CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208653Orig1s000

CLINICAL REVIEW(S)

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, MD
Subject	Division Director Summary Review
NDA #	208653
Applicant Name	KemPharm, Inc.
Date of Submission	December 9, 2015
PDUFA Goal Date	June 9, 2016
Proprietary Name / Established (USAN) Name	Apadaz Benzhydrocodone/Acetaminophen Tablets
Dosage Forms / Strength	Tablet/ 6.12 mg Benzhydrocodone/ 325 mg Acetaminophen
Proposed Indication(s)	The short-term (no more than 14 days) management of acute pain
Action:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Jacqueline Spaulding, MD, Pamela Horn, MD
Statistical Review	David Petullo, PhD
Pharmacology Toxicology Review	Marcus Delatte, PhD, R. Daniel Mellon, PhD
OPQ Review	Benjamin Stevens, PhD, Venkateswara Pavuluri, PhD, Yong Hu, PhD, Yong Hu, PhD, Sunita Lyer, Ciby Abraham, PhD, Steven Kinsley, PhD, Tien Mien Chen, PhD
Clinical Pharmacology Review	Suresh Naraharisetti, PhD, Yun Xu, PhD
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OSI	John Lee MD, Janice Pohlman, MD, MPH Susan Thompson, MD, Kassa Ayalew, MD, MPH
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OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Errors Prevention
OSI=Office of Scientific Investigations
OPDP=Office of Prescription Drug Promotion
DCDP=Division of Consumer Drug Promotion
OMP=Office of Medical Policy Initiatives
DMPP=Division of Medical Policy Programs

Signatory Authority Review Template

1. Introduction

KemPharm Inc. has submitted a 505(b)(2) application for Apadaz (benzhydrocodone and acetaminophen) capsules, an immediate-release formulation with properties intended to deter abuse primarily by the intranasal route of administration. The Applicant intends to rely on the Agency's prior findings of efficacy and safety for NDA 20716, Vicoprofen (hydrocodone and ibuprofen), and NDA 21123, Ultracet (tramadol and acetaminophen). In addition, the Applicant intends to rely on a comparison to Norco (hydrocodone bitartrate [HB] and acetaminophen) to demonstrate that the combination of hydrocodone and acetaminophen do not represent a novel combination drug product. The primary development goal for Apadaz was to reduce the intranasal (IN) and oral abuse potential of immediate-release (IR) hydrocodone/acetaminophen products. The product was formulated with a benzyl group attached to the hydrocodone molecule by an ester bond, creating a hydrocodone prodrug (benzhydrocodone, called KP201 during development and in sections of this review), which is hydrolyzed to hydrocodone and benzoic acid in the presence of esterases in the gastrointestinal system or blood. The purported abuse-deterrent properties are based on (b) (4)

The Applicant has provided the product-specific chemistry, manufacturing, and controls (CMC) information required for review of the NDA. Nonclinical support for hydrocodone is based on reliance on the Agency's previous findings for the referenced drug, Vicoprofen, and for acetaminophen hydrochloride, on the Agency's previous findings for the referenced drug, Ultracet. The Applicant has provided adequate nonclinical data to support benzhydrocodone and the formulation, including novel excipients and excipients that exceed the amount present in the Inactive Ingredients Guide. Support for the clinical efficacy and safety of the benzhydrocodone and acetaminophen in Apadaz is based in part on reliance on the Agency's previous findings for the referenced drugs using relative bioavailability studies as the scientific bridge for doing so. Bioequivalence to the hydrocodone and acetaminophen in Norco, a marketed product containing hydrocodone bitartrate and acetaminophen, is used to demonstrate that the combination is not novel and does not require factorial design efficacy studies as described in 21 CFR 300.50. The approved and marketed hydrocodone and acetaminophen products are all generic products approved under 505(j). There has not been any hydrocodone and acetaminophen product approved under 505(b). For this reason, to rely on the Agency's prior findings of safety and efficacy, the approach described using bioequivalence to a marketed product containing hydrocodone and acetaminophen has been developed to provide novel products a path forward under 505(b)(2). The Applicant conducted in vitro and in vivo studies to evaluate the abuse-deterrent properties of the formulation. This review will focus on the nonclinical support for the safety of benzhydrocodone, data from pharmacokinetic studies of Apadaz, and the results of studies evaluating the abuse-deterrent properties of the formulation. An analysis by the Division of Epidemiology in the Office of Surveillance and Epidemiology of the relevance of the nasal route of abuse for hydrocodone and acetaminophen products was discussed at the May 5, 2016 advisory committee meeting and is not discussed in this review.

2. Background

As described in the Guidance for Industry, Abuse-Deterrent Opioids – Evaluation and Labeling[1], the development of abuse-deterrent formulations of opioid analgesics is recognized by FDA as an

important approach to reducing abuse of prescription opioids. Prescription opioid products are an important component of modern pain management. However, abuse and misuse of these products have created a serious and growing public health problem. One potentially important step towards the goal of creating safer opioid analgesics has been the development of opioids that are formulated to deter abuse. FDA considers the development of these products a high public health priority.

In general, the primary route of abuse of opioid analgesics is oral, followed by different frequencies of intranasal and intravenous abuse depending on the specific product. This is true for both immediate-release and extended-release products. It is important to remember that even when a product has abuse-deterrent properties that may reduce abuse by one or several routes, it does not mean that there is no risk of abuse or addiction. It means, rather, that the risk of abuse by certain routes is lower than it would be without the abuse-deterrent properties. Abuse-deterrent is not synonymous with abuse-proof. If approved, Apadaz would remain under schedule II of the Controlled Substances Act.

There are currently no single-entity or combination (opioid/non-opioid) immediate-release opioid analgesics labelled with abuse-deterrent properties as described in the guidance. There are six approved extended-release/long-acting opioid analgesic products with labeling language describing studies conducted in support of abuse-deterrent properties; OxyContin (oxycodone extended-release tablets), Targiniq (oxycodone and naloxone extended-release tablets), Embeda (morphine sulfate and naltrexone extended-release capsules), Hysingla ER (hydrocodone extended-release tablets), Morphabond (morphine sulfate extended-release tablets), and Xtampza ER (oxycodone hydrochloride extended-release capsules). Oxaydo (oxycodone immediate-release tablets) was approved June, 2011. There is a description of studies evaluating whether the formulation might have an abuse-deterrent effect in Section 12 of the labeling as the approval pre-dates the publication of the guidance.

Apadaz has been formulated with the intent to provide abuse-deterrent properties. According to the Applicant, benzhydrocodone is hydrolyzed to hydrocodone and benzoic acid by esterases in the gastrointestinal (GI) tract more efficiently than by esterases elsewhere. The Applicant states that this requirement for conversion in the GI tract can modify the pharmacokinetic profile and decrease the exposure to the active drug when taken by the nasal or intravenous routes of administration for the purposes of abuse. They also state that the nasal route of abuse is relevant for their product despite the known irritating effects of acetaminophen.

3. CMC and Biopharmaceutics

The drug product is an immediate-release formulation containing 6.67mg of benzhydrocodone hydrochloride, a benzyl ester prodrug of hydrocodone and 325mg of acetaminophen. Benzhydrocodone hydrolyzes to the active hydrocodone and benzoic acid. The drug substance benzhydrocodone is referenced to a new DMF (b) (4) and has been found to be adequate. Benzhydrocodone drug substance contains impurities (b) (4) (b) (4) which is a structural alert for mutagenicity. As noted by Dr. Delatte in the pharm/tox review:

[1] http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf

"Other than [(b) (4)] which contains a structural alert for mutagenicity, the proposed specifications are within ICH Q3A(R2) guidelines. For [(b) (4)] the Applicant has proposed a specification of NMT [(b) (4)]%. At this specification, a person would be exposed to [(b) (4)]mcg/day. This is acceptable as per ICH M7 for the proposed acute indication.

Of note, an additional drug substance impurity [(b) (4)] was identified by our CMC review team during the review of the DMF. The levels of this impurity, which is not specified by the Applicant in the drug product, are controlled at the level of the drug substance by the DMF holder and specified to be within the levels recommended by ICH M7."

The drug substance acetaminophen is referenced to DMF [(b) (4)] which has been referenced by a number of approved drug products and has been previously reviewed and found to be adequate. As noted by Dr. Delatte, drug substance specifications list [(b) (4)] impurities for acetaminophen that have structural alerts for mutagenicity: [(b) (4)] [(b) (4)] Regarding these impurities, Dr. Delatte notes the following:

[(b) (4)]

There are no novel excipients in the drug product. As noted by Dr. Delatte, "The KP201-related drug product specifications are consistent with the ICH Q3B(R2) qualification thresholds and are acceptable. The only drug product degradant specified related to acetaminophen is [(b) (4)] At the proposed specification and at the maximum daily dose of 3900 mg/day acetaminophen via this drug product, a person would ingest [(b) (4)] mcg [(b) (4)] The proposed specification is within that of the referenced drug product, therefore it is acceptable based on the Agency previous finding of safety."

As noted by the biopharmaceutics reviewer, the in vitro dissolution method for the drug product "was derived directly from the USP monograph for Hydrocodone Bitartrate and Acetaminophen Tablets. The dissolution method of KP201 had been determined in buffers with different pH conditions. This method also showed that the dissolving conditions of acetaminophen matched those in the USP monograph. Therefore, the proposed dissolution method as Apparatus II (paddle), 0.1N HCl, 900 mL, 50 rpm, is acceptable for the drug product." The in vitro dissolution method was adequately validated, and the mean and individual dissolution data were acceptable for the drug product.

The CMC microbiology review found the drug product to be a low microbial risk solid oral tablet, (b) (4) and found the Applicant's request for waiver of microbial limit testing (MLT) specifications for drug product release and stability specifications acceptable. The Applicant has committed to MLT and (b) (4) tests on these stability batches annually and to report additional stability data from these studies in post-approval Annual Reports to the NDA.

The tablets are stored in HDPE bottles (b) (4)

The facilities, the site responsible for drug product manufacture, packaging and labeling, and release and stability testing, is (b) (4) As noted in the CMC review (b) (4):

(b) (4)

The response to the information request was adequate and the reviewer concluded that "based on the acceptable inspectional history of this facility, their experience with these unit operations, and the adequate IR responses received, (b) (4) is **acceptable** for NDA 208653."

Sufficient data were provided to support the quality and safety of the manufacture and release of the drug substance and drug product. I concur with the conclusions reached by the chemistry review team regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of (b) (4) months when stored at 20 – 25 °C (68 –77 °F) with excursions permitted between 15 – 30 °C (59 – 86°F). There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

The following is from Dr. Delatte's review:

> "The Applicant submitted 14- and 28-day repeat-dose toxicology studies in the rat and dog and the fully battery of genetic toxicology studies for KP201 and its comparator drug hydrocodone bitartrate. The toxicological profile of KP201 was consistent with the expected toxicological profile of hydrocodone and the drug product does not appear to present any different safety profile from comparable generic drug products containing hydrocodone and acetaminophen.
>
> In regard to the genetic toxicology studies conducted, in vitro findings demonstrated that KP201 was positive for the induction of structural chromosomal aberrations in the S9-activated test system at the four-hour exposure time point; whereas it was negative under all other conditions in this assay. KP201 was not mutagenic in the Ames assay. KP201 and hydrocodone bitartrate in male rats were both negative in the in vivo micronucleus and comet assays.
>
> Overall, there are no unique safety concerns with the KP201 component of this product given that the excipients (including benzoic acid coupled to hydrocodone to make the prodrug) used in the benzhydrocodone/APAP drug combination do not exceed that used in FDA-approved products and the toxicity profiles for KP201 overlap with that of hydrocodone bitartrate."

Regarding pediatric studies, Dr. Delatte notes the following:

> "As per the agreed Pediatric Study Plan (PSP), the Applicant will conduct a juvenile animal study to assess the impact of benzhydrocodone to support pediatric studies in neonates and infants aged 0 to < 2 years. This study will be as a post marketing requirement. Final agreement on the study protocol will be obtained from the Agency prior to study initiation."

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology

The Applicant submitted five clinical pharmacokinetic studies in support of the application :

- KP201.105: Relative bioavailability study of KP201/acetaminophen tablet to Vicoprofen tablet with respect to hydrocodone under fasted condition
- KP201.106: Relative bioavailability study of KP201/acetaminophen tablet to Ultracet tablet with respect to acetaminophen under fasted condition
- KP201.102: Bioequivalence study of KP201/acetaminophen tablet to Norco tablet, 7.5 mg/325 mg under fasted condition
- KP201.104: Effect of food on the bioavailability and pharmacokinetic of hydrocodone and acetaminophen from KP201/acetaminophen tablet, and the relative bioavailability of KP201/acetaminophen to Norco tablets under fed condition
- KP201.103: Single- and multiple-dose pharmacokinetics of KP201/acetaminophen

In all human pharmacokinetic studies following oral administration of the drug product, plasma concentrations of KP201 were below the limit of quantitation of 25 pg/mL. Benzhydrocodone

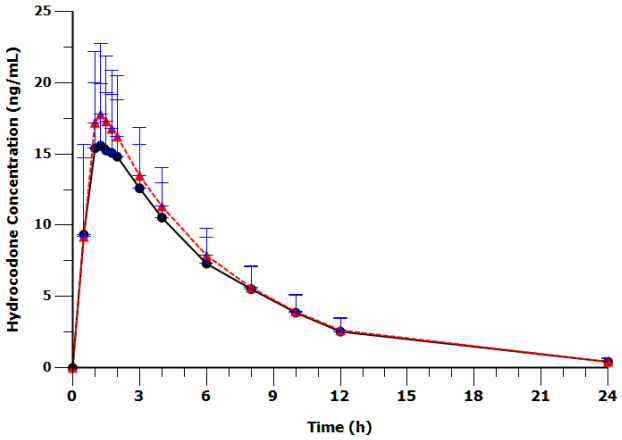
levels were measureable in plasma following intranasal administration of the crushed product in human abuse liability studies. The median T_{max} range of KP201 was 0.46 to 0.73 hours post-dose. The half-life of KP201 was short, ranging from 1 to 1.48 hours. Mean C_{max} and AUC values for KP201 increased with an increase in dose. The mean C_{max} and AUC_{inf} for KP201 ranged from 9.4 ± 2.8 ng/mL and 7.6 ± 2.4 h·ng/mL (KP201/acetaminophen 6.67/325 mg, crushed) to 27.0 ± 25.7 ng/mL and 26.1± 20.6 h·ng/mL (KP201/acetaminophen 26.68/1300 mg, crushed).

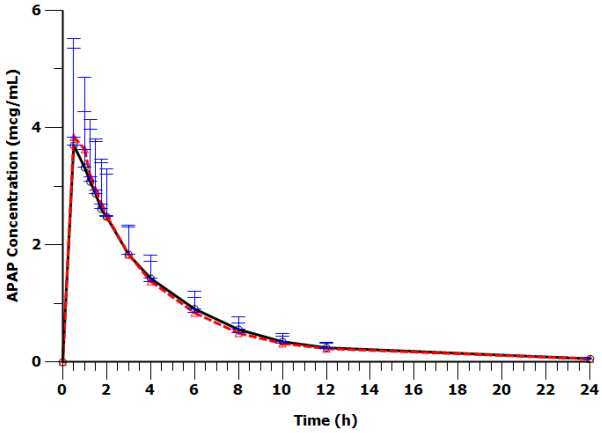
KemPharm is relying on the FDA's findings of efficacy and safety for two listed drugs, Vicoprofen (7.5 mg hydrocodone bitartrate/ 200 mg ibuprofen oral tablet; NDA 020716), and Ultracet (37.5 mg tramadol hydrochloride/325 mg acetaminophen oral tablet; NDA 021123). To establish the scientific bridge for relying on the Agency's findings of safety and efficacy for the two listed drugs, two relative bioavailability studies were conducted in the fasted state comparing KP201/acetaminophen with Vicoprofen for hydrocodone (Study KP201.105) and Ultracet for acetaminophen (Study KP201.106). KP201/acetaminophen met the bioequivalence criteria for AUC and C_{max} for hydrocodone compared to Vicoprofen, and for acetaminophen compared to Ultracet. The details of these two studies can be found in Dr. Naraharisetti's review.

As discussed in the background, KP201/acetaminophen was compared to Norco (7.5 mg hydrocodone bitartrate/ 325 mg acetaminophen) to support that the delivery of hydrocodone and acetaminophen from KP201/ acetaminophen does not represent a novel combination. Study KP201.102 compared the plasma concentrations versus time profiles for hydrocodone and acetaminophen following a single dose of KP201/ acetaminophen and a single dose of Norco administered orally under fasted conditions in 23 subjects. The following figure is from Dr. Naraharisetti's review.

