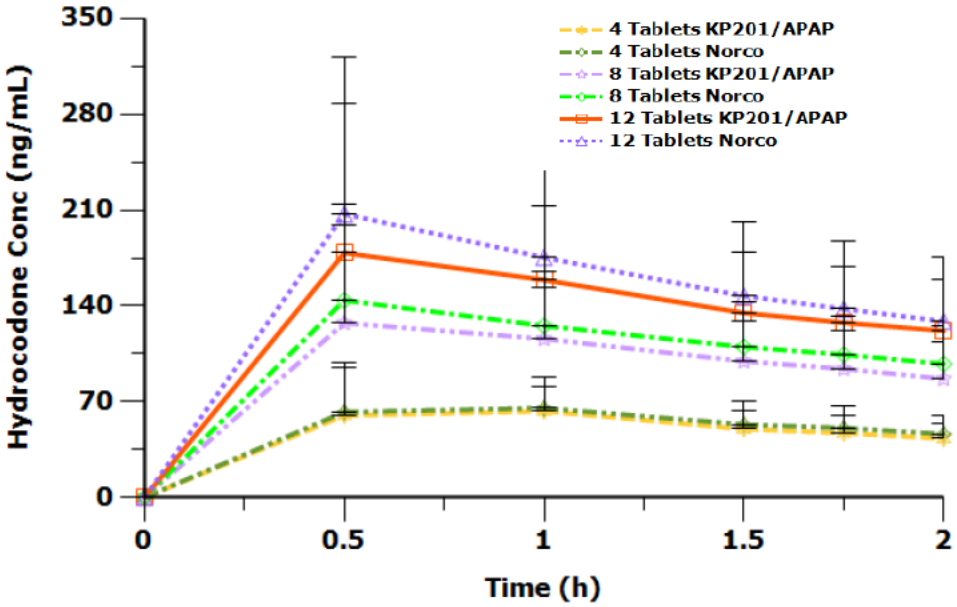
**Table 2.5.1** Summary of pharmacokinetic parameters of hydrocodone after administration of a high dose of either 12 KP201/APAP tablets or 12 Hydrocodone/APAP tablets (Study KP201.A01)

| **Parameter** [a] | **12 KP201/APAP 6.67 mg/325 mg Tablets (Treatment B)** | **12 Hydrocodone/APAP 7.5 mg/325 mg Tablets (Treatment E)** |
|---|---|---|
| Cmax (ng/mL) | 208 ± 87 (61) | 229 ± 95 (65) |
| Tmax (h) | 0.60 (0.60 - 4.12 h) (61) | 0.60 (0.60 - 6.12 h) (65) |
| AUC0-t (h×ng/mL) | 1218 ± 297 (61) | 1271 ± 302 (65) |
| AUCinf (h×ng/mL) | 1272 ± 327 (61) | 1310 ± 314 (65) |
| t½ (h) | 5.00 ± 1.79 (61) | 4.63 ± 0.75 (65) |

[a] Arithmetic mean ± standard deviation (N) expect Tmax where it is median (range) (N)

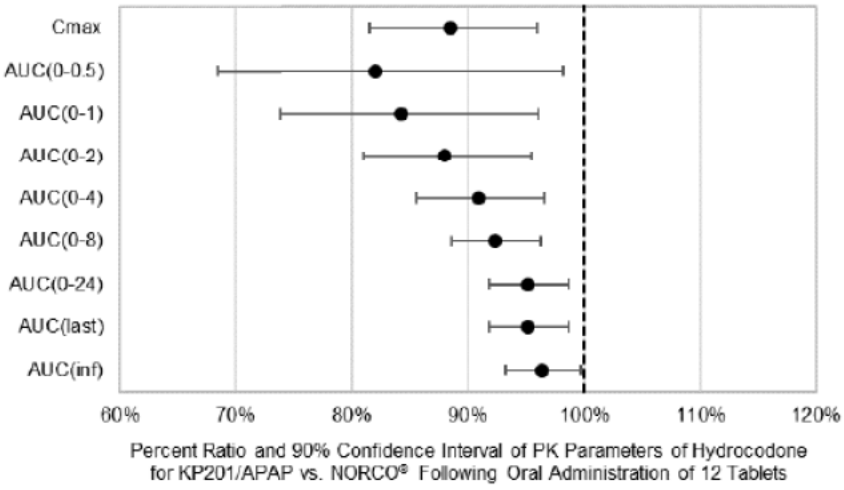
The administration of the 12-tablet dose KP201/APAP resulted in an approximately 11.5% reduction in Cmax and 15.8% and 12.0% reduction in early systemic exposure (AUC0-1 and AUC0-2) to hydrocodone compared to that following the 12-tablet dose of HB/APAP. The mean plasma hydrocodone concentration-time profiles following single oral doses of KP201/APAP is presented in the Figure 2.5.1a below.