Figure 1: Mean ± SD plasma hydrocodone (left figure) and acetaminophen (right figure) concentration-time profiles (0-24 h) following administration of single doses of KP201/acetaminophen and Norco to healthy subjects under fasted conditions (Study KP201.102)

KP201_APAP
Norco





The results are presented in tabular form in the following tables from Dr. Naraharisetti's review. Bioequivalence criteria were met for both hydrocodone and acetaminophen. Beyond C_{max} and AUC, it can also be seen from the figures that the T_{max} values are nearly identical for both hydrocodone and acetaminophen (APAP) in the fasted state.

Table 1: Study KP201.102: Relative bioavailability of hydrocodone from KP201/acetaminophen and Norco under fasted conditions

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.

Table 2: Study KP201.102: Relative bioavailability of acetaminophen from KP201/acetaminophen and Norco under fasted conditions

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

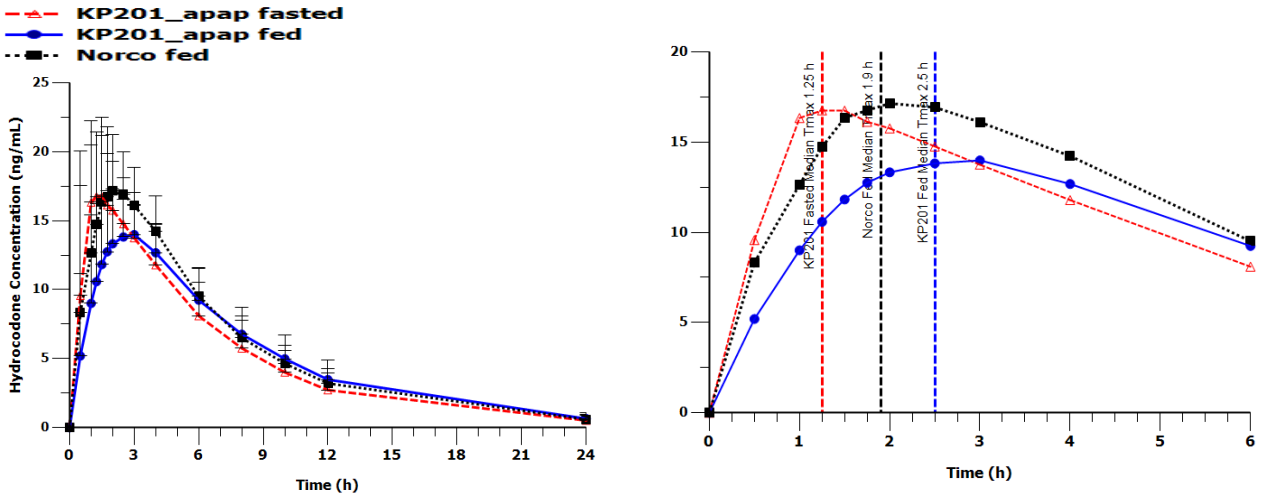
[a] Least squares geometric means, based on the analysis of natural log-transformed data.

Study KP201.104 evaluated the effect of food on the pharmacokinetics and relative bioavailability and of hydrocodone and acetaminophen from KP201/acetaminophen and Norco under fed conditions in healthy volunteers. The three treatment groups were:

- Treatment A: KP201/acetaminophen, 1 x 6.67 mg/325 mg tablet with 240 mL of water under fed conditions
- Treatment B: KP201/acetaminophen, 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

The results for the effects on plasma hydrocodone concentration over time for the 0 to 24 hour and 0 to 6 hour periods are provided in the following figure from Dr. Naraharisetti's review.

Figure 2: Study KP201.104 - Mean plasma hydrocodone concentration-time profile for 0-24h (left) and 0-6h (right).



The pharmacokinetic parameters for hydrocodone are summarized in the following tables.

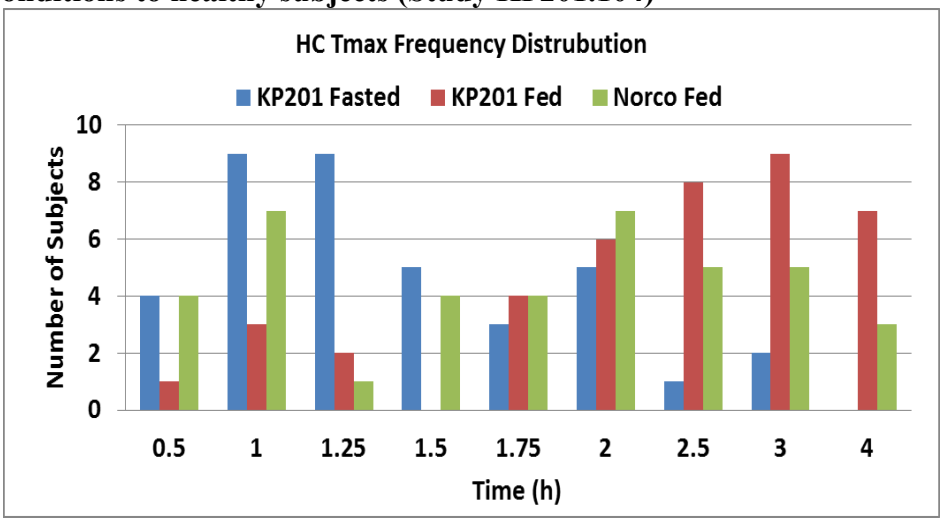
Table 3: Study KP201.104: Summary of pharmacokinetic parameters for hydrocodone, single-dose, fed and fasted conditions

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

[a] Arithmetic mean ± standard deviation except T_{max} for which the median. [Range] is reported.

As described in Dr. Naraharisetti's review, the comparison of hydrocodone C_{max} and AUC is similar to Norco under fed condition with a delay in the T_{max} of hydrocodone from KP201/ acetaminophen from a mean of 1.25 hours to a mean of 2.5 hours. Review of the individual T_{max} values found that there were no individuals with a delay in onset beyond the dosing interval of four hours. A frequency histogram for the T_{max} of hydrocodone from KP201/acetaminophen and Norco is presented in Figure 6. This is an important parameter for review, as some immediate-release abuse-deterrent formulations have demonstrated substantial delays in the onset of absorption of drug in the fed state (as discussed in the September 10, 2015, advisory committee meeting for NDA 206830, Avridi).

Figure 3: Frequency histogram for hydrocodone T_{max} following administration of single doses of KP201/acetaminophen under fasted and fed conditions and Norco under fed conditions to healthy subjects (Study KP201.104)

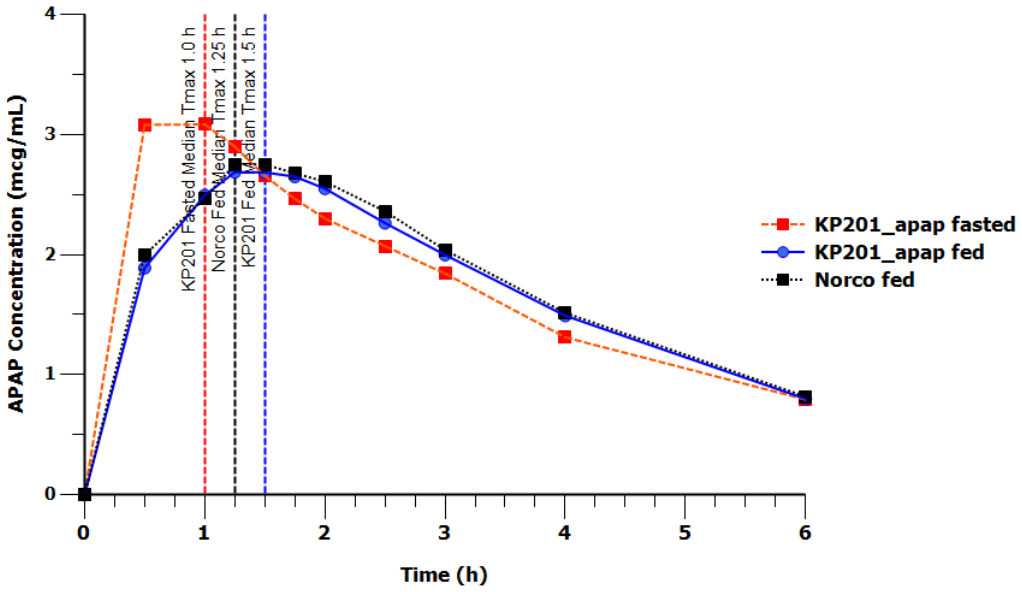


Dosing KP201/acetaminophen and Norco in the fed state led to median hydrocodone T_{max} values of 2.5 and 1.9 hours, respectively. The T_{max} ranges were identical and within the minimum recommended dosing interval of 4 hours (0.5 to 4 hours for both products). While the hydrocodone C_{max} for KP201/acetaminophen under fed condition is 78% compared to

Norco, the overall exposure to hydrocodone (AUC_{last} and AUC_{inf}) was within the 80% to 125% range. When hydrocodone partial AUCs in a typical dosing interval (4 to 6 hours) were compared for KP201/acetaminophen fed and Norco fed, the data demonstrated a slight decrease in hydrocodone partial exposure for KP201/acetaminophen compared to Norco. However, numerically it is not much lower and the standard deviations in hydrocodone partial AUCs overlapped between the two treatments.

The mean plasma acetaminophen concentration-time profile over a typical dosing regimen, (every 6 hours) with median T_{max} representation for KP201/acetaminophen under fasted and fed conditions and Norco under fed conditions is presented in Figure 9 and shows that there is little difference between KP201 and Norco for acetaminophen T_{max}, $C_{max,}$ and AUC in the fed state.

Figure 4: Mean plasma acetaminophen concentration-time profile (0-6h) following administration of single dose of KP201/acetaminophen under fasted and fed conditions and Norco under fed conditions to healthy subjects (Study KP201.104)



As noted by Dr. Naraharisetti, a there was a small delay in T_{max} for both hydrocodone and acetaminophen from KP201 under fed conditions compared to fasted conditions, the pharmacokinetic profiles and parameters under the fed condition are similar to those of Norco under the fed condition and the data support dosing without regard to the timing of food.

The multiple-dose pharmacokinetics of KP201, hydrocodone, and acetaminophen following a single dose on Day 1, and following multiple dosing as two tablets every four hours under fasted conditions were evaluated in Study KP201.03. The results are summarized in the following two tables from Dr. Naraharisetti's review.

Table 4: Study KP201.103: Single-dose and Multiple-dose pharmacokinetic parameters for hydrocodone

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)

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

Table 5: Study KP201.103: Single-dose and Multiple-dose pharmacokinetic parameters for acetaminophen

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)

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

Steady-state was reached for hydrocodone approximately 24 hours after the initiation of multiple dosing. The accumulation of hydrocodone for C_{max}, AUC_{0-4}, and AUC_{0-t} values (Day 4/Day1 or 14th dose/ 1st dose of KP201/acetaminophen) were 1.85-fold, 2.10-fold, and 2.03-fold, respectively.

Steady-state for acetaminophen was reached approximately between 24 and 36 hours after the initiation of multiple dosing. The accumulation of Cmax, AUC0-4, and AUC0-t values (Day 4/Day1 or 14th dose/ 1st dose of KP201/acetaminophen) were 1.38-fold, 1.69-fold, and 1.80-fold, respectively.

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

This section is not applicable to this application.

7. Clinical/Statistical: Efficacy

Support for the clinical efficacy of the benzhydrocodone and acetaminophen in Apadaz is based in part on reliance on the Agency's previous findings for the referenced drugs, Vicoprofen, a product containing hydrocodone and ibuprofen, and Ultracet, a product containing tramadol and acetaminophen. The Applicant conducted relative bioavailability studies as the scientific bridge for doing so. In addition, the Applicant has demonstrated bioequivalence to the hydrocodone and acetaminophen in Norco, a marketed product containing hydrocodone and acetaminophen, providing support that the exposure to hydrocodone and acetaminophen from Apadaz is consistent with an approved product and demonstrates that the combination is not novel and does not require factorial design efficacy studies as described in 21 CFR 300.50. No additional efficacy data are needed.

8. Safety

The primary support for the safety of Apadaz is based on the Agency's prior findings of safety for hydrocodone and acetaminophen. No additional data were required to assess the clinical safety of the benzhydrocodone because the prodrug was not present in the blood after oral dosing in humans long enough for detection. This supports the Applicant's contention that benzhydrocodone is rapidly hydrolyzed to hydrocodone. Safety data were collected during the pharmacokinetic and human abuse liability studies. A total of 418 healthy subjects received at least one dose of KP201/acetaminophen and 245 healthy subjects received multiple doses of KP201/acetaminophen across ten clinical studies. Twenty six of the subjects were pre-treated with naltrexone during Study KP201.103. There were no deaths or serious adverse events. Seven patients discontinued study participation due to adverse events. Four of these patients experienced hypotension including one with presyncope, two nausea and vomiting, and one supraventricular and ventricular extrasystoles. The hypotension and nausea and vomiting were likely related to study drug and all resolved spontaneously. The one patient with the supraventricular and ventricular extrasystoles had no history of cardiac disease, but was found to have left ventricular hypertrophy at baseline and on follow up electrocardiogram with premature ventricular complexes on ECG three weeks after study discontinuation. The findings are unlikely related to study participation.

The most common adverse events reported were constipation, nausea, somnolence, fatigue, headache and dizziness. Overall, the safety data indicate that Apadaz has a similar safety profile to existing hydrocodone/acetaminophen formulations and no new safety concerns were identified with this product.

9. Advisory Committee Meeting

This application was taken to a joint meeting of the Anesthesia and Analgesia Drug Advisory Committee and the Drug Safety and Risk Management Advisory Committee on May 5, 2016. The discussion points for the committees were focused on two areas, whether the nasal route of

abuse is relevant for hydrocodone and acetaminophen combination products and whether the studies conducted by the Applicant demonstrated properties likely to deter abuse. As described in the Guidance for Industry, Abuse-Deterrent Opioids — Evaluation and Labeling, it is important that abuse-deterrent opioid analgesic products be assessed for the relevant routes of abuse. In general, the most common route of abuse of prescription opioid products is oral. The amount of abuse by nasal or intravenous routes, or by smoking, varies substantially based on the individual products. Progression to nasal or intravenous routes of abuse generally occurs as individuals seek more rapid onset and intensity of the euphoric effects. Acetaminophen-containing opioid analgesic products tend not to be abused by the nasal or intravenous routes nearly as much as single-entity opioid analgesics. This may be due to several reasons including nasal irritation from the acetaminophen, larger volume of powder when crushed because of the acetaminophen, a relatively small amount of opioid per tablet relative to the amount of acetaminophen, and concern about hepatotoxicity due to the acetaminophen.

The Applicant conducted in vitro and in vivo studies to evaluate the abuse-deterrent properties of Apadaz. The clinical studies used for this assessment are very similar in design and conduct to the studies used to determine the abuse potential of a novel product. For the latter, the primary question is to determine the abuse liability, often as part of an assessment for scheduling under the Controlled Substances Act and the outcomes of Drug High and Drug Liking relative to a comparator with similar pharmacological properties. When used to evaluate possible abuse-deterrent properties, the primary question is whether the purported abuse-deterrent properties of the product will decrease the likelihood of abuse by any of the routes tested relative to either a non-abuse deterrent comparator of the same product, or another abuse-deterrent product. In this setting, the important outcomes include Drug Liking and Drug High, but more importantly, whether there is a difference in the subject's willingness to take the drug again relative to the comparator. Depending on the nature of the abuse-deterrent properties, the pattern of results of Take Drug Again, Drug Liking, and Drug High can differ substantially. For example, a product designed with aversive abuse-deterrent features may result in the same Drug High as a comparator, but the aversive properties may make the subject less willing to take the drug again, while a product with physicochemical properties intended to prevent crushing or dissolution may result in lower scores for Drug Liking, Drug High, and Take Drug Again. For Apadaz, the Applicant expected to see a change in the pharmacokinetic profile of hydrocodone following insufflation of crushed tablets hypothesizing that there would be less or slower conversion to hydrocodone by the nasal route than by the oral route. As described in the review of the clinical abuse liability studies, there were no statistically significant differences in the responses to KP201/acetaminophen as compared to Norco, with a small numerical reduction in Drug High, but no difference in Drug Liking, and importantly, no difference in willingness to take the product again.

The following is a summary of the discussion and voting questions from the advisory committee meeting.

Question #1
Discuss whether the data presented for hydrocodone and acetaminophen combination drug products support that the nasal route of abuse is relevant for KP201/acetaminophen?

The overall consensus of the committees was that while the nasal route of abuse is less common than the oral route, it may be relevant for hydrocodone/acetaminophen products and Apadaz, even if there is only a small amount of abuse occurs by this route. The committee noted that this route may be more relevant in certain communities and age groups, such as adolescents, based on the data presented.

Question #2
Please discuss whether there are sufficient data to support a finding that KP201/acetaminophen has properties that can be expected to deter abuse for each of these possible routes of abuse:

a. Oral
b. Nasal
c. IV

The general consensus of the committees was that the data did not support a finding that Apadaz was likely to deter abuse by the oral or intranasal routes of abuse, nor was the in vitro data supportive of an advantage in resistance to separation of the acetaminophen from the opioid.

Question #3
Should KP201/acetaminophen be approved for the proposed indication?

The committees voted 16 to 4 in favor of approving Apadaz for the proposed indication, noting that there was bioequivalence of hydrocodone and acetaminophen to the comparators and it would be likely be effective for the proposed indication without any greater safety risk for patients. The four committee members who voted against approval commented that they did not find the product to be any safer than currently available therapies. One committee member voted against approval because of the lack of abuse-deterrent properties.

Question #4
If approved, should KP201/acetaminophen be labeled as an abuse-deterrent product?

The committees voted 18 to 2 against labeling Apadaz with abuse-deterrent language. The committees expressed concern that the data presented did not support a finding of abuse-deterrent properties and were concerned that labeling the product as abuse-deterrent would misguide prescribers into thinking that it may be safer, and would potentially undermine the standard for labeling products as abuse-deterrent properties. The two committee members who voted to label Apadaz with abuse-deterrent language stated that they thought the data supported an incremental improvement over currently available therapies.

10. Pediatrics

As Apadaz contains a novel drug substance, the product is subject to the requirements of the Pediatric Research Equity Act (PREA). The Applicant reached agreement with the Division on an Initial Pediatric Study Plan (IPSP) on October 13, 2015. The proposed IPSP was discussed at the Pediatric Review Committee (PeRC) meeting on May 4, 2016. There was consensus that a

deferral was appropriate for all the following required studies because the product is ready for approval in adults:

1. Pharmacokinetic, safety, and efficacy study for ages birth to < 2
2. Open-label pharmacokinetic, safety and efficacy study for ages 2 to < 7
3. Open-label pharmacokinetic, safety and efficacy study for ages 7 to < 17

11. Other Regulatory Issues

Evaluation of Abuse-Deterrent Properties

In Vitro Studies

The Applicant conducted studies to evaluate the solubility and extraction of benzhydrocodone from the tablet in large and small volume extraction studies using a range of solvents, pH buffers, temperature, and agitation. As noted in the chemistry review, additional testing conditions were requested and the Applicant submitted the results. Studies were also conducted to assess the potential of releasing (hydrolyzing) hydrocodone from KP201 under a range of conditions. Small volume extractability and syringeability studies were designed to assess the solubility profiles of KP201 and hydrocodone bitartrate in aqueous solutions of varying pH and salinity that bracket physiological conditions. Smokability was assessed using a "two-trap" system at the temperature just above which 90% of the API mass was lost during the TGA studies. Studies were carried out using hydrocodone free base, hydrocodone bitartrate, KP201 free base, KP201, the drug product, and the immediate-release comparator tablet. The details of the study designs and study variables can be found in the chemistry review.

The large volume extraction studies demonstrated that under certain conditions, the extraction behavior of KP201 diverges from hydrocodone bitartrate and hydrocodone. Under some conditions where the solubility of KP201 remains low, acetaminophen continued to partition into solution, possibly facilitating separation of the two drug substances. There were some hydrolyzing solvents that did yield hydrocodone from KP201. The small volume extraction studies showed that KP201 was generally less soluble than hydrocodone bitartrate/hydrocodone. The Apadaz formulation does not offer resistance to syringing and there were no differences from the comparator for syringeability or injectability. Neither product was suitable for smoking.

Clinical Studies

Three clinical studies were conducted to evaluate the abuse-deterrent properties of Apadaz. One oral abuse potential study and one intranasal abuse potential study were adequately designed and controlled studies of benzhydrocodone and acetaminophen compared with a generic formulation of hydrocodone and acetaminophen, Norco. A third intranasal study was not adequately designed to evaluate the abuse-deterrent properties of Apadaz, in part because the treatment groups did not include acetaminophen, but also due to problems with the study design.

Study KP201.A01 was a randomized, double-blind, placebo- and active-controlled, single-dose, seven-way crossover study that evaluated the relative bioavailability, abuse potential, and safety of equivalent oral doses of KP201/acetaminophen compared to an immediate-release hydrocodone/acetaminophen tablet in opioid experienced, nondependent subjects. Subjects who completed a naloxone challenge without signs or symptoms of opioid withdrawal went on to the Drug Discrimination phase of the study to establish whether they could differentiate active drug from matching placebo using six over-encapsulated Norco tablets, 7.5 mg/325 mg, for a total of 45 mg or hydrocodone bitartrate and 1950 mg of acetaminophen. Subjects who demonstrated adequate separation of active drug from placebo were then randomized to the double-blind, randomized, seven-period crossover Treatment Phase. The study drugs were over-encapsulated for blinding, and 12 capsules were administered for each treatment.

The treatment groups were:

- 12 KP201/acetaminophen 6.67 mg/325 mg tablets
- 8 KP201/acetaminophen 6.67 mg/325 mg tablets with 4 placebo capsules
- 4 KP201/acetaminophen 6.67 mg/325 mg tablets with 8 placebo capsules
- 12 Norco 7.5/325 mg tablets
- 8 Norco 7.5/325 mg tablets with 4 placebo capsules
- 4 Norco 7.5/325 mg tablets with 8 placebo capsules
- 12 placebo capsules

The study outcomes were:

- Bipolar Drug Liking VAS
- Bipolar Take Drug Again VAS
- Bipolar Overall Drug Liking VAS
- Drug Effects Questionnaire consisting of unipolar VAS to assess any drug effects, good effects, bad effects, feeling high, feeling sick, nausea, feeling sleepy, and feeling dizzy.
- Addiction Research Center Inventory-Morphine-Benzedrine Group Subscale (ARCI-MBG)

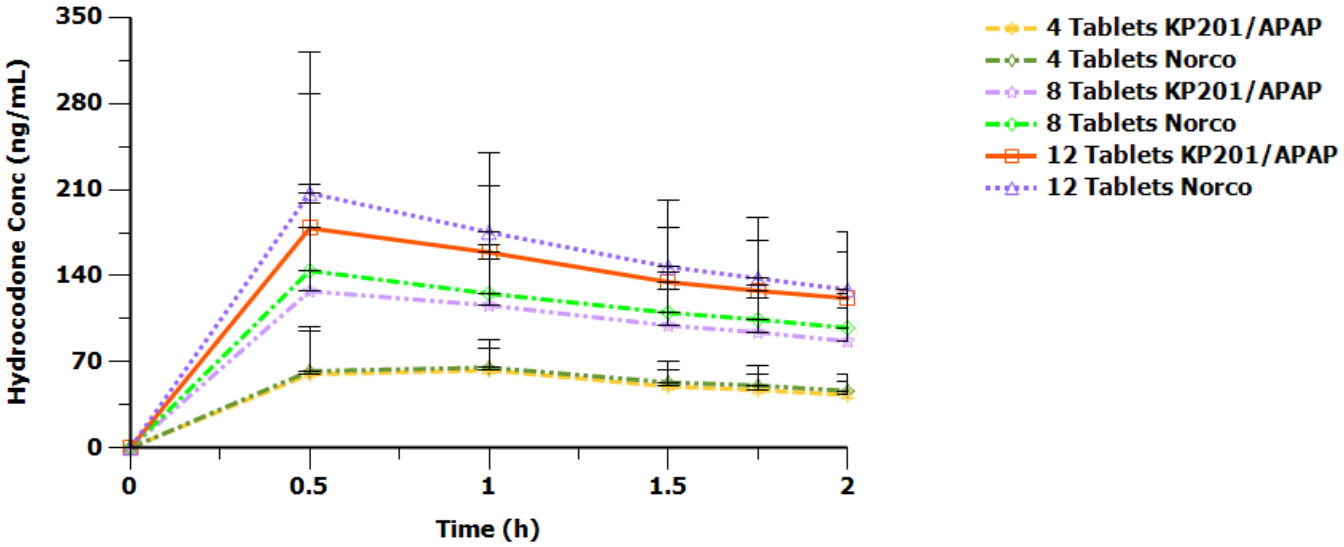
Blood samples for pharmacokinetic analysis were taken pre-dose and at selected times for 24 hours following the dose.

Of the 151 subjects screened, 125 underwent the naloxone challenge, and 119 went on to the Drug Discrimination phase. Thirty-seven subjects failed to meet the criteria for drug discrimination and an additional 11 discontinued due to adverse events, positive urine drug screen, investigator decision, or withdrew consent. Sixty-two of the remaining 71 subjects completed the Treatment Phase.

The results of the pharmacokinetic analysis are shown in the following figure from Dr. Tolliver's review. There is a slightly lower hydrocodone level from the KP201/acetaminophen high dose group, but as shown below, this difference was not sufficient to have an effect on the pharmacodynamic outcomes.

Figure 5: Mean plasma hydrocodone concentration-time profiles following single oral

doses of KP201/acetaminophen in opioid-experienced, non-dependent recreational users, Study KP201.A01



The results of the pharmacodynamic outcome measures showed a dose response, but no statistically significant differences between the active and comparator for Drug High, Drug Liking, or Take Drug Again. There were small numerically greater responses for Take Drug Again for KP201/acetaminophen. The summary statistics from Dr. Chen's review are provided below in a modified table.

Table 6: Summary statistics for Drug Liking, High, and Take Drug Again, E_{max} (N=62), Study KP201.A01

	TRT	Mean	SD	Min	Q1	Med	Q3	Max
Drug Liking	HB/APAP L	72.5	16.46	50	60	68.5	82.5	100
	HB/APAP M	83.4	16.41	50	71.75	86	100	100
	HB/APAP H	87.4	15.63	50	78.75	93	100	100
	KP201/APAP L	72.6	17.17	50	56.75	71.5	84	100
	KP201/APAP M	82.4	16.42	50	69.25	83	100	100
	KP201/APAP H	87.8	14.78	50	77.75	94	100	100
	P	51.5	3.38	50	50	51	51	69
High Effects	HB/APAP L	48.2	30.79	0	21.5	49	72.25	100
	HB/APAP M	76.6	25.84	4	62	83.5	100	100
	HB/APAP H	85.1	21.68	0	76	97	100	100
	KP201/APAP L	49.6	32.98	0	16.5	56.5	72.25	100
	KP201/APAP M	72.6	25.06	4	57.25	77	96	100
	KP201/APAP H	85.5	19.32	9	76.5	95	100	100
	P	2.6	9.79	0	0	0	1	67
Take Drug	HB/APAP L	66.3	20.65	37	49	52	84.5	100

	HB/APAP M	66.0	28.30	0	49	66.5	94	100
	HB/APAP H	66.5	25.51	0	49	63	94.5	100
	KP201/APAP L	69.3	22.48	11	49	65	91.5	100
	KP201/APAP M	71.5	23.28	0	49	73	93	100
	KP201/APAP H	72.4	24.44	0	49.75	75.5	100	100
	P	49.6	9.86	1	49	49	50	99

Study KP201.A02 was a randomized, double-blind, placebo- and active-controlled, single-dose, seven-way crossover study that evaluated the relative bioavailability, abuse potential, and safety of equivalent intranasal doses of KP201/acetaminophen compared to an immediate-release hydrocodone/acetaminophen tablet in opioid experienced, nondependent subjects, with a history of intranasal abuse of opioids. Subjects who completed a naloxone challenge without signs or symptoms of opioid withdrawal went on to participate further in the study. Part A of the study was used for dose selection. After successful completion of the Qualification Phase in which subjects adequately distinguished 40 mg of hydrocodone bitartrate from placebo, subjects were assigned to receive either KP201/acetaminophen or Norco and a matching placebo. Cohorts of four subjects evaluated doses up to four crushed tablets of KP201/acetaminophen and Norco.

The Part B treatment groups were:

Treatment	Intranasal Dose	Oral Dose with 240 mL Water
A	**Placebo Powder** (975 mg Microcrystalline Cellulose Powder)	**Placebo** (2 over-encapsulated lactose tablets)
B	**Placebo Powder** (975 mg Microcrystalline Cellulose Powder)	**KP201/APAP (13.34 mg/650 mg)** (2 over-encapsulated tablets)
C	**KP201/APAP (13.34/650 mg)** (2 Crushed Tablets) (1100 mg Powder)	**Placebo** (2 over-encapsulated lactose tablets)
D	**Norco (15 mg/650 mg)** (2 crushed Norco Tablets) (850 mg Powder)	**Placebo** (2 over-encapsulated lactose tablets)
E	**Placebo Powder** (975 mg Microcrystalline Cellulose Powder)	**Norco (15 mg/650mg)** (2 over-encapsulated tablets)

As noted by Dr. Tolliver, "Intranasal treatments were prepared by crushing KP201/acetaminophen and Norco tablets for 2 minutes using a mortar and pestle. Subjects were instructed to insufflate the IN treatment within 10 minutes. Subjects were not allowed to blow their nose for at least two hours post-dose, and any episodes of sneezing within two hours post-dose were documented. Start and stop times for intranasal administration were recorded and the amount (%) of study drug not insufflated was recorded. Any difficulties, problems, and adverse effects during insufflation and their cause(s) were also documented."

The dose selected for Part B was two tablets. The reasons for this selection were summarized by Dr. Tolliver:

> "Treatment with 2 Tablets of KP201/acetaminophen and Norco – Selected for Main Study (Part B)
> - Six out of 7 subjects (cohorts 1W and 2 W combined) displayed a greater than 15 mm difference for E_{max} of Drug Liking between KP201/acetaminophen and placebo.

- Five out of 8 subjects (cohorts 1X and 2X combined) displayed a greater than 15 mm difference for E_{max} of Drug Liking between Norco and placebo.
- All 7 subjects (cohorts 1W and 2 W combined) completely insufflated the dose of KP201/acetaminophen and indicated insufflation was easy rather than difficult based on Ease of Snorting scores.
- Six out of 8 subjects were able to insufflate greater than 95% of the Norco dose and considered insufflation easy based on Ease of Insufflation VAS. Two remaining subjects noted insufflation was difficult, insufflating 67.3% and 55.4% of the HB/acetaminophen dose.

The three-tablet dose was not considered for evaluation in Part B because in Cohort 6X (4 subjects, only cohort used) the active control (HB/acetaminophen) did not produce reliable significant Drug Liking effects at this dose level. In only 1 of the 4 subjects, was there a greater (i.e., 76 mm vs 51 mm) than 15 mm for E_{max} of Drug Liking between Norco and placebo.

Due to the intranasal irritation observed at the highest dose tested (i.e., four-tablet dose) for both KP201/APAP and Norco, with KP201/APAP producing overall higher scores on the Likert scale and adverse nasal effects compared to Norco, the Sponsor concluded that a four-tablet dose administered intranasally would not have been well tolerated in the Main Study (Part B)."

The study outcomes were:

- Bipolar Drug Liking VAS
- Bipolar Take Drug Again VAS
- Bipolar Overall Drug Liking VAS
- Drug Effects Questionnaire consisting of unipolar VAS to assess any drug effects, good effects, bad effects, feeling high, feeling sick, nausea, feeling sleepy, and feeling dizzy.
- Addiction Research Center Inventory-Morphine-Benzedrine Group Subscale (ARCI-MBG)

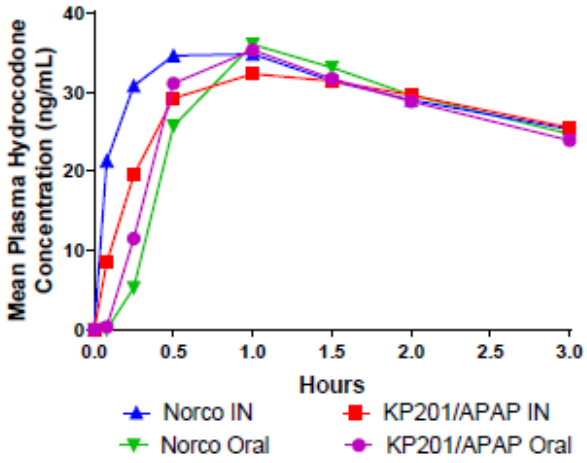
Blood samples for pharmacokinetic analysis were taken pre-dose and at selected times for 24 hours following the dose.

Part B enrolled 71 subjects who successfully completed a naloxone challenge test. Twenty-three of these subjects failed the Drug Discrimination Test and two subjects withdrew consent, leaving 46 subjects eligible for the Treatment Phase of Part B. Forty-two subjects completed the Treatment Phase. One subject was withdrawn in following adverse events of mild supraventricular and ventricular extrasystoles that resolved on the same day as onset and one subject was lost to follow-up after completing Treatment Period 1. Two subjects were withdrawn after completing Treatment Period 1 because the sponsor decided to stop enrollment after 40 subjects had completed all 5 treatment periods in accordance with the protocol.