**Figure 2.5.1a:** Mean plasma hydrocodone concentration-time profiles following single oral doses of KP201/APAP in opioid-experienced, non-dependent recreational users (KP201.A01):




The forest plot below (Figure 2.5.1b) shows the geometric mean ratios and 90% confidence intervals of the PK parameters of hydrocodone after oral administration.

**Figure 2.5.1b:** Forest plot of geometric mean ratios and 90% confidence intervals of the PK parameters of hydrocodone after oral administration of 12 tablets of KP201/APAP versus HB/APAP (Norco®) in opioid-experienced, non-dependent recreational users (KP201.A01)




In general, for orally administered drug products, bioequivalence can generally be demonstrated by measurements of peak (e.g. Cmax) and total exposure (e.g. AUClast and AUCinf). Usually the bioequivalence criteria are met if the 90% CIs of geometric means ratio for Cmax or AUC are within the 80% to 125% limits.

Under certain circumstances (e.g., to assess onset of an analgesic effect), an evaluation of the partial exposure (e.g. partial AUC) could be used to support the performance of different

formulations by providing further evidence of therapeutic effect. For partial areas, demonstration of bioequivalence based on the 80% to 125% limits is generally not a requirement for all time points in the plasma-concentration time curve. The partial areas are evaluated case by case, to determine whether the differences in partial areas between two products will translate to any clinical significance.

In study KP201.A01, the confidence intervals for partial AUC ratios of hydrocodone for KP201/APAP vs. Norco did not meet 80% limit for the lower bound at time points, 0 to 0.5h (AUC 0-0.5) and 0 to 1h (AUC 0-1). However, the mean ratios are not far away from 100%. The slight decrease in partial exposure from 0 to 0.5h and 0 to 1h should not be interpreted alone without drug liking measurements; it need to be translated to a clinically meaningful effect (e.g. drug liking score) for an abuse deterrent claim.

**2.5.2 Study KP201.A02 – Abuse Liability Study IN Administration Compared to Norco**

This was a randomized, double-blind, double-dummy, placebo-controlled, single-dose, two-part, five-way crossover study to determine the relative bioavailability, abuse potential, and safety of equivalent doses of crushed and intact KP201/APAP compared with hydrocodone/APAP or placebo in opioid-experienced, non-dependent subjects following IN administration. The first part of this study was a Dose Selection Phase (Part A) to identify the maximum tolerated dose of both KP201/APAP and the active comparator hydrocodone/APAP, in order to select a dose that was well tolerated and produced robust responses on pharmacodynamic measures for inclusion into the Main Study (Part B).

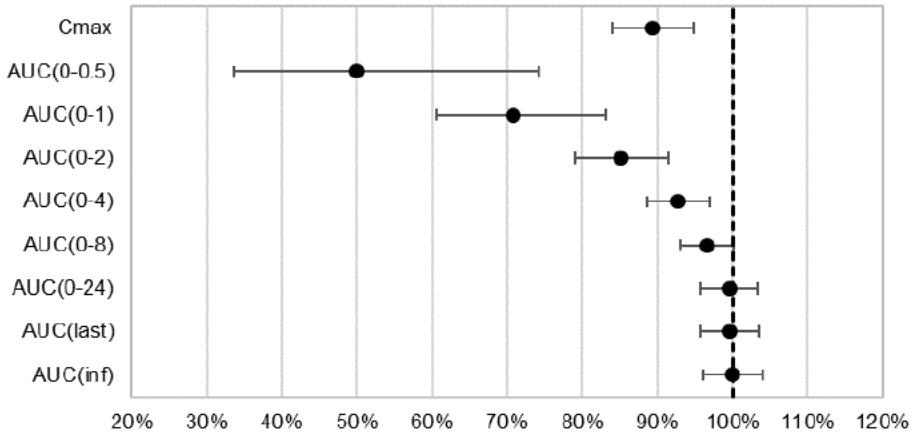
**Part A:**

KP201 is measureable in plasma following intranasal (IN) administration of the crushed product in human abuse liability studies. Mean Cmax and AUC values for KP201 increased with an increase in dose. The mean Cmax and AUCinf for KP201 ranged from 9.4 ± 2.8 ng/mL and 7.6 ± 2.4 h·ng/mL (KP201/APAP 6.67/325 mg, crushed) to 27.0 ± 25.7 ng/mL and 26.1± 20.6 h·ng/mL (KP201/APAP 26.68/1300 mg, crushed). The median Tmax range of KP201 was 0.46 to 0.73 hours post-dose. The T1/2 of KP201 was short, ranging from 1 to 1.48 hours.