The results of the pharmacokinetic analysis are shown in the following figure from Dr. Tolliver's review. The earliest exposure to hydrocodone was from the intranasal Norco group, followed by

intranasal KP201/acetaminophen, oral KP201/acetaminophen , and then oral Norco. C_{max} levels were similar across all four groups.

Figure 6. Plasma Hydrocodone Concentrations as a Function of Time Following Oral and Intranasal Treatments with KP201/acetaminophen (13.34 mg/650 mg) and Norco (15 mg/650 mg) (N=43 Subjects for Intranasal Treatments and 42 for Oral Treatments) Study KP201.A02)



The pharmacokinetic data were somewhat surprising in that the exposure to hydrocodone following insufflation of KP201/acetaminophen was comparable to oral ingestion of KP201/acetaminophen and Norco, and only slightly delayed compared to insufflation of Norco. This suggests that either conversion of KP201 in the blood occurs nearly as quickly in the GI tract, or most of the insufflated powder was swallowed and effectively mimicked oral ingestion.

The following table from Dr. Tolliver's review shows the pharmacodynamic endpoint results. There were no statistically significant differences for Drug Liking, Drug High, or Take Drug Again when comparing intranasal KP201/acetaminophen and Norco administered orally or administered nasally. These findings were not surprising given the results of the pharmacokinetic data.

Table 7. Descriptive Statistics for Drug Liking VAS, High VAS, and Take Drug Again VAS Oral and Intranasal Administration of Norco (15 mg/650 mg) and KP201/acetaminophen (13.34/650 mg). (Completer Population = 42 Subjects) KP201.A02

VAS	Treatment	Mean Emax	Standard Deviation	Minimum	1st Quadrile	Median	3rd Quadrile	Maximum
Bipolar Drug Liking	Crushed Norco IN	79.0	17.59	50	64.75	80	100	100
	Intact Norco Oral	77.9	16.71	50	64.75	74.5	99.25	100
	Crushed KP201/APAP IN	75.9	15.08	50	64.5	74	88.25	100
	Intact KP201/APAP Oral	76.9	17.28	50	63.5	76	93.25	100
	Placebo	53.0	7.68	50	50	51	51	85
Unipolar High	Crushed Norco IN	59.1	32.74	0	28.75	67.5	85.25	100
	Intact Norco Oral	60.3	31.54	0	33.75	69	84.5	100
	Crushed KP201/APAP IN	61.8	30.13	0	39	68.5	84	100
	Intact KP201/APAP Oral	61.2	33.24	0	32.75	70	88	100
	Placebo	8.8	24.56	0	0	0	3	100
Bipolar Take Drug Again	Crushed Norco IN	74.5	25.54	0	55	81.5	100	100
	Intact Norco Oral	75.6	23.59	0	61.75	75	100	100
	Crushed KP201/APAP IN	69.5	25.11	0	52.5	68	97	100
	Intact KP201/APAP Oral	73.3	26.46	0	51	78.5	100	100
	Placebo	48.2	14.55	0	50	50	51	100

Study KP201.A03 was not designed properly to evaluate the abuse-deterrent characteristics of KP201/acetaminophen relative to Norco. As noted by Dr. Tolliver, "Study KP201.A03 was originally designed as a pharmacokinetic/nasal tolerability study to which was added an assessment for Drug Liking VAS. This study was conducted on the active pharmaceutical ingredients (API), namely KP201 and hydrocodone bitartrate, and not on the products KP201/acetaminophen and hydrocodone bitartrate/acetaminophen (Norco). There was no placebo treatment arm and therefore, no validation of the Drug Liking VAS. There was no Drug Discrimination Phase in this study. As such it is not known to what extent subjects were able to discriminate active treatments (KP201 API (13.34 mg) and hydrocodone bitartrate API (15.00 mg)) from a placebo with regard to Drug Liking VAS." This study will not be considered further.

Overall, the results of the in vitro and clinical abuse potential studies do not demonstrate any differentiation of Apadaz from the non-abuse-deterrent hydrocodone/acetaminophen product. These data do not support a finding that Apadaz can be expected to reduce abuse by any route of administration.

12. Labeling

Labeling reviews were conducted by the Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis, Office of Prescription Drug Promotion, Division of Consumer Drug Promotion and by the Office of Medical Policy Initiatives, Division of Medical Policy Programs. Proposed changes to the package insert and carton and container labels were conveyed to the Applicant. The proprietary name, Apadaz, was reviewed and found acceptable.

The Division of Pediatric and Maternal Health provided recommendations for sections 8.1, 8.2, 8.3 and 17 of the prescribing information to make the labeling compliant with the Pregnancy and Lactation Labeling Rule and to be consistent with other opioid and acetaminophen products indicated for short-term management of acute pain.

The Applicant submitted proposed labeling [redacted] (b) (4) The following language was provided to the Applicant:

> In vitro and human abuse potential studies comparing Apadaz to an immediate-release hydrocodone/acetaminophen tablet control were conducted to assess the potential abuse deterrent properties of Apadaz. In vitro studies that evaluated physical manipulation and extraction for the purpose of preparing Apadaz for abuse by the intravenous route or by smoking did not find an advantage for Apadaz over the hydrocodone/ acetaminophen control. In an oral, single-center, randomized, double-blind, active- and placebo-controlled, 7-period, crossover, human abuse potential study there were no statistically significant differences between Apadaz and the hydrocodone/ acetaminophen control observed for the pre-specified primary endpoint, maximum effect on Drug Liking VAS (Emax), or for the secondary endpoints, High VAS and Take Drug Again VAS. In an intranasal single-center, randomized, double-blind, double-dummy, two-part human abuse potential study, there were no statistically significant differences between Apadaz and the hydrocodone-acetaminophen control observed for the pre-specified primary endpoint, maximum effect on Drug Liking VAS (Emax), or the secondary endpoints, High VAS and Take Drug Again VAS.
>
> The results do not support a finding that APADAZ can be expected to deter abuse by the oral, nasal, intravenous, or smoking routes of administration.

Following receipt of the Agency's proposed changes to the package insert, the Applicant declined to accept the proposed language nor to continue negotiation of the labeling. As a result, the label, as proposed by the Applicant, is false and misleading with respect to the description of abuse-deterrent properties for Apadaz.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Complete Response

- Risk Benefit Assessment

The efficacy and safety data provided support the finding that Apadaz could be approved. The proposed indication of the short-term (no more than 14 days) management of acute pain would require modification to better account for the risk that must be taken into account when choosing to prescribe an opioid. An indication such as for the short-term (no more than 14 days) management of pain severe enough to warrant use of an opioid analgesic, and for which non-opioid analgesics are not sufficient could be considered. However, the data provided do not support a finding that Apadaz has abuse-deterrent properties that can be expected to deter abuse by any route. In particular, the data provided from in vitro and clinical studies did not demonstrate any meaningful differences for Apadaz when compared to a non-abuse-deterrent formulation of hydrocodone bitartrate and acetaminophen. The labeling in

Section 9.2, [redacted] (b) (4) proposed by the Applicant does not accurately convey the outcome of the studies submitted, and makes claims about the properties of Apadaz that are false and misleading. Therefore, according to 21 CFR 314.125(b)(6) the application may not be approved.

To address this deficiency, the Applicant must submit labeling that accurately conveys the results of the assessment of abuse-deterrent properties and that conveys that there are no clinically relevant differences from the non-abuse-deterrent comparator

- Recommendation for Postmarketing Risk Management Activities

None at this time

- Recommendation for other Postmarketing Study Commitments

None at this time.

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/s/

SHARON H HERTZ
06/10/2016

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208653
Priority or Standard	Priority
Submit Date(s)	12/09/2015
Received Date(s)	12/09/2015
PDUFA Goal Date	06/09/2016
Division / Office	Division of Anesthesia, Analgesia & Addiction Products (DAAAP)
Reviewer Name(s)	Jacqueline Spaulding
Review Completion Date	May 8, 2016
Established Name	Benzohydrocodone hydrochloride/acetaminophen
(Proposed) Trade Name	APADAZ
Therapeutic Class	Opioid
Applicant	KemPharm, Inc.
Formulation(s)	Tablet
Dosing Regimen	1-2 tablets Every 4-6 hrs. as needed for pain
Indication(s)	Short-term (no more than 14 days) management of acute pain
Intended Population(s)	Adults

APPEARS THIS WAY ON ORIGINAL

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend an approval action for the new drug application (NDA) 208653, APADAZ (immediate-release benzhydrocodone/acetaminophen) tablets for the indication for the short-term management of acute pain in adults. This recommendation for Approval is based on the Applicant demonstrating a positive risk-benefit profile in the intended population. APADAZ was submitted as a Section 505(b)(2) that relied on the Agency's previous findings of safety and effectiveness for hydrocodone and acetaminophen using relative bioavailability studies with the listed drugs Vicoprofen (hydrocodone and ibuprofen) and Ultracet (tramadol and acetaminophen), in addition to comparison to Norco (hydrocodone and acetaminophen). No additional efficacy studies were required.

The safety profile of APADAZ is similar to that of other opioids. No unexpected safety findings were observed.

APADAZ was designed as an abuse-deterrent opioid. The primary development goal for APADAZ was to reduce the intranasal (IN) and oral abuse potential of immediate-release (IR) hydrocodone/acetaminophen products. Results of *in vitro* experiments and human abuse potential (HAP) studies do not support the Applicant's notion that APADAZ has abuse-deterrent properties. Therefore, my recommendation for approval of APADAZ for short-management of acute pain does not include labeling for abuse-deterrence.

1.2 Risk Benefit Assessment

Benefit

The Applicant submitted NDA 208653 as a 505(b)(2) application. APADAZ contains 6.67 mg benzhydrocodone (KP201) and 325 mg acetaminophen. KemPharm has relied on the FDA's findings of efficacy and safety of two listed drugs: Vicoprofen (7.5 mg hydrocodone bitartrate/ 200 mg ibuprofen oral tablet; NDA 020716), and Ultracet (37.5 mg tramadol hydrochloride/325 mg APAP oral tablet; NDA 021123). To establish the scientific bridge with each listed drug, two bioequivalence studies were conducted in the fasted state comparing KP201/APAP with Vicoprofen for hydrocodone and Ultracet for APAP. APADAZ met the bioequivalence criteria for AUC and Cmax for hydrocodone compared to Vicoprofen and for APAP compared to Ultracet.

No additional efficacy studies were required.

Risk
The assessment of the safety of APADAZ relies on the clinical data provided from the Applicant's studies and the Agency's prior findings of safety for the listed drugs, Vicoprofen and Ultracet. No additional data was required to assess the safety of the benzhydrocodone because there was no detectable systemic exposure, indicating that hydrolysis to hydrocodone was rapid and complete. The safety profile of APADAZ was assessed in 418 healthy subjects who received at least one dose of KP201/APAP and 245 healthy subjects who received multiple doses of KP201/APAP across ten clinical studies. There were no serious adverse events or deaths reported during clinical development of APADAZ.

The majority of adverse events was reported as mild in severity, and reflects typical opioid-associated adverse reactions. The most common adverse events occurred in the gastrointestinal and nervous system disorder classes with specific adverse events including nausea, vomiting, and constipation; dizziness and somnolence.

The Applicant developed APADAZ to deter intranasal and intravenous abuse. However, APADAZ has no properties to deter oral abuse, which is the most common form of abuse. In the oral human abuse potential (HAP) study, at similar dosage levels APADAZ failed to demonstrate any difference in drug liking compared to reference product Norco. In the intranasal study, similar to the oral HAP study, APADAZ failed to demonstrate any difference in drug liking compared to reference product Norco. The third intranasal HAP study could not be used to assess abuse potential or abuse deterrent effects of APADAZ compared against Norco due to study design flaws and deficiencies.

The risks of APADAZ (including overdose, misuse, abuse and addiction) appear to be comparable to other IR opioids. At this time, I believe the NDA meets the regulatory standard for approval for the proposed indication for the short-term management of acute pain in adult patients.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

In order to comply with the Pediatric Research Equity Act (PREA), the Applicant submitted an Initial Pediatric Study Plan (IPSP) that was agreed upon with the Division on October 13, 2015. The proposed IPSP was discussed at the Pediatric Review Committee (PeRC) meeting on May 4, 2016. There was consensus that a deferral was

appropriate for all the following required studies because the product is ready for approval in adults:

1. PK, safety, and efficacy study for ages birth to < 2
2. open-label PK, safety and efficacy study for ages 2 to < 7
3. open-label PK, safety and efficacy study for ages 7 to < 17

2 Introduction and Regulatory Background

Product description: Benzhydrocodone Hydrochloride/Acetaminophen Tablets, 6.67 mg/325 mg, is a fixed-dose combination of 6.67 mg of benzhydrocodone hydrochloride (KP201) (equivalent to 7.5 mg of hydrocodone bitartrate, both of which contain 4.54 mg of hydrocodone base) and 325 mg of acetaminophen (APAP).
Dosage Strengths: 6.67mg/325 mg
Dosing regimen: Every 4-6 hrs.; up to 6 times per day
Pharmacological class: opioid and synthetic nonopioid p-aminophenol derivative
Trade name and established name: APADAZ (benzhydrocodone hydrochloride-acetaminophen tablets)
Proposed Indication: short-term (no more than 14 days) management of acute pain

2.2 Tables of Currently Available Treatments for Proposed Indications

Multiple products are available for the management of moderate to severe acute pain including: single ingredient IR opioid (oxycodone); combination opioids/analgesics such as oxycodone/APAP, hydrocodone/APAP, nonsteroidal anti-inflammatory drugs (NSAIDS) such as ibuprofen, and naproxen; ketorolac, and ultracet (tramadol and acetaminophen).

2.3 Availability of Proposed Active Ingredient in the United States

Hydrocodone bitartrate is currently approved and marketed in the United States (US) in combination with the nonopioid analgesic drugs including: acetaminophen, aspirin and ibuprofen. These combination products contain immediate-release hydrocodone at doses of 5, 7.5 or 10 mg and are to be administered every four to six hours as necessary for pain.

Hydrocodone bitartrate is approved as a single-entity product in an extended-release (ER) capsule formulation in doses of 10, 15, 20, 30, 40 and 50 mg. In addition, there is a single-entity ER hydrocodone bitartrate tablet with abuse-deterrent properties that is available in 20, 40, 60, 80, 100 and 120 mg dose tablets.

Hydrocodone is also available in combination with cough and cold preparations including guaifenesin, chlorpheniramine maleate, pseudoephedrine hydrochloride, and homatropine methylbromide.

2.4 Important Safety Issues With Consideration to Related Drugs

Hydrocodone and other mu opioid agonists are associated with known and potentially serious safety events including: respiratory depression (possibly leading to coma and death), withdrawal, physical dependence and abuse, and the risk of overdosage. Similar to other opioids, the hydrocodone label contains a boxed warning, which in addition to the above reactions discusses events such as accidental exposure, neonatal opioid withdrawal syndrome and interaction with alcohol.

The product insert also contains a boxed warning concerning acetaminophen and the risk of hepatotoxicity.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Important aspects of the presubmission regulatory activity for this NDA are described below.

Pre- IND Meeting **[June 1, 2010]**

- KP201 may be designated as a New Chemical Entity [NCE] if hydrocodone is the *in vivo* hydrolysis product (active moiety)
- Your product may be eligible for exclusivity; however the Division will not make this decision until after approval of drug product. Rarely, exclusivity has been granted in the absence of clinical studies.

End-of-Phase 1 Meeting **[November 15, 2012]**

- Applicant must rely on two NDAs to bridge to previous findings of safety and efficacy by conducting relative bioavailability (BA) studies with Vicoprofen for the hydrocodone component and Ultracet for the APAP component
- If KP201 is a novel combination, efficacy studies would be required, however Applicant may possibly avoid this requirement by demonstrating bioequivalence of KP201 to an approved combination of hydrocodone and acetaminophen (e.g., Norco – despite being an ANDA)

End-of-Phase 2 Meeting **[October 31, 2013]**

- There was agreement between the Division and the Applicant that based on the current data provided and pending the results from future studies (including applicable literature), the completed and proposed clinical and nonclinical program is adequate to support filing an NDA submission for an acute indication of no more than 14 days
- Division clarified that Norco (APAP 325 mg; hydrocodone bitartrate 7.5 mg) would be an appropriate reference product with which to conduct a food effect study

- The Division confirmed that the Applicant's planned safety database, which at the time was estimated to be 265 subjects that will have received a single dose and 176 subjects that will have received multiple doses of KP201/APAP, was acceptable

Pre-NDA Meeting **[May 19, 2015]**

- Applicant informs Division that they reference Vicoprofen (7.5 mg hydrocodone/200 mg ibuprofen) to create the scientific bridge to the Agency's prior findings of safety and effectiveness for the hydrocodone component of KP201/APAP
- Agreement between the Division and Applicant that the Ultracet (37.5 mg tramadol hydrochloride 325 mg APAP) study (KP201.106) would provide an adequate bridge to reference the previous findings of safety and efficacy for the APAP component
- Division stated that the comparison of KP201/APAP to Norco (APAP 325 mg; hydrocodone bitartrate 7.5 mg) in studies KP201.102 and KP201.104 supports the idea that the combination of hydrocodone and acetaminophen does not represent a novel combination, so factorial studies are will not be required
- There was agreement between the Division and the Applicant that an NDA package consisting of a scientific bridge to Vicoprofen and Ultracet and a study comparing their product to Norco to support that KP201/APAP is not a novel combination appears acceptable for submission of a 505(b)(2) application
- Division provided guidance to the Applicant on the abuse deterrence studies and requirements as well as commented on the potential for precipitation of KP201 and risks associated with injection

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of the submission was adequate and reasonably well-organized and paginated to allow for a review.

3.2 Compliance with Good Clinical Practices

The Division requested inspections of clinical bioequivalence study and analytical sites. The Division of New Drug Bioequivalence Evaluation within the Office of Study Integrity and Surveillance (OSIS) responded to the Division with a recommendation to accept data without an onsite inspection.

Rationale

OSIS recently inspected the sites below. The inspectional outcome from the inspection was No Action Indicated. (NAI)

Requested Inspected 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)	

3.3 Financial Disclosures

The Applicant submitted form FDA 3454 "Certification: Financial Interests and Arrangements of Clinical Investigators." There were no financial arrangements reported between the Applicant and investigators. At this time there does not appear to be any financial conflict of interests related to data integrity.

In accordance with 21 CFR 54.4, Certification and Disclosure Requirements; information supplied by the Applicant was used to complete the Financial Certification and Disclosure document as recommended in the FDA Guidance for Industry on Financial Disclosure by Clinical Investigators. I completed the disclosure document and scanned it at the end of this review.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Chemistry, Manufacturing and Controls (CMC) review was conducted by Ben Stevens, PhD from the Office of Product Quality (OPQ).

For a detailed discussion of the CMC aspects of this application, refer to Dr. Stevens' review. A brief summary of Dr. Stevens' interpretation of the Applicant's findings follows:

Summary of In Vitro Studies (CMC)
Extensive in vitro abuse-deterrent studies were conducted to assess the relative difficulty and effectiveness of various potential manipulation methods to defeat the drug product's abuse-deterrent properties. When used, the comparator was IR hydrocodone bitartrate (HB)/APAP tablets.

A. Physical Manipulation (Size Reduction)
No extensive crushing or grinding studies were carried out for this product since it is an IR tablet with no formulation-based abuse-deterrent features.

B. Large Volume Extraction Studies
Test 1 – Solubility and Extraction
These studies were designed to determine the extraction potential and solubility of KP201, HC, and APAP when extracted from their respective tablet formulations with Common and Less Common Solvents under Non-Stressing conditions

Results:
In general, large volume extractions with Common and Less Common Solvents under Non-Stressing conditions led to comparable amounts KP201 and HC extraction from KP201/APAP and HB/APAP tablets, respectively.

There were several important exceptions.
Common Solvents X, Y, and Z led to negligible KP201 extraction while liberating measurable amounts of HC (8.8-37.1%) from KP201/APAP tablets; under these conditions, levels of extracted HC (72-90%) from HB/APAP tablets remained similar to results observed with other Common Solvents. APAP extraction levels remained comparable across most Common Solvent conditions (see below for exception with Common Solvent O). This observation represents a class effect (i.e., are related) and therefore highlights the fact that under certain conditions, the extraction behavior of KP201 and HB/HC diverges. While the propensity for extraction of KP201 appears to be reduced using these solvents, the fact that APAP continues to partition rapidly into solution may enable facile separation of these two APIs. The fate of the non-extracted KP201 under these conditions was also uncertain (i.e., an analysis of any remaining solid material was not originally provided). Therefore, while solution levels of HC were low with KP201/APAP using Common Solvents X-Z under Non-Stressing conditions, it cannot be categorically concluded that KP201 in any remaining solid was intact

Test 2 – Extraction Variables
These studies were designed to evaluate the effects of Stressing Conditions 1 on the extraction potential and solubility of KP201, HC, and APAP from their respective tablets with Common Solvents only. Additional studies using Stressing Conditions 2 and Common Solvents G & H were requested and developed in agreement with FDA.

Results:
In general, large volume extractions under Stressing Conditions 1 led to higher extraction rates for KP201 and HC from both KP201/APAP and HB/APAP when compared to Non-Stressing Conditions. Increased release (rate and amount) of HC from KP201/APAP was observed with Common Solvents X (59.6%), Y (62.7%), and Z (46.0%) under Stressing Conditions 1; however a decrease in HC titer was observed over time for solutions generated from KP201/APAP or HB/APAP under these conditions. The origin of this decrease over time has not been well-established, although it has been ascribed to HC degradation by the applicant. No release of HC was observed with Common Solvent W under Non-Stressing conditions; however, under Stressing Conditions 1, considerable HC was released (60.9%) although the rate was moderately slow (Time to ~30% = 240 min). Common Solvent W is relevant to solutions that would be used by a typical abuser. Under harsher Stressing Conditions 2, Common Solvents G and H (additionally requested by FDA) released comparable amounts of HC from KP201/APAP (80.3 and 70.4%, respectively) at 180 min. Levels of HC from HB/APAP were similar at 180 min with Common Solvents G and H (80.3 and 89.5% respectively), although higher amounts were observed initially (100% HC at T = 15 min). Note that Common Solvent G in particular is safe and highly relevant to IV use; this solvent supplements the harsher and more toxic conditions used for hydrolysis studies under Test 3. Also notable was the fact that HC extraction with Common Solvent A under Stressing Conditions 1 and with Common Solvent F (requested by FDA) under Stressing Conditions 2 exhibit different results (no HC release under the former conditions at 180 min; 10% HC release at 180 min, 42% at 1440 min under the latter conditions). Common Solvent A and F are nearly identical, but this study indicates that subtle changes may considerably affect hydrolysis of the prodrug. Both solutions are ingestible and injectable.

Test 3 – Hydrolysis
These studies were designed to assess the potential of releasing HC from KP201 tablets (extracted, crushed, and intact) using two major classes of hydrolyzing solvents (Hydrolyzing Solvents 1 and 2) under Stressing Conditions 1 and Non-Stressing conditions.

Results:
In general, stronger class 1 and 2 Hydrolyzing Solvents were required to afford high solution concentrations of HC from KP201/APAP tablets. There were several notable exceptions. Hydrolyzing Solvents HS17 and HS18 are relatively mild and would be commonly available to abusers. While total HC release with these solvents was relatively low (23.4 and 11.4% respectfully at T = 60 using crushed tablets under Stressing Conditions 1), a closely related set of conditions carried out on KP201/APAP tablet extracts (Hydrolyzing Solvent C/HS18) leads to good yields (74%) of HC under Non-Stressing conditions, although extended times were required (T = 1440 min).

Stressing Conditions have not been applied to Hydrolyzing Solvent C/HS18 at this point. This difference in results is likely due to the presence of a solubility-enhancing solvent.

C. Small Volume Extractability and Syringeability Studies

Test 1 – Solubility

These studies were designed to assess the solubility profiles of KP201 and HB in aqueous solutions under various conditions (Solubility Conditions 1). Some concerns with the initial methodology led to a second set of conditions determined in agreement with FDA (Solubility Conditions 2).

Results:

The solubility profile of KP201 and HB/HC differs under certain conditions. In general, KP201 is less soluble than HB/HC.

Test 2 – Extractability and Syringeability

These studies were designed to evaluate the feasibility of creating injectable solutions from KP201/APAP and HB/APAP tablets (Injectable Extracts 1 and 2) under Stressing (Injectable Extracts, Stressing) and Non-Stressing (Injectable Extracts, Non-stressing) conditions that are suitable for IV abuse. Glide forces for the solutions were evaluated using Bracketing Common Needle Gauges.

Results:

Under the majority of the evaluated injectable extraction conditions (Injectable Extracts 1), levels of KP201 (54.9-71.6%) and HC (67.1-78.9%) extracted from KP201/APAP and HB/APAP tablets were similar. Stressing and Non-Stressing conditions did not appear to make a considerable difference in recovery and HC was not observed during extraction of the KP201/APAP tablets. A smaller subset of conditions (Injectable Extracts 2) led to lower solution levels of KP201 (12.6-24.2%) from KP201/APAP tablets than HC from HB/APAP tablets. These conditions are related to Common Solvents X-Z used in the large volume extractions and KP201 was likely precipitated and filtered out during preparation of the IV solution. It is noted that under many of the evaluated conditions, precipitate was formed that made isolation or filtration of IV solutions challenging for KP201/APAP tablets; however, given that the drug product formulation was not designed to prevent abuse, this effect may be of limited impact. This is supported by the negligible difference in glide forces reported for injectable solutions of KP201/APAP and HB/APAP using bracketing common needle gauges.

4.2 Clinical Microbiology

This section is not applicable to the application.

4.3 Preclinical Pharmacology/Toxicology

The Preclinical Pharmacology/Toxicology was conducted by Marcus Delatte PhD.

For a detailed discussion of the nonclinical aspects of this application, refer to Dr. Delatte's review which is ongoing at this time.

4.4 Clinical Pharmacology

The Clinical Pharmacology review was conducted by Suresh Naraharisetti Ph.D.

For a detailed discussion of the clinical pharmacology aspects of this application, refer to Dr. Naraharisetti's review. Below is a summary of Dr. Naraharisetti's review.

4.4.1 Mechanism of Action

Benzhydrocodone
Benzhydrocodone is a prodrug of hydrocodone. Benzhydrocodone does not generate any significant pharmacologic effect and requires conversion to active hydrocodone by enzymes in the intestinal tract.

Hydrocodone
Hydrocodone is a semi-synthetic opioid agonist with relative selectivity for the μ-opioid receptor, although it can interact with other opioid receptors at higher doses. Hydrocodone acts as a full agonist, binding to and activating opioid receptors at sites in the peri-aquaductal and peri-ventricular gray matter, the ventro-medial medulla and the spinal cord to produce analgesia. The analgesia, as well as the euphoriant, respiratory depressant, and physiologic dependence properties of μ-opioid receptor agonists like hydrocodone, result principally from agonist action at the μ-opioid receptors.

In addition to analgesia, opioid agonists may produce drowsiness, changes in mood, and mental clouding.

Acetaminophen

Acetaminophen is a weak inhibitor of the synthesis of prostaglandins, but the specific mechanism is as yet undetermined.

4.4.2 Pharmacodynamics

Hydrocodone

Effects on the Central Nervous System

Hydrocodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.

Hydrocodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle
Hydrocodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System
Hydrocodone produces peripheral vasodilation, which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating and/or orthostatic hypotension.

Caution must be used in hypovolemic patients, such as those suffering acute myocardial infarction, because hydrocodone may cause or further aggravate their hypotension. Caution must also be used in patients with cor pulmonale who have received therapeutic doses of opioids.

Effects on the Endocrine System
Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.
Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

Effects on the Immune System
Opioids have been shown to have a variety of effects on components of the immune system in in vitro and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration–Efficacy Relationships
The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of hydrocodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance.

Concentration–Adverse Reaction Relationships
There is a relationship between increasing hydrocodone plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions

4.4.3 Pharmacokinetics

APADAZ met the bioequivalence criteria for hydrocodone AUC and Cmax; the data provided demonstrated that it is bioequivalent to another immediate-release hydrocodone combination product. 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 two comparative bioavailability studies following oral administration of a single dose to healthy subjects under fasted conditions, 6.67 mg/325 mg APADAZ tablet met the bioequivalence criteria for hydrocodone AUC and Cmax compared to immediate-release tablet of Vicoprofen, 7.5 mg hydrocodone/200 mg ibuprofen and met the bioequivalence criteria for acetaminophen AUC and Cmax compared to immediate-release tablet of Ultracet, 37.5 mg tramadol/325 mg acetaminophen.

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

AUC with regard to hydrocodone; and met the bioequivalence criteria for APAP AUC, with almost comparable APAP 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 an FDA standard high-fat, high-calorie breakfast indicated no significant overall change in exposure to hydrocodone and acetaminophen. The data showed a slight decrease in the rate but no change in the extent of hydrocodone exposure absorption to hydrocodone; and no difference in rate and extent of acetaminophen exposure absorption. The effect of a high-fat, high-calorie meal on pharmacokinetics is similar between after oral administration of a single dose of APADAZ compared with and immediate-release tablet of 7.5 mg hydrocodone/325 mg acetaminophen hydrocodone/APAP when both were administered with food. 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 are displayed in Table 1 following.

Table 1: PK Parameters of Hydrocodone and Acetaminophen after Oral Administration of APADAZ Tablet 6.67 mg/325 mg under Fasted and Fed Conditions

Hydrocodone

Parameter [a]	KP201/APAP, 6.67 mg/325 mg	
	Fed	Fasted
Cmax (ng/mL)	16.04 ± 3.61 (40)	19.18 ± 4.84 (38)
Tmax (h)	2.50 (40) [0.50–4.00]	1.25 (38) [0.50–3.00]
AUC0-t (h×ng/mL)	125.80 ± 26.90 (40)	121.40 ± 35.18 (38)
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]
AUC0-t (h×µg/mL)	14.5 ± 3.41 (39)	14.6 ± 4.42 (38)
AUCinf (h×µg/mL)	15.0 ± 3.53 (36)	14.7 ± 3.87 (36)
t½ (h)	5.64 ± 1.58 (36)	4.78 ± 1.30 (36)

Source: Clinical Pharmacology Review, Table1.3.3a and Table 1.3.3b,pp 4-5/59

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 (multiple dose / single dose) Cmax and, AUC0-4, were 1.85-fold, and 2.03-fold, respectively. The accumulation ratios for acetaminophen (multiple dose / single dose) for Cmax and, AUC0-4 values were 1.38-fold, and 1.80-fold, respectively.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Refer to Section 7.1

5.2 Review Strategy

The strategy employed in reviewing the NDA involved:

- Evaluation of safety in the Phase 1 studies
- Evaluation of safety in the human abuse potential (HAP) studies
- Review of consultation from the Controlled Substance Staff (CSS), which was obtained to assess the HAP studies.

5.3 Discussion of Individual Studies/Clinical Trials

Study KP201.101
Study 101 was a Phase 1, randomized, open-label, single-dose, three-treatment, three-period, six-sequence, crossover BA study in 24 healthy adult subjects to assess the PK of KP201 and KP201-derived hydrocodone and hydromorphone after oral administration of a 5 mg dose as 1 x 5 mg neat filled capsule and a 10 mg dose as 2 x 5 mg neat filled capsules compared to the PK of hydrocodone and hydromorphone observed after oral administration of the commercially available tablet version of Norco® (hydrocodone bitartrate and acetaminophen 10/325 mg) under fasted conditions. The safety and tolerability KP201 in healthy subject volunteers was also assessed.

Of note, in Study 101 an earlier formulation of KP201 was administered to subjects and was not the proposed to-be-marketed formulation.

The study consisted of two single doses of KP201 5 mg (1 x 5 mg) and 10 mg (2 x 5 mg) and one single dose of hydrocodone bitartrate and acetaminophen (1 x 10/325 mg, Norco) being administered to each subject (who served as their own control) in three dosing periods under fasting conditions

PK Results

The Applicant reports that for the log-transformed hydrocodone exposure parameters Cmax, AUClast, and AUCinf, the geometric mean ratios of the comparison of 5 mg KP201 (Treatment A) and 10/325 mg Norco (Treatment C) were 51.15%, 44.66%, and 47.37%, respectively. The maximum and total hydrocodone exposure following the administration of 5 mg KP201 is approximately half of that following the administration of 10/325 mg Norco (Treatment C).

The Applicant also reports that the 90% confidence interval for comparing the maximum exposure to hydrocodone following the administrations of 10 mg KP201 (Treatment B) and 10/325 mg Norco (Treatment C), based on ln(Cmax), is within the accepted 80% to 125% limits.

Finally, the Applicant reports that the 90% confidence intervals for comparing total systemic exposure to hydrocodone, following the administrations of 10 mg KP201 (Treatment B) and 10/325 mg Norco(Treatment C), based on ln(AUClast) and ln(AUCinf), are within the accepted 80% to 125% limits.