**Part B**

For the IN crushed KP201/APAP compared to IN crushed HB/APAP, the hydrocodone Cmax was reduced by approximately 11% and the partial AUC for AUC0-0.5h, AUC0-1h, and AUC0-2h were reduced by 50%, 29% and 15%, respectively. The forest plot (Figure 2.5.2a) of geometric mean ratios and 90% confidence intervals of the PK parameters of hydrocodone after IN administration is shown in the Figure below. Although the partial exposure from 0 to 0.5h is numerically lower for IN crushed KP201/APAP compared to IN crushed HB/APAP, it needs to translate to a clinical significant effect (e.g. drug liking score) for an abuse deterrent claim.

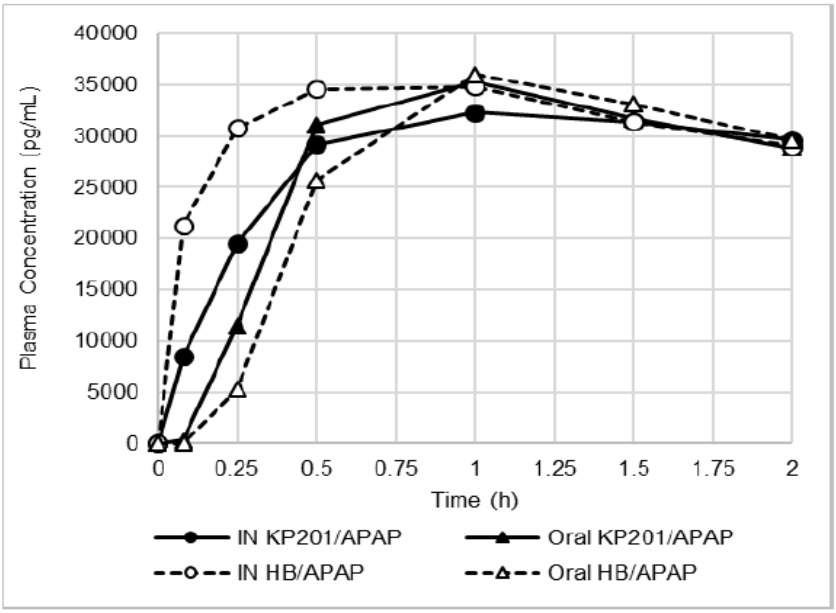
**Figure 2.5.2a:** Forest plot of geometric mean ratios and 90% confidence intervals of the PK parameters of hydrocodone after IN administration of KP201/APAP (13.34/650 mg) versus HB/APAP (15/650 mg) in opioid-experienced, non-dependent recreational users (KP201.A02)




Percent Ratio and 90% Confidence Interval of PK Parameters of Hydrocodone for KP201/APAP vs. NORCO® Following Intranasal Administration of 2 crushed Tablets

Compared to the 2-tablet oral dose of KP201/APAP, the partial AUC following IN crushed KP201/APAP was approximately 474% higher for AUC0-0.5h and 38% higher for AUC0-1h. At 2 hours postdose and later, hydrocodone exposure from the IN dose and the oral dose of KP201/APAP were bioequivalent. The PK profiles are shown in Figure 2.5.2b below.

**Figure 2.5.2b:** Hydrocodone plasma concentration-time profiles after IN and oral administration of KP201/APAP and HB/APAP (Study KP201.A02).




**2.5.3 Study KP201.A03 – Abuse Liability Study IN Administration of KP201 API (active pharmaceutical ingredient) Compared With Hydrocodone Bitartrate API**

This was a randomized, double-blind, single-dose, two-way crossover study to determine the relative bioavailability of equivalent doses of KP201 API, 13.34 mg, compared with

hydrocodone bitartrate API, 15.00 mg, in opioid experienced, non-dependent subjects, following IN administration.

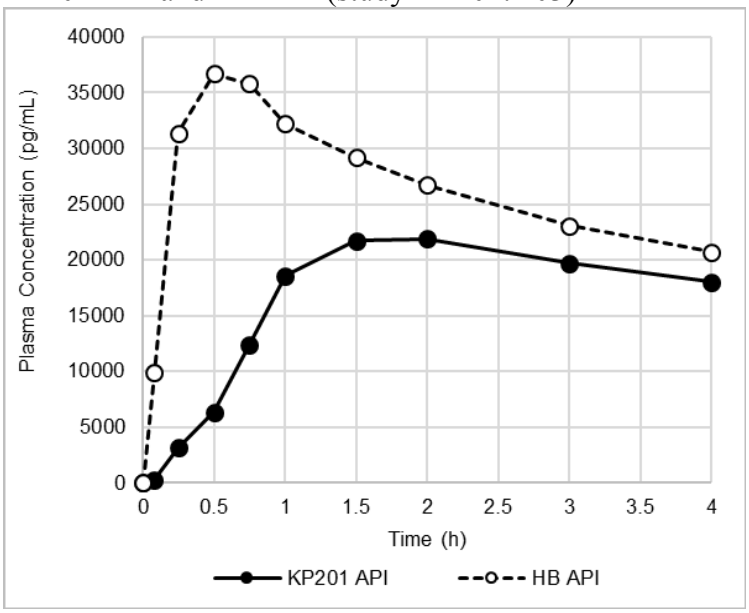
The mean (SD) Cmax for KP201 after IN administration of KP201 API 13.34 mg was 2.4 (1.9) ng/mL and mean (SD) t1/2 was 1.42 (0.59) hours. A summary of pharmacokinetic parameters for hydrocodone is presented in Table below.

**Table2.5.3:** Summary of pharmacokinetic parameters of hydrocodone (Study KP201.A03)

| **Parameter** | **Treatment A: KP201 API (13.34 mg) Administered IN** | | | | **Treatment B: Hydrocodone Bitartrate API (15.00 mg) Administered IN** | | | |
|---|---|---|---|---|---|---|---|---|
| | **n** | **Mean** | **SD** | **CV%** | **n** | **Mean** | **SD** | **CV%** |
| | | | | | | | | |
| **Cmax (ng/mL)** | 24 | 256.0 | 63.9 | 25 | 24 | 404.0 | 118.0 | 29 |
| **AUClast (h*ng/mL)** | 24 | 185.5 | 50.5 | 27 | 24 | 231.0 | 54.6 | 24 |
| **AUCinf (h*ng/mL)** | 24 | 194.7 | 55.7 | 29 | 24 | 239.4 | 58.4 | 24 |
| **t1/2 (h)** | 24 | 5.29 | 0.78 | 15 | 24 | 5.13 | 0.74 | 14 |
| **Tmax (h)** | 1.75 (0.75 -4.0) | | | | 0.5 (0.25 -2.02) | | | |

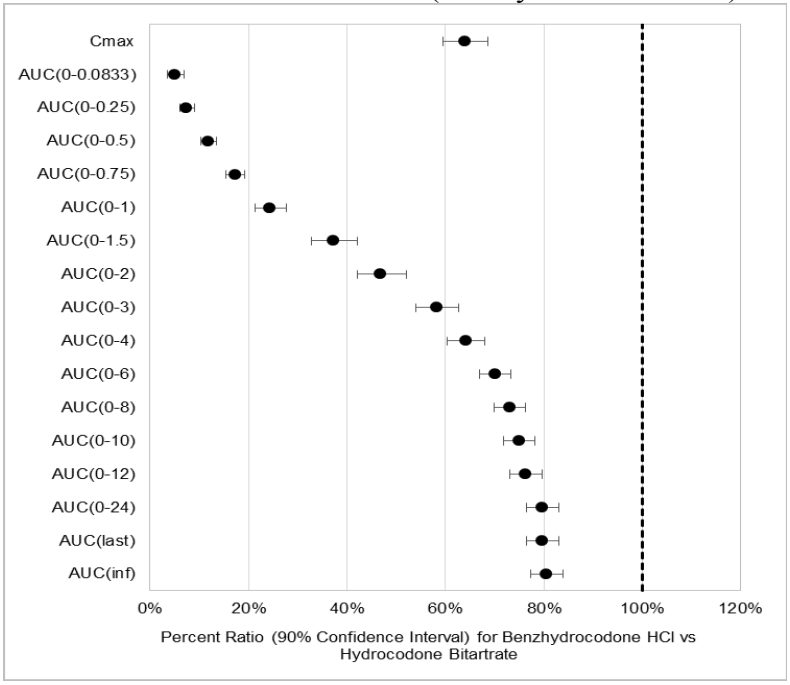
Hydrocodone plasma-concentration-time profiles for IN KP201 API and IN HB API are shown in Figure 2.5.3a below

**Figure 2.5.3a:** Hydrocodone plasma concentration-time profiles after IN administration of KP201 API and HB API (study KP201.A03)




The partial exposure (AUC0-0.0833h through AUC0-24h) parameters of hydrocodone following IN administration of KP201 API 13.34 mg results in an approximately 20%-95% compared to IN administration of hydrocodone bitartrate API 15.00 mg as shown in the Figure 2.5.3b below.