The Applicant believes that the test formulation of 10 mg KP201 capsule manufactured (b) (4) for KemPharm, Inc. meets the bioequivalence criteria for hydrocodone compared to the reference listed drug product (RLD) Norco® 10/325 mg tablet by Watson Pharmaceuticals, Inc. under fasted conditions.

SAFETY RESULTS

Subject Disposition

Of the 24 subjects randomized, 21 subjects completed the study. Three subjects were reported to have been withdrawn from the study due to meeting stop criteria for vital signs out of range. No AEs were associated with subject discontinuation.

There were no SAEs including deaths reported for this study. The most commonly reported AEs for this study were dizziness and nausea.

In addition, there were no reported clinically significant labs, ECG, or physical exam findings. Also, there were no reported unusual or unexpected AEs related to KP201 in this study.

In summary, this study used an early formulation of KP201 (5-mg capsule) to compare the bioavailability of KP201 to Norco (hydrocodone/APAP) under fasted conditions. The

Applicant's results showed that the early formulation a statistically significant dose-dependent increase in Cmax, AUClast, AUCinf, and t1/2 for hydrocodone was observed; the maximum and total hydrocodone exposure following the administration of 5 mg KP201 capsule was approximately half of that following the administration of 10 mg/325 mg Norco and KP201 and the 10 mg dose was BE to Norco (10 mg hydrocodone/325 mg APAP) with respect to hydrocodone). There were no unusual safety events in the study.

Study KP201.102

Study 102 was an open-label, single-dose, randomized, 2-treatment, 2-period, 2-sequence, crossover bioequivalence study in 30 healthy adults to compare the rate and extent of absorption of hydrocodone, hydromorphone, and APAP from a single dose of KP201/APAP relative to a single dose of Norco tablet (7.5 mg hydrocodone/325 mg APAP) when administered orally under fasted conditions. The safety and tolerability of KP201/APAP in healthy subject volunteers was also assessed.

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 total dose administered to each subject who completed both study periods was 6.67 mg of KP201, 7.5 mg of hydrocodone, and 650 mg of APAP.

PK Results

The Applicant reports the following results for KP201/APAP Compared to Norco under Fasted Conditions:

- Geometric means for the Cmax, AUC0-t, and AUCinf for hydrocodone were lower for KP201/APAP than for Norco, with geometric mean ratios of 86.79%, 94.17%, and 94.05%, respectively. The associated 90% confidence intervals (CI) for all 3 parameters were contained within 80.00% to 125.00%, demonstrating bioequivalence of the 2 products with respect to hydrocodone.
- For hydromorphone, geometric means for Cmax and AUC0-t were 89.15% and 94.87%, respectively, and both associated 90% CIs were contained within 80.00% to 125.00%. Based on Cmax and AUC0-t, the 2 products are bioequivalent with respect to hydromorphone, supporting the bioequivalence demonstrated with hydrocodone

Table 2 shows the statistical comparison of PK parameters for acetaminophen after oral administration of single doses of KP201 (6.67/325) and Norco (7.5/325) to healthy subjects under fasted conditions.

Table 2: Statistical Comparison of PK parameters for APAP after Oral Adminisrationof Single Doses of KP201 (6.67) and Norco (7.5/325 mg) to Healthy Subjects under Fasted Conditions:

Parameter	Geometric Mean*		Geometric Mean Ratio (%)	
	Test	Reference	Estimate	90% Confidence Interval
KP201 (6.67/325) vs. Norco (7.5/325)				
Cmax	3.79	4.18	90.76	79.81 → 103.20
AUC(0-t)	15.82	15.64	101.15	98.08 → 104.32
AUC(inf)	16.76	16.63	100.76	97.66 → 103.96

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

Source: NDA 208653, KP201/APAP, PK Report, Table 6, pg. 20/130

The Applicant reports despite missing the lower bound of the APAP Cmax 90% CI (79.81) 80% bioequivalence limit in this study is not likely to have a clinical impact on the efficacy and safety of KP201/APAP.

SAFETY RESULTS

Subject Disposition

Of the 30 subjects randomized 24 subjects completed the study. Six subjects were reported to have been withdrawn from the study due to meeting the vital sign criteria for withdrawal. Two out of the six subjects withdrawn by the Sponsor experienced AEs that were reported to have been clinically significant by the Investigator. One subject (# (b) (6)) reportedly experienced significant AEs of presyncope and hypotension. Another subject (# (b) (6)) reportedly experienced a significant AE of presyncope. No AEs were reported to have been associated with subject discontinuation.

There were no deaths, or serious adverse events reported for this study. One subject (# (b) (6)) assigned to the KP201/APAP treatment arm was reportedly withdrawn by the sponsor for meeting the vital sign criteria for withdrawal; and this subject was also reported to have experienced clinically significant AEs of presyncope and hypotension. The most commonly reported AEs for this study were dizziness and nausea.

In summary, the purpose of this bioequivalence study with Norco was to demonstrate that KP201/APAP was not a novel drug-drug combination. Although the lower bound of the APAP Cmax 90% CI slightly missed the 80% bioequivalence limit; per discussion with the Clinical Pharmacology review team we believe this result does not affect the 505(b)(2) previous findings of safety and efficacy. Safety findings for subjects treated with KP201 were consistent with most opioids. There were no unusual or unexpected AEs related to KP201 in the study.

Study KP201.103

Study 103 was an open-label, single-period, single- and multiple-dose PK study of KP201, hydrocodone, hydromorphone, and APAP following a single dose of KP201/APAP Tablets (2 × 6.67 mg/325 mg) under fasted conditions and to assess the steady-state pharmacokinetics of KP201, hydrocodone, hydromorphone, and APAP

following multiple doses of KP201/APAP Tablets (2 × 6.67 mg/325 mg) administered every 4 hours under fasted conditions in 26 healthy adult subjects. After completing an overnight fast (10 hours), 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 (24) hours after the first dose (Day 2), subjects entered the multi-dose portion of the study and received KP201/APAP Tablets (Dose 2 through Dose 14) every 4 hours for a total of 14 doses in a confined setting.

PK Results

The pharmacokinetic parameters of hydrocodone and APAP after administration of KP201/APAP are summarized in Tables 3 and 4.

Table 3: Summary of PK parameters for hydrocodone during Oral Administration of Two KP201/APAP tablets on Day 1 followed by two KP201/APAP tablets Q4H X 14 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)

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

Source: Suresh Naraharisetti, PhD. Open Session Clinical Pharmacology Background Document, NDA 208653, Table 9, Pg. 13/13,

Table 4: Summary of PK parameters for APAP during Oral Administration of Two KP201/APAP tablets on Day 1 followed by two KP201/APAP tablets Q4H X 14 doses (Days 2 to 4) to healthy subjects under fasted conditions (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)

Source: Suresh Naraharisetti, PhD. Open Session Clinical Pharmacology Background Document, NDA 208653, Table 10, Pg. 13/13,

The Applicant reported their results as all plasma concentrations of the prodrug, KP201, were < LOQ (25 pg/mL) after the 1st dose, before Doses 4 and 6 on Day 2 and Doses 8, 10, and 12 on Day 3, and before and after the 14th dose on Day 4, demonstrating

that there is no measureable exposure to the prodrug even after administration of the maximum daily dose of 2 tablets Q4H for 13 doses.

In addition, the PK of hydrocodone and acetaminophen were reported as linear and predictable after administration of single and multiple doses of KP201. Although there were discordances between the single and multiple dose PK of hydromorphone, accumulation was lower than predicted.

SAFETY RESULTS

Subject Disposition

A total of 26 subjects were enrolled in the study; 24 subjects completed the study. Two subjects withdrew their consent.

There were no deaths, or SAEs or clinically significant AEs reported in this study. The most commonly (>10%) reported AEs by preferred term were abdominal distension, abdominal pain, constipation and nausea.

In summary, plasma levels of KP201 were not detectable after multiple doses of KP201/APAP. Steady-state for hydrocodone was reached at approximately 24 hrs. after initiation of multiple dosing. The hydrocodone accumulations for Cmax, AUC0-4, and AUC0-t values (Day 4/Day1 or 14th dose/ 1st dose of KP201/APAP) were 1.85-fold, 2.10-fold, and 2.03-fold, respectively. The steady state for APAP was reached approached 24-36 hrs. after initiation of multiple dosing. The APAP accumulations for Cmax, AUC0-4, and AUC0-t values (Day 4/Day1 or 14th dose/ 1st dose of KP201/APAP) were 1.38-fold, 1.69-fold, and 1.80-fold, respectively. With respect to safety, subjects received multiple doses of KP201/APAP with naltrexone block with commonly reported TEAEs ≥10% being dizziness and nausea.

Study KP201.104

Study 104 was an open-label, single-dose, randomized, three-treatment, three-period, six-sequence crossover study to assess the effect of food on the bioavailability and PK of hydrocodone and APAP from KP201/APAP and the relative BA of KP201/APAP and Norco under fed conditions in 42 healthy adult volunteers of both genders.

Subjects received a single dose of KP201/APAP tablet, 6.67 mg/325 mg under fed conditions in one period, a single dose of KP201/APAP tablet, 6.67 mg/325 mg under fasted conditions in one period, and a single dose of Norco Tablet, 7.5 mg/325 mg in one period. Of note, the FDA standard for the fed state is a high fat, high calorie breakfast. Each period was separated by a washout of 7 days.

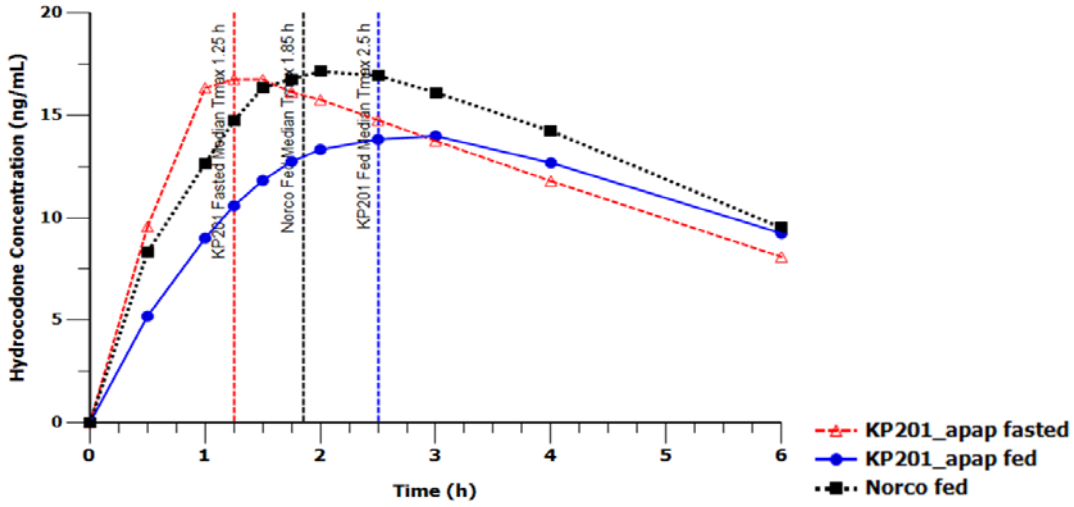
Safety measurements were taken at screening and at the end of the study and they included: adverse events, physical exam, vital signs (blood pressure, pulse, respiratory rate, temperature, and pulse oximetry), ECG, clinical laboratory tests (serum chemistry, hematology, and urinalysis), C-SSRS and concomitant medications.

PK Results

KP201 – The Applicant reports that all plasma concentration of the prodrugs, KP201, were less than the validated lower limit of the bioanalytical method (<LLOQ) of 25pg/mL after administration of K201/APAP (6.67 mg/325 mg)

Figure 1 shows the mean concentrations of hydrocodone after administration of KP201/APAP under both fed and fasted states.

Figure 1 Mean SE plasma concentrations of hydrocodone after oral administration of single doses of KP201/APAP (6.67 mg/325 mg) under fed and fasted conditions and Norco (7.5 mg/325 mg) under fed conditions to healthy subjects)



Source: NDA 208653, Suresh Naraharisetti's Midcycle PowerPoint Presentation, slide 9/17

The Applicant's results show that the mean plasma concentrations of hydrocodone were lower after administration of KP201/APAP in the fed state compared to the fasted state.

Table 5 shows the summary of PK results for hydrocodone after oral administration of single doses of KP201/APAP (6.67 mg/325 mg) under fed and fasted conditions and Norco (7.5 mg/325 mg) under fed conditions to healthy subjects.

Table 5: Summary of PK parameters for hydrocodone after oral administration of single doses of KP201/APAP (6.67 mg/325 mg) under fed and fasted conditions and Norco (7.5 mg/325 mg) under fed conditions to healthy subjects

Parameter[a]	KP201/APAP tablet, 6.67 mg/325 mg		Norco® tablet, 7.5 mg/325 mg
	Fed	Fasted	Fed
C_{max} [pg/mL]	16,044 ± 3,608 (40)	19,175 ± 4,840 (38)	20,953 ± 7,645 (40)
T_{max} [h]	2.50 (40) [0.50–4.00]	1.25 (38) [0.50–3.00]	1.90 (40) [0.50–4.00]
AUC_{0-t} [h×pg/mL]	125,798 ± 26,900 (40)	121,404 ± 35,183 (38)	135,365 ± 30,297 (40)
AUC_{inf} [h×pg/mL]	130,905 ± 29,451 (40)	125,729 ± 36,783 (38)	140,162 ± 31,661 (40)
λz [1/h]	0.1566 ± 0.0238 (40)	0.1645 ± 0.0290 (38)	0.1632 ± 0.0289 (40)
$t_{½}$ [h]	4.53 ± 0.70 (40)	4.33 ± 0.67 (38)	4.36 ± 0.68 (40)

Source: NDA 208653, KP201.104 PK Study Report

The Applicant's results revealed a decreased Cmax when KP201 was administered in the fed state with a geometric mean ratio (GMR) of 85.3% and an associated 90% CI of 79.4% to 91.6%. In addition, the median Tmax increased from 1.25 in the fasted state to 2.5 h in the fed state. The AUC(0-t) and AUC(inf) were higher when KP201 was administered in the fed state.

SAFETY RESULTS

Subject Disposition

A total of 42 subjects were enrolled in the study and 38 subjects completed the study. Four subjects [redacted] (b) (6) were reported to have been discontinued from the study due to meeting the vital sign criteria for withdrawal. No AEs were reported to have been associated with subject discontinuation.

There were no SAEs (including deaths) and no severe AEs reported for this study. Three subjects [redacted] (b) (6) were reported to have experienced clinically significant AEs of hypotension after receiving KP201/AP01 treatment during the study. The most commonly reported TEAEs ≥ 10% were dizziness and nausea.

In summary, administration of KP201/APAP under fed conditions 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. Subjects treated with KP201 experienced adverse events consistent with mu opioids.

Study KP201.105

Study 105 was an open-label, single-dose, randomized, 2-treatment, 2-period, 2-sequence crossover relative bioavailability study to compare the PK of hydrocodone/hydromorphone from KP201/APAP tablet with that of a Vicoprofen tablet in 30 healthy adults of both genders.

All study doses were administered after a standard overnight fast (approximately 10 hours). In a random fashion, subjects received a single-dose of KP201/APAP or Vicoprofen (7.5 mg hydrocodone/ 200 mg ibuprofen) on 2 separate occasions separated by a 7-day washout period.

PK Results

Table 6 displays the Applicant's results for hydrocodone and hydromorphone when KP201/APAP was compared with Vicoprofen.

Table 6: Statistical Comparison of PK parameters for Hydrocodone and Hydromorphone After Oral Administration of Single Doses of KP201/APAP (6.67 mg/325 mg) and Vicoprofen (7.5 mg/200 mg) to Healthy Subjects Under Fasted Conditions (Study KP201.105

Parameter	Geometric Mean[a]		Geometric Mean Ratio [%]	
	Test	Reference	Estimate	90% Confidence Interval
Hydrocodone				
C_{max}	20,575.07	20,463.22	100.55	94.50 → 106.99
AUC_{0-t}	128,401.91	128,898.71	99.61	95.39 → 104.03
AUC_{inf}	132,371.24	132,608.72	99.82	95.62 → 104.20
Hydromorphone				
C_{max}	226.06	217.78	103.80	95.32 → 113.03
AUC_{0-t}	1,530.38	1,518.89	100.76	94.52 → 107.40
AUC_{inf}	_[b]	_[b]	_[b]	_[b]

Source: NDA 208653, Clinical Overview, Table 2.5:5, pg. 16/49

The Applicant's reports that their results study showed equivalence in exposure to hydrocodone and hydromorphone, as measured by Cmax, AUC0-t, and AUCinf after oral administration of KP201/APAP or Vicoprofen.