**Figure 2.5.3b:** Percent ratio and 90% CI of LSM ratios of PK parameters for hydrocodone after IN administration of KP201 API (benzhydrocodone HCl) vs HB API (hydrocodone bitartrate)




## 2.5.1. Pediatrics

KP201/APAP ER has an 'agreed upon' iPSP. The iPSP was discussed in the PERC meetings. The summary of planned pediatrics studies for KP201/APAP with age appropriate formulation for all age groups is as follows:

**Planned Pediatric Clinical Studies For KP201/APAP:**

| Age Group (Body Weight) | Type of Study | Study | Deferral Request Planned for the Study (Y/N) |
|---|---|---|---|
| 0 to <2 years (b) (4) | PK, safety and efficacy study | (b) (4) | Y |
| 2 to <7 years (b) (4) | Open-label PK and safety study | | Y |
| 7 to (b) (4) | Open-label PK and safety | | Y |

| | | | |
|---|---|---|---|
| (b) (4) ≤17 years (b) (4) | study | (b) (4) | |

**2.6 Analytical Section**

**2.6.1 Are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? What is the QC sample plan? What are the accuracy, precision and selectivity of the method?**

**Clinical Center:** Worldwide Clinical Trials Early Phase Services/ Bioanalytical Sciences, Inc. (WCT) Austin, Texas 78754

**Bio-analytical Facility:** (b) (4)

**OSI Inspection:**
The KP201.102 and KP201.104 studies of this application were requested for OSI inspection of the bioanalytical data (01/05/2016 DARRTS). The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below

**Rationale**
OSIS recently inspected the sites listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Requested Inspection Sites

| Facility Type | Facility Name | Facility Address |
|---|---|---|
| Clinical | Worldwide Clinical Trials Early Phase Services, LLC | 2455 N.E Loop 410, Suite 150 San Antonio, TX |
| Analytical | (b) (4) | |

**Bioanalytical method validation:**

**KP201:**
The plasma concentrations of KP201 analyzed using validated HPLC-MS/MS assay. The range of calibrators and QCs used for studies were:

- Calibrators: 25.0, 50.0, 100, 250, 1000, 2000, 4500, and 5000 pg/mL
- Quality controls: 75 , 500, and 4000 pg/mL
- LLOQ- 25 pg/mL

Accuracy and Precision over the range:

- Accuracy (expressed as % bias) : < ± 15% for all studies
- Precision (expressed as % CV) : < 15% for all studies

Internal standard: KP201-D5

**Hydrocodone:**

The plasma concentrations of hydrocodone analyzed using validated HPLC-MS/MS assay. The range of calibrators and QCs used for studies were:

- Calibrators: 250, 500, 1000,2500, 10,000, 20,000, 45000 and 50000 pg/mL
- Quality controls: 750, 5000, 40000 pg/mL
- LLOQ- 250 pg/mL

Accuracy and Precision over the range:

- Accuracy (expressed as % bias) : < ± 15% for all studies
- Precision (expressed as % CV) : < 15% for all studies

Internal standards: Hydrocodone-d6,

**Acetaminophen:**

The plasma concentrations of APAP analyzed using validated HPLC-MS/MS assay. The range of calibrators and QCs used for studies were:

- Calibrators: 0.0250, 0.0500, 0.250, 1.00, 2.50, 7.50, 13.5, and 15.0 µg/mL
- Quality controls: 0.075, 3.0, 12.0 µg/mL

Accuracy and Precision over the range:

- Accuracy (expressed as % bias) : < ± 15% for all studies
- Precision (expressed as % CV) : < 15% for all studies