SAFETY RESULTS

Subject Disposition

A total of 30 subjects were enrolled in the study with 28 subjects being reported to have completed the study. Two subjects (#401 and #420) were reported to have been discontinued from study due to meeting the vital sign criteria for withdrawal. No AEs were reported to have been associated with subject discontinuation.

There were no deaths or other SAEs reported in this study. Also there were no severe or clinical significant AEs reported for this study. The most commonly reported TEAEs >10% for any treatment group were nausea and dizziness.

In summary, after oral administration of KP201/APAP tablet or vicoprofen tablet the study showed BE to hydrocodone and hydromorphone as measured by Cmax, AUC0-t, and AUCinf. There were no unusual or unexpected safety findings reported for this study.

KP201.106

Study 106 was an open-label, single-dose, randomized, 2-treatment, 2-period, 2-sequence crossover relative bioavailability study to compare the pharmacokinetics, safety and tolerability of APAP from a KP201/APAP tablet with that of an Ultracet tablet in 30 healthy adult subjects under fasted conditions.

Subjects received two single-dose treatments. Each treatment was separated by a 7-day washout period. All study doses were administered after a standard 10-hour overnight fast

PK Results

Table 7 displays the Applicants' results for APAP when KP201/APAP was compared with Ultracet

Table 7: Statistical Comparison of PK Parameters for APAP after Oral Administration of Single Doses of KP201/APAP (6.67 mg/325 mg) and Ultracet (37.5 mg/APAP 325 mg) to Healthy Subjects under Fasted Conditions (Study KP2010.106)

Parameter	Geometric Mean[a]		Geometric Mean Ratio [%]	
	Test	Reference	Estimate	90% Confidence Interval
C_{max}	3.60	3.60	99.99	91.73 → 108.98
AUC_{0-t}	14.78	15.42	95.86	88.71 → 103.59
AUC_{inf}	14.94	15.36	97.28	93.32 → 101.39

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

Source: NDA 208653, KP201/APAP, Clinical Overview Table 2.5:6, pg. 17/49

The Applicant reports that their results show exposure to APAP as measured by Cmax, AUC0-t, and AUCinf was equivalent after oral administration of KP201/APAP or Ultracet.

SAFETY RESULTS

Study Disposition

A total of 30 subjects were enrolled in the study, and 27 were reported to have completed the study. Three subjects (b) (6) that received KP201/APAP treatment were reportedly discontinued from the study due to meeting vital sign criteria for withdrawal. However, there were no reported discontinuations due to AEs in the study.

There were no deaths, SAEs, or severe AEs reported during the study. There were three KP201-treated subjects who reportedly experienced clinically significant AEs by the investigator (i.e., vital signs associated with symptomatic hypotension). The most commonly reported AEs in the study were nausea, dizziness, and headache.

In summary, KP201/APAP product met the bioequivalence criteria for AUC and Cmax for APAP compared to Ultracet. Safety results showed clinically significant AEs of hypotension associated with KP201 treatment in addition to other expected opioid class effect AEs (gastrointestinal and nervous system system organ class (SOC)).

KP201.S01

Study S01 was a randomized, 2-way, crossover study to assess the gastrointestinal effect of KP201/APAP compared with Norco; and to evaluate the total digestive tract transit time in hours (defined as the transit time from swallowing the SmartPill to anus) in 50 healthy subject volunteers of both genders with normal gastrointestinal function and bowel movement patterns

Eligible subjects were randomized in a 1:1 ratio to one of the following study drug treatment sequence:

Treatment Assignment	First In-Patient Period	Second In-Patient Period
Sequence A	KP201/APAP 6.67 mg/325 mg: 1 tablet every 4 hours for 72 hours	Norco®, 7.5 mg/325 mg: 1 tablet every 4 hours for 72 hours
Sequence B	Norco®, 7.5 mg/325 mg: 1 tablet every 4 hours for 72 hours	KP201/APAP 6.67 mg/325 mg: 1 tablet every 4 hours for 72 hours

Source: NDA 208653, KP201/APAP, Clinical Study Report KP201.S01, pg. 17/159

Subjects were admitted to the research center on the day (Day 1, Period 1 and Day 22, Period 2) of the scheduled first dose of study medication and were confined until Day 4 (Period 1) or Day 25 (Period 2) after study procedures were completed.

During each in-patient period, the following key procedures and assessments were performed:

- Subjects administered study med according to sequence assignment at randomization. Study drug was administered every 4 hours for 72 hours.
- Subjects were administered a wireless motility capsule about 4 hours after treatment initiation. Prior to ingestion, the capsule was calibrated and activated. A small, lightweight external data recorder containing a rechargeable battery was attached and worn around the subject's waist, and the subject was instructed to keep the data receiver within 3 feet of his or her body during the testing period (Day 1 to 4 or Day 22 to 25). Subjects were instructed to manually record each bowel movement by pressing an event button on the data receiver

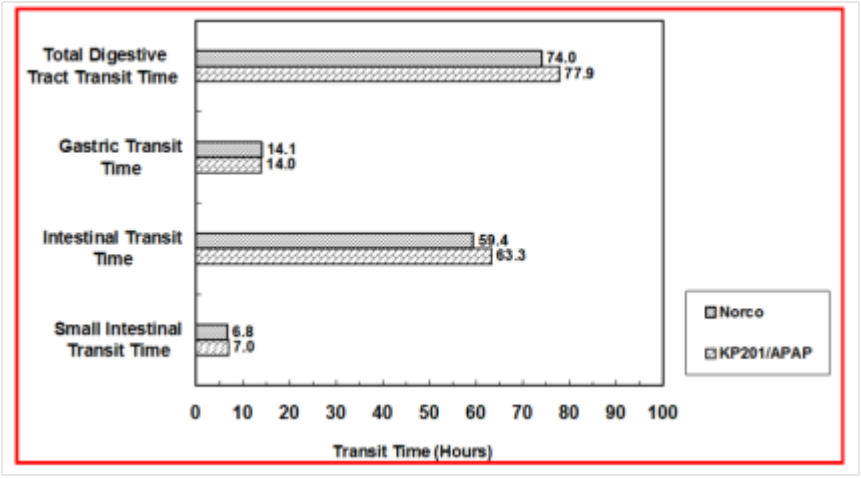
- Subjects were given a diary to record the time of each bowel movement, time of meals, time of sleep (e.g., bedtime to wake-up), and time(s) of laxative use, if applicable
- Vital signs (respiratory rate, heart rate, blood pressure, and oral temperature as well as oxygen saturation) were measured after 5 minutes of resting quietly at pre-dose and then twice daily. Out-of-range vital signs were repeated once (within 2 minutes) in order to ensure accuracy.
- Bowel movements were monitored and recorded. Character of bowel movement was assessed using the Bristol Stool Scale.
- Numerical rating scales for constipation, nausea, itching/pruritus, and somnolence were completed every night.
- A global assessment of how bothersome the symptoms of constipation, nausea, pruritus, and/or somnolence were during the treatment period was completed on Day 4 (Period 1) and Day 25 (Period 2) prior to discharge.
- Adverse events (AEs) were elicited by non-directed questioning, while in the research center.
- Subjects were screened for suicidal ideation or suicidal behavior as assessed by the C-SSRS (since last visit) on each day of dosing.
- Subjects were discharged from the research center after Day 4 or Day 25 procedures were completed. Following discharge from the study unit, subjects continued to report AEs during the follow-up safety period. In the event a subject had not excreted the motility capsule after Day 4 or Day 25 procedures had been completed, that subject was sent home with the external data receiver with instructions for handling until the motility capsule had been excreted and with the subject diary for recording time of bowel movements. Once the motility capsule had been excreted, the subject returned to the unit for an unscheduled visit to return the external data receiver and diary.
- A follow-up safety call was completed about 3 days after each discharge for assessment of AEs and concomitant medication.

Efficacy Evaluation

Pharmacodynamic Digestive Tract Transitive Time (MTDTTT)

The primary analysis of PD measures was conducted on the PD primary endpoint of the total digestive tract transit time (STTT) to evaluate the difference of KP201/APAP vs. Norco, using a mixed-effects model of analysis of variance (ANOVA) for the evaluable population (EP) and per-protocol population (PP). SmartPill digestive tract transit times are presented in Figure 2.

Figure 2: SmartPill Digestive Tract Transit Time: Evaluable Population (N=39)



Source: NDA 208653, KP201/APAP, Clinical Study Report DP201.S01, Figure 1, pg. 35/159

The Applicant 's reports their results as follows: the mean total digestive tract transit time was 77.9 hours following administration of KP201/APAP compared to 74.0 hours following administration of HB/APAP. The mean gastric transit time was 14.0 after KP201/APAP was administered compared to 14.1 hours oral administration of HB/APAP. The mean Intestinal transit time was 63.3 hours following administration KP201/APAP compared to 59.4 hours after administration of HB/APAP. The mean small intestinal transit time was 7.0 hours after administration KP201/APAP compared to 6.8 hours after administration of HB/APAP.

SAFETY RESULTS

Subject Disposition

A total of 50 subjects were randomized to treatment in Period 1; 41 completed the study. Of the nine subjects that terminated the study early; three withdrew consent, three were terminated by the investigator; and three were prematurely discontinued due to AEs. Overall, five subjects were discontinued from the study early due to TEAEs.

There were no deaths, or SAEs reported in this study. Two (b) (6) of the five subjects that were discontinued early due to AEs reportedly received KP201/APAP treatment. A brief summary of these two subjects can be found in Section 7.3.3

Table 8 summarizes the incidence of AEs for Study KP201.S01

Table 8: Incidence of TEAEs by PT for Study KP201.S01

Preferred Term	KP201/APAP (n = 47)		Norco (n = 47)		Any Treatment (n = 50)	
	N (%)	AE Counts	N (%)	AE Counts	N (%)	AE Counts
Any event	41 (87.2)	149	44 (93.6)	132	49 (98.0)	281
Gastrointestinal disorder	36 (76.6)	78	36 (76.6)	71	45 (90.0)	149
Abdominal pain	0	0	1 (2.1)	1	1 (2.0)	1
Abdominal pain lower	1 (2.1)	1	0	0	1 (2.0)	1
Constipation	20 (42.6)	21	19 (40.4)	20	28 (56.0)	41
Diarrhea	0	0	1 (2.1)	1	1 (2.0)	1
Flatulence	2 (4.3)	2	1 (2.1)	1	3 (6.0)	3
Gastritis	1 (2.1)	1	0	0	1 (2.0)	1
Nausea	29 (61.7)	34	32 (68.1)	33	39 (78.0)	67
Vomiting	19 (40.4)	19	15 (31.9)	15	22 (44.0)	34
Infections and Infestations	1 (2.1)	1	0	0	1 (2.0)	1
Upper respiratory tract infection	1 (2.1)	1	0	0	1 (2.0)	1
Musculoskeletal and connective tissue disorders	1 (2.1)	1	1 (2.1)	1	1 (2.0)	1
Muscle twitching	0	0	1 (2.1)	1	1 (2.0)	1
Pain in extremity	1 (2.1)	1	0	0	1 (2.0)	1
Nervous system disorders	35 (74.5)	43	33 (70.2)	39	41 (82.0)	82
Dizziness	4 (8.5)	4	4 (8.5)	4	7 (14.0)	8
Headache	5 (10.6)	5	3 (6.4)	4	6 (12.0)	9
Somnolence	33 (70.2)	34	31 (66.0)	31	39 (78.0)	65
Respiratory, thoracic and mediastinal disorders	1 (2.1)	1	0	0	1 (2.0)	1
Epistaxis	1 (2.1)	1	0	0	1 (2.0)	1
Skin and subcutaneous tissue disorders	24 (51.1)	25	21 (44.7)	21	28 (56.6)	46
Pruritus	9 (19.1)	9	10 (21.3)	10	13 (26.0)	19
Pruritus generalized	15 (31.9)	16	11 (23.4)	11	17 (34.0)	27

Source: NDA 208653, KP201/APAP, SCS, Table 2.7.4.2:2, pg. 18/42

The most frequent AEs reported for the KP201/APAP treatment group were consistent with the safety profile of the opioid hydrocodone and included: somnolence, nausea, constipation and vomiting.

In summary, part of the Applicant's rationale for conducting the GI motility study was to evaluate if KP201 could demonstrate gut effects that were unique compared to equivalent doses of narcotics (i.e. Norco). Results of digestive transit times revealed no clinically meaningful differences between subjects administered KP201/APAP (6.67mg/325 mg) compared to subjects administered Norco (7.5 mg/325 mg). With respect to safety, the most frequently reported AEs in KP201 treated subjects were those consistent with opioids' safety profile.

Dr. James Tolliver, Pharmacologist, from the Controlled Substances Staff (CSS), reviewed the oral human abuse potential study KP201.A01, intranasal human abuse potential study KP201.A02, and Clinical Study KP201.A03 and evaluated the Applicant's results for these studies. Brief descriptions of these studies and his interpretation of the Applicants' results follow:

For a detailed discussion of the human abuse potential (HAP) studies, refer to Dr. Tolliver's review.

Study KP201.A01

Study A01 was a single-center, randomized, double-blind, placebo-controlled, single-dose, 7-way crossover study to determine relative bioavailability, abuse potential and safety of KP201/APAP relative to hydrocodone/APAP when administered orally to nondependent, recreational opioid users.

The study consisted of a Screening Period, Naloxone Challenge Test, an in-clinic Qualification and Treatment Phase, and a Follow-up Period.

Sixty-two subjects comprised the pharmacodynamic completer population. Subjects who successfully completed the Naloxone Challenge Test completed a Drug Discrimination Test to determine whether they could move to the Treatment Phase. In a 2-way crossover, 1:1 ratio, double-blind, randomized design, subjects received a single, oral dose of HB/APAP 45 mg/1,950 mg (6 over-encapsulated Norco tablets, 7.5 mg/325 mg each) and placebo (6 capsules). Subjects were required to discriminate active treatment from placebo based on the following criteria:
A minimum peak effect (Emax) of 65 points for Drug Liking in response to active treatment during the first 2 hours post-dose;

- A ≥ 15-point Emax difference between active and placebo treatments at 1 or more time points during the first 2 hours following drug administration; and
- A placebo response ≥40 and≤ 60 points for Drug Liking during the first 2 hours following drug administration.

Subjects were also required to demonstrate tolerance to the treatments as demonstrated by no emesis within the first 2 hours after dosing.

Products used for treatments in the Treatment Phase included the following:

- Test Drug: KP201/APAP, 6.67 mg/325 mg tablets, over-encapsulated
- Comparator: Hydrocodone Bitartrate (HB)/Acetaminophen (APAP), USP, 7.5/325 mg tablets, over-encapsulated
- Placebo: Microcrystalline cellulose powder in capsules

For the Treatment Phase, subjects were randomized to 1 of 14 treatment sequences using a computer-generated randomization scheme based on a William's pair design. Subjects received the treatments listed below in a double blind, double dummy design following an overnight fast of at least 8 hours and with a separation of at least 72-hours.

- Placebo
- KP201/APAP (80.04mg/3,900mg)- 12 Tablets
- KP2011APAP (53.36 mg/2,400 mg) - 8 Tablets
- KP201/APAP (26.68 mg/1,300 mg) - 4 Tablets
- HB/APAP (90 mg/3,900 mg)- 12 Tablets
- HB/APAP (60 mg/2,600 mg) - 8 Tablets
- HB/APAP (30 mg/1,300 mg)- 4 Tablets

During each Treatment Period of the Double-blind Treatment Phase, serial 3 mL blood samples for PK evaluation were collected pre-dose and at selected times out to 36.0 hours post-dose. PK parameters determined for plasma hydrocodone included:

- Cmax = Maximum plasma level of hydrocodone achieved
- Tmax = Time to achieve Cmax
- AUCo-x= Area under the hydrocodone plasma concentration curve from time 0 to x, where x denotes 0.5, 1, 2, 4, 8, and 24 hours

Single primary endpoint was maximum Drug Liking (Emax) as determined using the 0-100 mm bipolar Drug Liking VAS. For assessing Drug Liking, subjects were asked the question "Do you like the effect that you are feeling now?" The question was scored using a 0-100 mm bipolar VAS anchored on the left with "strong disliking" (score of 0); "neither like nor dislike" (score of 50) in the middle; and anchored on the right with "strong liking" (score of 100).

Secondary measures included but were not limited to the following:

- Unipolar High VAS in which subjects were asked the question "How high are you now?" Subjects were required to mark a vertical line on a unipolar 0-100 mm VAS anchored on the left by "none" (score of 0) and on the right by "extremely" (score of 100).
- Bipolar Take Drug Again VAS in which subjects were asked the question, "Would you want to take the drug you just received again, if given the opportunity?" The question was scored using a 0-100 mm bipolar VAS anchored on the left with "definitely would not" (score of 0); "do not care" (score of 50) in the middle; and anchored on the right with "definitely would" (score of 100).