Internal standards: Acetaminophen -$D_4$

**Stability:**

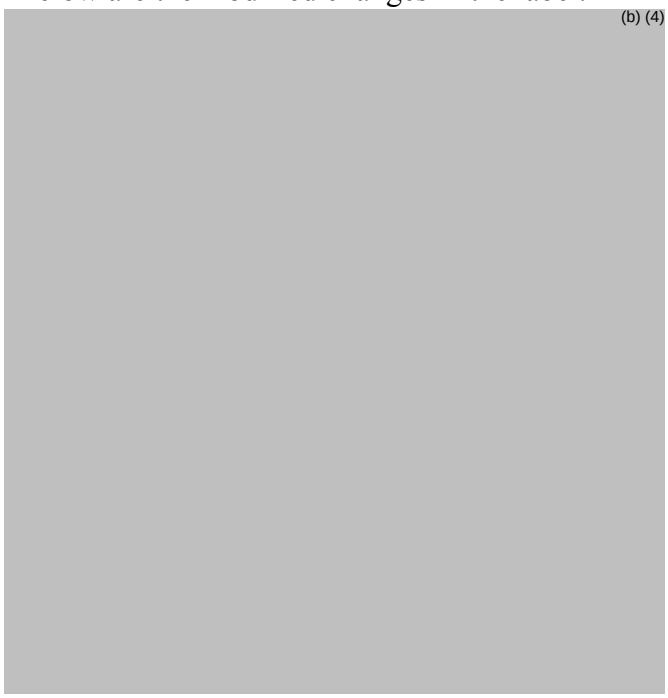
- Bench Top :
  - KP201 and hydrocodone: 26 h at 1°C
  - APAP: 25 h at 22°C
- Freeze thaw stability:
  - KP201 and Hydrocodone: 4 cycles at -20°C
  - APAP: 5 cycles
- Extract stability:
  - KP201 and Hydrocodone: 66 h at 4°C
  - APAP: 71 h at 22°C
- Long-term stability:
  - KP201 and Hydrocodone 75 days at -20 °C; 473 days at -20 °C human citric acid treated K2-EDTA plasm
  - APAP: 624 days at -20 °C
- Human plasma specimens were stored at -20°C until analysis and assayed within the following days of established stability data for each study:
  - KP201.103: 16 days (KP201, hydrocodone) and 14 days (APAP)
  - KP201.102: 19 days -KP201, hydrocodone and APAP
  - KP201.105: 17 days- KP201, 23 days-hydrocodone

- KP201.106: 12 days- KP201, 16 days- hydrocodone and 38 days- APAP
- KP201.106: 31 days- KP201 and hydrocodone and 38 days- APAP
- KP201.A01: 116 days- KP201, 184 days- hydrocodone and 130 days- APAP
- KP201.A02: KP201 hydrocodone and APAP 298 days

## 3.0 LABELING COMMENTS

The labelling comments have been made to the following sections in the Label:

Below are the modified changes in the label.



## 7 DRUG INTERACTIONS

Table 1 includes clinically significant drug interactions with APADAZ.

Table 1. Clinically Significant Drug Internactions with APADAZ

| | |
|---|---|
| **CYP3A4 and 2D6 Inhibitors** | |
| *Clinical Impact:* | The concomitant use of APADAZ and CYP3A4 inhibitors can increase the plasma concentration of hydrocodone, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of APADAZ and CYP2D6 and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of APADAZ is achieved *[see Warnings and Precautions (5.4)]*.<br>After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the hydrocodone plasma concentration will decrease *[see Clinical Pharmacology (12.3)]*, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to hydrocodone. |
| *Intervention:* | If concomitant use is necessary, consider dosage reduction of APADAZ until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals.<br>If a CYP3A4 inhibitor is discontinued, consider increasing the APADAZ dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. |
| *Examples:* | Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketokonizole), protease inhibitors (e.g., ritonavir) etc. |
| **CYP3A4 Inducers** | |
| *Clinical Impact:* | The concomitant use of APADAZ and CYP3A4 inducers can decrease the plasma concentration of hydrocodone *[see Clinical Pharmacology (12.3)]*, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to hydrocodone] *[see Warnings and Precautions (5.X)]*.<br>After stopping a CYP3A4 inducer, as the effects of the inducer decline, the hydrocodone plasma concentration will increase *[see Clinical Pharmacology (12.3)]*, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression. |
| *Intervention:* | If concomitant use is necessary, consider increasing the APADAZ dosage until stable drug effects are achieved *[see Dosage and Administration (2.X)]*. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider APADAZ dosage reduction and monitor for signs of respiratory depression. |
| *Examples:* | Rifampin, carbamazepine, phenytoin etc. |

### 8.6 Renal Impairment

The effect of renal impairment on the pharmacokinetics of the APADAZ has not been determined. Patients with renal impairment may have higher plasma concentrations than those with normal function. Use a low initial dose of APADAZ in patients with renal impairment and monitor closely for adverse events such as respiratory depression.

(b) (4)

## 8.7 Hepatic impairment

(b) (4)

(b) (4) The effect of hepatic impairment on the pharmacokinetics of the APADAZ has not been determined. Patients with hepatic impairment may have higher plasma concentrations than those with normal function. Use a low initial dose of APADAZ in patients with hepatic impairment or active liver disease and monitor closely for adverse events such as respiratory depression and hepatotoxicity *[see Warnings and Precautions (5.7)]*.

(b) (4)

(b) (4)

**12.3 Pharmacokinetics**

APADAZ has met the bioequivalence criteria for hydrocodone AUC and Cmax to other immediate-release hydrocodone combination products. Benzhydrocodone was not detectable in plasma after oral administration in clinical studies, indicating that exposure to benzhydrocodone was minimal and transient. Steady state with APADAZ is attained within 24 to 36 hours of dosing. The systemic exposure to hydrocodone from APADAZ increases linearly after administration of single and multiple doses of 2 tablets of APADAZ.

Absorption

*Single–Dose Studies*

In 2 comparative bioavailability studies following oral administration of single dose to healthy subjects under fasted conditions, 6.67 mg/325 mg APADAZ tablet met the bioequivalence criteria for hydrocodone AUC and Cmax to immediate-release tablet of 7.5 mg hydrocodone/200 mg ibuprofen (N = 28), and the bioequivalence criteria for acetaminophen AUC and Cmax to immediate-release tablet of 37.5 mg tramadol/325 mg acetaminophen (N = 27).

In a comparative bioavailability study following oral administration of single dose under fasted conditions in 24 healthy subjects comaparing 6.67 mg/325 mg APADAZ to immediate-release tablet of 7.5 mg hydrocodone/325 mg acetaminophen, APADAZ met the bioequivalence criteria for hydrocodone Cmax and AUC, and met the bioequivalence criteria for acetaminophen AUC, with comaparble acetaminophen Cmax.

In a study to assess the effect of food on the bioavailability and pharmacokinetics of APADAZ in 38 healthy subjects, compared to fasted condition, coadministration of APADAZ with a high-fat, high-calorie meal showed a slight decrease in the rate but no change in the extent of hydrocodone absorption; and no difference in rate and extent of acetaminophen absorption. The effect of a high-fat, high-calorie meal on pharmacokinetics is similar between APADAZ and immediate-release tablet of 7.5 mg hydrocodone/325 mg acetaminophen. APADAZ can be administered without regard to food. The PK parameters for hydrocodone and acetaminophen after oral administration of APADAZ tablet, 6.67 mg/325 mg under fasted and fed conditions is shown in the Table below.

**Table XX: PK parameters of hydrocodone and acetaminophen after oral administration of APADAZ tablet, 6.67 mg/325 mg under fasted and fed conditions.**

| Parameter [a] | Fed | Fasted |
|---|---|---|
| **Hydrocodone** | | |
| Cmax (ng/mL) | 16.04 ± 3.60 (40) | 19.18 ± 4.84 (38) |
| Tmax (h) | 2.50 (40) [0.50–4.00] | 1.25 (38) [0.50–3.00] |
| AUCinf (h×ng/mL) | 130.91 ± 29.45 (40) | 125.73 ± 36.78 (38) |
| t½ (h) | 4.53 ± 0.70 (40) | 4.33 ± 0.67 (38) |
| **Acetaminophen** | | |
| Cmax (µg/mL) | 3.34 ± 1.01 (39) | 4.05 ± 1.30 (38) |
| Tmax (h) | 1.50 (39) [0.50–4.00] | 1.00 (38) [0.50–3.00] |
| AUCinf (h×µg/mL) | 15.0 ± 3.53 (36) | 14.7 ± 3.87 (36) |
| t½ (h) | 5.64 ± 1.58 (30) | 4.78 ± 1.30 (36) |

[a] Arithmetic mean ± standard deviation (N) except Tmax for which the median (N) [Range] is reported

(b) (4)

*Multiple-Dose Study*

A multiple-dose study in 24 healthy subjects showed no measurable exposure to the prodrug, benzhydrocodone, when 2 tablets of APADAZ, 6.67 mg/325 mg, was administered orally every 4 hours for a total of 13 doses. Steady state for hydrocodone and acetaminophen was achieved after 24 hours and between 24 and 36 hours, respectively. The accumulation ratios for hydrocodone Cmax and AUC values were 1.85-fold and 2.03-fold, respectively. The accumulation ratios for acetaminophen Cmax and AUC values were 1.38-fold and 1.80-fold, respectively.

Elimination

Hydrocodone is eliminated primarily from the kidneys. Elimination of acetaminophen is principally by liver metabolism and subsequent renal excretion of metabolites.

*Metabolism*

Benzhydrocodone is an inactive prodrug of hydrocodone and is converted rapidly to active hydrocodone by enzymes in the intestinal tract.

Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves 3 principal separate pathways: conjugation with glucuronide, conjugation with sulfate, and oxidation via the cytochrome P450-dependent, mixed-function oxidase enzyme pathway to form a reactive intermediate metabolite, which conjugates with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates. The principal cytochrome P450 isoenzyme involved appears to be CYP2E1, with CYP1A2 and CYP3A4 as additional pathways.

In adults, the majority of acetaminophen is conjugated with glucuronic acid and, to a lesser extent, with sulfate. These glucuronide-, sulfate-, and glutathione-derived metabolites lack biologic activity. In premature infants, newborns, and young infants, the sulfate conjugate predominates.

Special Populations

*Age*

For hydrocodone, no significant pharmacokinetic differences based on age have been demonstrated. For APAP, a population pharmacokinetic analysis of data obtained from a clinical trial in patients with chronic pain treated with immediate-release tablet of 7.5 mg hydrocodone/325 mg acetaminophen, which included 55 patients between 65 and 75 years of age and 19 patients over 75 years of age, showed no significant changes in the pharmacokinetics of -acetaminophen in elderly patients with normal renal and hepatic function (see (b) (4)).

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*Gender*

For hydrocodone, no significant pharmacokinetic differences based on gender have been demonstrated.

*Renal Impairment*

The effect of renal insufficiency on the pharmacokinetics of APADAZ has not been determined *[see* (b) (4)*]*.

*Hepatic Impairment*

(b) (4) acetaminophen is extensively metabolized by the liver, the use of APADAZ in patients with hepatic impairment is not recommended. The pharmacokinetics and tolerability of APADAZ in patients with impaired hepatic function have not been studied *[see* (b) (4) (b) (4)*]*.

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## 4.0 Appendices

## 4.1 Sponsor's Proposed Label

19 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

**4.2 Study Designs:**

***Clinical Pharmacology Studies:***
*KP201.102: A Single-Dose, Two-Period, Two-Treatment, Two-Sequence, Two-Way Crossover Relative Bioavailability Study of KP201/Acetaminophen Tablets, 6.67 mg/325 mg and Norco® Tablets, 7.5 mg/325 mg under Fasted Conditions*

*KP201.103: A Pharmacokinetic Study of KP201, Hydrocodone, Hydromorphone, and Acetaminophen following Single and Multiple Doses of KP201/Acetaminophen Tablets, 6.67 mg/325 mg, in Healthy Volunteers*

*KP201.104: A Single-Dose, Three-Period, Three-Treatment, Six-Sequence Study of the Effect of Food on the Bioavailability and Pharmacokinetics of Hydrocodone and Acetaminophen from KP201 Tablets, 6.67 mg/325 mg, and the Relative Bioavailability of KP201 and Norco Tablets, 7.5 mg/325 mg under Fed Conditions, in Healthy Volunteers*

*KP201.105: A Single-Dose, Two-Period, Two-Treatment, Two-Sequence Crossover Comparative Bioavailability Study of KP201/Acetaminophen Tablets, 6.67 mg/325 mg, and Vicoprofen Tablets, 7.5 mg/200 mg, with Respect to Hydrocodone and Hydromorphone under Fasted Conditions*

*KP201.106: A Single-Dose, Two-Period, Two-Treatment, Two-Sequence Crossover Comparative Bioavailability Study of KP201/Acetaminophen Tablets, 6.67 mg/325 mg, and Ultracet® Tablets, 37.5 mg/325 mg, with Respect to Acetaminophen under Fasted Conditions*

***Abuse Potential Studies**:*
*KP201.A01: A Randomized, Double-Blind, Placebo-Controlled, Single-Dose, Seven-Way Crossover Study to Determine the Relative Bioavailability, Abuse Potential, and Safety of Equivalent Oral Doses of KP201/Acetaminophen Compared with Hydrocodone/Acetaminophen in Opioid Experienced, Nondependent Subjects*

*KP201.A02: A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Single-Dose, Two-Part, Five-Way Crossover Study to Determine the Relative Bioavailability, Abuse Potential, and Safety of Equivalent Doses of Crushed and Intact KP201/APAP Compared with Hydrocodone Bitartrate/APAP and Placebo in Opioid-Experienced, Non-Dependent Subjects Following Intranasal Administration*

*KP201.A03: A randomized, double-blind, single-dose, Two-way crossover study to determine the Relative bioavailability of equivalent Doses of KP201 API compared with Hydrocodone bitartrate API in opioid Experienced, non-dependent subjects, Following intranasal administration*

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/s/

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SURESH B NARAHARISETTI
05/17/2016

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05/17/2016