Drug Liking VAS and High VAS, were administered at selected time points out to 24 hours post-dosing. The Take Drug Again VAS was administered at 8 hours and 24 hours post-dosing.

Statistical analysis of the pharmacodynamic measures, including Drug Liking VAS, High VAS, and Take Drug Again VAS was conducted by the FDA Center for Drug Evaluation and Research, Office of Biostatistics.

Dr. Tolliver's Findings Regarding HAP Study KP201.A01

1. With respect to the primary measure of Drug Liking VAS, KP201APAP at oral doses of 26.68 mg/1,300 mg (4 tablets), 53.36 mg/2,400 mg (8 tablets), and 80.04mg/3,900mg (12 tablets), as well as HB/APAP at oral doses of 30 mg/1,300 mg (4 tablets), 60 mg/2,600 mg (8 tablets), and 90 mg/3,900 mg, produced maximum Drug Liking statistically significantly above those produced by oral placebo ($p<0.025$). This indicates that following oral administration of either KP201/APAP or HB/APAP at the three dosage levels, subjects liked the treatment they received.
2. With respect to the primary measure of Drug Liking VAS, within each dosage level (4, 8, or 12 tablets), maximum Drug Liking was not statistically significantly different between KP201/APAP and the comparator HB/APAP ($p = 0.4658$, 0.3631, and 0.5315 for one sided test, respectively).
3. With respect to the secondary measures of High VAS and Take Drug Again VAS, all three oral doses of either KP20 11 APAP or HB/ APAP produced mean maximum scores that were statistically significantly higher than the scores produced by oral placebo ($p<0.025$). This indicates that following oral administration of KP201/APAP or HB/APAP at the three doses examined, subjects did experience some euphoria (High) and that subjects would be willing to take the treatments again if given the opportunity.
4. Within each dosage level (4, 8, or 12 tablets), the mean maximum scores of High ($p = 0.6461$, 0.1401, and 0.5646, respectively) and Take Drug Again ($p = 0.8855$, 0.9497, 0.9658, respectively) were not statistically significantly different between oral KP201/APAP and HB/APAP.
5. As the oral dosages of either KP201/APAP or HB/APAP were increased from 4 to 8 to 12 tablets there was a corresponding increase in the mean maximum plasma levels of hydrocodone. For each dosage level, the maximum plasma hydrocodone concentration (Cmax) was statistically similar following KP201/APAP and HB/APAP administration. For all six active treatments, times to maximum hydrocodone plasma levels (Tmax) were achieved within about 1 hour. With respect to hydrocodone exposure as reflected by area under the plasma hydrocodone concentration curve (AUC), at the two highest doses (8 and 12 tablets), but not at the low dose of 4 tablets, there was a limited, but significant reduction in the AUCo.5hrs and AUCo-Ihr for hydrocodone following oral KP201/APAP compared to HB/ APAP. At later time intervals for AUC, no significant reductions were observed.

SAFETY RESULTS

Subject Disposition

A total of 151 subjects were enrolled in the study. A total of 125 subjects received the naloxone challenge test, of which 119 were dosed in the drug discrimination test. Of these 119 subjects, 48 discontinued the study and 1 discontinued and re-entered the study. Then, 71 subjects entered the treatment Phase (randomized population). Of these, 62 completed the study and constituted the primary analysis population.

No deaths or SAEs were reported during the study. Five subjects were discontinued from treatment or from the study due to TEAEs; however, none of these subjects were in the KP201/APAP treatment arm.

The safety profile of KP201/APAP was similar to that of HB/APAP, with primarily opioid-related TEAEs observed. For HB/APAP and KP201/APAP, the most commonly reported TEAEs included nausea, vomiting, somnolence, euphoric mood, hypoxia, pruritus, pruritus generalized, and hot flush. Both active treatments were associated with a higher number of TEAEs than placebo.

Study KP201.A02

Study A02 was a randomized, double-blind, double-dummy, placebo-controlled, single-dose, 2-part, 5-way crossover study. The study consisted of two parts, namely a dose-selection pilot study (Part A) and the main study (Part B).

The pilot study consisted of a Screening Phase, Drug Discrimination Phase, and Dose Selection Phase and was conducted in order to determine a dose of KP201/APAP and HB/APAP for use via insufflation in the main study (Part B). Using cohorts of 9 subjects each, the Sponsor evaluated the use of 1, 2, 3, and 4 crushed tablets of KP201/APAP and HB/ APAP. Based on criteria including ease of snorting, subjective reinforcing effects observed (i.e. Drug Liking), and safety, the decision was made to use in the main study (Part B) two tablets of KP201/APAP (13.32 mg/650mg) and, as the positive comparator, 2 tablets of HB/APAP (15 mg/650mg).

The primary objective of the Main Study (Part B) was to determine the abuse potential of crushed KP201/APAP relative to crushed hydrocodone bitartrate (HB)/APAP at the dose determined in the Dose Selection Phase (Part A) when administered IN to non-dependent, recreational opioid users. Part B, the main study, included a Screening Phase, Qualification Phase, Treatment Phase, and Follow-up Visit.

The Completer Population, consisting of 42 subjects, served as the primary population for PD analysis. Subjects were non-dependent and had experience in both using opioids for nontherapeutic purposes and administering drugs via the intranasal route. Subjects were subjected to Naloxone Challenge Tests to ensure they were and remained non-opioid dependent.

In the Drug Discrimination Phase, subjects were required to distinguish between a single dose of two crushed HB/APAP tablets (15mg/650 mg) and weight-matched placebo powder, each given intranasally. The criteria used to determine the ability to discriminate using the Drug Liking VAS were identical to that described for the Drug Discrimination Phase for study KP201.A01.

The Treatment Phase consisted of five treatment periods, each of which involved a single treatment followed by a minimum 96-hour washout. Treatments were administered to subjects using a randomized, crossover, double-blind, and double-dummy design. Subjects received each treatment after at least an eight-hour fast according to a randomization scheme. The five treatments are listed below.

- Intranasal Placebo Powder (Microcrystalline Cellulose Powder)
- Oral Intact KP201/APAP (13.34 mg/650 mg)
- Intranasal Crushed KP201/APAP (13.34 mg/650 mg)
- Intranasal Crushed HB/APAP (15 mg/650 mg)
- Oral Intact HB/APAP (15 mg/650mg)

The primary endpoint was the maximum level of drug liking (Emax) determined using Drug Liking VAS.

Secondary measures included but were not limited to High VAS and Take Drug Again VAS. For Drug Liking VAS and High VAS, data was collected at selected time points out to 24 hours. The Take Drug Again VAS was administered at 12 hours and 24 hours post-dosing.

Dr. Tolliver's Findings Regarding HAP Study KP201.A02

1. All subjects (N=43) were able in insufflate the entire dose (100%) of crushed HB/APAP 15nmg/650 mg, amounting to 850 mg of powder (2 crushed tablets). Thirty-eight out of 44 subjects were able to insufflate the entire dose of crushed KP201/APAP (1,100 mg of powder from 2 tablets). The remaining 5 subjects insufflated between 91.5% and 99.4% of then powder.
2. Intranasal administration of crushed KP201/APAP (13.32 mg/650 mg) and crushed HB/APAP (15 mg/650 mg) produced maximum levels of Drug Liking, representing the single primary endpoint, that were not statistically significantly different ($p = 0.1654$). At the same time, maximum Drug Liking for both intranasal treatments was statistically significantly larger than placebo ($p<0.025$). The median times to maximum Drug Liking were 0.6 hours and 1.1 hours for intranasal HB/APAP and intranasal KP201/APAP, respectively. The area under the effect curves for Drug Liking at 0 to 0.5 hours (AUE0-0.5hr), 0 to 1 hour (AUE0-1hr) and 0 to 2 hours (AUE0-2hrs) were significantly lower following KP201/APAP intranasal compared to HB/APAP IN by 5.9 (36.1 - 30.2) (16% reduction), 9.1 (72.6- 63.5)(13% reduction), and 12 (141.8 - 129.8) (9% reduction) units, respectively. The clinical significance of these reductions is not known.

- With regard to the secondary measure of High VAS, intranasal administration of crushed KP201/APAP and crushed HB/APAP produced maximum levels of High that were statistically greater than that produced by intranasal placebo ($p<0.25$). Thus, subjects experienced euphoria (High). In addition, there were no statistically significant differences between maximum levels of High ($p = 0.7304$) between intranasal KP201/APAP and intranasal HB/APAP. With regard to the area under the effect curves for High VAS over the first half hour (AUE0-0.5hr), first hour (AUE0-

1hr) and first two hours (AUE0-2hrs), there were no significant differences between the two intranasal treatments (p= 0.0807, 0.1161, and 0.4890, respectively).

- With regard to Take Drug Again VAS as measured at 12 or 24 hours, the maximum scores produced by intranasal KP201/APAP or by intranasal HB/APAP were significantly above that produced by placebo, indicating that subjects were willing if given the opportunity to take these treatments again. In addition, there were no statistically significant differences between maximum levels of Take Drug Again (p=0.1569), between intranasal KP201/APAP and intranasal HB/APAP.
- In the subject-rated Nasal Effects Assessment, mean peak scores for the six nasal effects of nasal burning, facial pain/pressure, need to blow nose, nasal irritation, nasal congestion, and runny nose/nasal discharge ranged from 1.0 to 1.6 following KP201/APAP insufflation and from 0.0 to 1.0 following HB/ APAP insufflation. Statistical analysis of least square means differences between intranasal HB/AP versus intranasal KP201/APAP as conducted by the Sponsor, which demonstrated statistically significant (p<0.0009) differences for each of the six nasal assessments.
- Intranasal KP201/APAP and intranasal HB/APAP produced statistically similar maximum hydrocodone plasma concentrations (Cmax), reached with a median time of 1.23 hours. For both treatments, more than 80% of the rise in the mean hydrocodone plasma concentrations was reached within 30 minutes. Following intranasal KP201/APAP as compared to intranasal HB/APAP, the reduction in systemic exposure to hydrocodone was 50% over the first 30 minutes (AUC0-0.5hrs), 29% over the first hour (AUC0-1hr), and 15% over the first 2 hours (AUC0-2hrs)·

SAFETY RESULTS

Subject Disposition

For Part A of the study a total of 110 eligible subjects participated in the Qualification phase of which 109 subjects successfully completed the Naloxone Challenge and of these subjects 100 subjects were eligible for and participated in the Drug Discrimination Test. Fifty-two subjects participated in the Dose Selection Phase and 49 subjects completed the study.

For Part B, the Main part of the study, a total of 80 subjects participated in the Qualification phase of which 71 successfully completed the Naloxone Challenge and were eligible to participate in the Drug Discrimination Test. Following the Drug Discrimination Test, 46 of 71 subjects were eligible for the Treatment Phase and 42 subjects completed the study.

There were no deaths or SAEs during the study. Five subjects (Subject # (b) (6) from Part B and Subjects # (b) (6) from Part A) were withdrawn from the study due to TEAEs.

Subject # (b) (6) was the only study participant withdrawn from the study due to a TEAE that received KP201/APAP treatment. The case summary involving this subject's

discontinuation is discussed in Section 7.3.3. Table 9 summarizes the TEAEs by SOC and PT reported in ≥10% of subjects for any treatment group during the Treatment Phase in Part B of Study KP201.A02 (Randomized Population)

Table 9: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Reported in >10% of Subjects for any Treatment Group during the Treatment Phase in Part B of Study KP201.A02 (Randomized Population)

	Number of Subjects (%)				
MedDRA System Organ Class Preferred Term	Placebo (N=42)	Oral intact KP201/APAP (13.34/650 mg) (N=42)	IN crushed KP201/APAP (13.34/650 mg) (N=44)	IN crushed HB/APAP (15/650 mg) (N=43)	Oral intact HB/APAP (15/650 mg) (N=44)
Any Event	21 (50.0)	35 (83.3)	41 (93.2)	37 (86.0)	40 (90.9)
Cardiac disorders	1 (2.4)		5 (11.4)	2 (4.7)	2 (4.5)
Gastrointestinal disorders	3 (7.1)	5 (11.9)	5 (11.4)	9 (20.9)	9 (20.5)
Dry mouth	2 (4.8)	2 (4.8)	3 (6.8)	5 (11.6)	6 (13.6)
General disorders and administration site conditions	5 (11.9)	5 (11.9)	3 (6.8)	3 (7.0)	4 (9.1)
Nervous system disorders	9 (21.4)	17 (40.5)	19 (43.2)	20 (46.5)	18 (40.9)
Somnolence	4 (9.5)	13 (31.0)	15 (34.1)	16 (37.2)	17 (38.6)
Headache	5 (11.9)	3 (7.1)	4 (9.1)	4 (9.3)	4 (9.1)
Psychiatric disorders	2 (4.8)	31 (73.8)	36 (81.8)	30 (69.8)	32 (72.7)
Euphoric mood	2 (4.8)	31 (73.8)	34 (77.3)	29 (67.4)	32 (72.7)
Respiratory, thoracic and mediastinal disorders	10 (23.8)	12 (28.6)	29 (65.9)	9 (20.9)	12 (27.3)
Nasal congestion	6 (14.3)	4 (9.5)	7 (15.9)	2 (4.7)	7 (15.9)
Nasal discomfort	2 (4.8)	1 (2.4)	16 (36.4)	2 (4.7)	2 (4.5)
Rhinorrhoea	3 (7.1)	3 (7.1)	7 (15.9)	4 (9.3)	1 (2.3)
Throat irritation	0	2 (4.8)	6 (13.6)	3 (7.0)	1 (2.3)
Skin and subcutaneous tissue disorders	0	5 (11.9)	4 (9.1)	6 (14.0)	8 (18.2)
Pruritus	0	5 (11.9)	3 (6.8)	5 (11.6)	4 (9.1)

APAP=acetaminophen; HB=hydrocodone bitartrate; IN=intranasal; MedDRA=Medical Dictionary for Regulatory Activities
Note: for oral intact KP201/APAP and HB/APAP treatments, intranasal administration of placebo during double-blind, double-dummy, drug administration should be considered regarding events related to respiratory, thoracic and mediastinal disorders.

Source: NDA 208653 KP201/APAP, Clinical Study Report KP201.A02, Table 74, pg. 207/739

The highest percentage of subjects with any TEAE was reported for IN crushed KP201/APAP treatment group (93.2%), followed by oral intact HB/APAP treatment group (90.9%), IN crushed HB/APAP treatment group (86.0%), oral intact KP201/APAP treatment group (83.3%), and last the placebo treatment group (50.0%). A greater proportion of subjects reported nasal discomfort, rhinorrhea, nasal congestion and throat irritation after IN crushed KP201/APAP compared to IN crushed hydrocodone/APAP.

Study KP201.A03

Study KP201.A03 was a randomized, double-blind, single-dose, 2-way crossover study to compare the rate and extent of absorption of hydrocodone and hydromorphone from KP201 13.34 mg relative to HB 15.00 mg when administered IN to non-dependent, recreational opioid users. Other study objectives were to determine the abuse potential of KP201 relative to HB when administered IN to non-dependent, recreational opioid users; and safety of KP201 compared with HB following IN administration in non-dependent, recreational opioid users.

Of note, this study did not use the products, KP20/1APAP or HB/APAP. Evaluation of the active pharmaceutical ingredients [APIs] (KP201 and Hydrocodone Bitartrate) alone for intranasal administration was undertaken in part after consideration that abusers may attempt to extract KP201 from the combination formulation thereby removing some of the unwanted excipients or APAP from the formulation, and thereby attempting abuse by intranasal administration of the extracted KP20 I. A further reason for conducting the study using KP201 API was to maximize exposure to the opioid while reducing the amount swallowed following insufflation compared to administering the crushed KP201 tablet formulation.

The study consisted of a Screening Phase, Naloxone Challenge Test, Treatment Phase, and Follow-up Phase.

Study KP20l.A03 was originally designed as a pharmacokinetic/nasal tolerability study to which was added an assessment for Drug Liking VAS, as an exploratory measure. Drug liking assessments were collected periodically up to 8 hours after each study drug administration. Because the Applicant reportedly was evaluating Drug Liking VAS as an exploratory measure, there was no Drug Discrimination Phase and no intranasal placebo arm in the Treatment Phase.

During the Treatment Phase subjects received each of the following treatments in a randomized, double-blind, crossover manner following an overnight fast of at least 8 hours:

- Treatment A: KP201 API (13.34 mg) administered intranasally
- Treatment B: HB API (15.00 mg) administered intranasally

Serial blood samples were obtained pre-dose and up to 24 hours after each study drug administration. Pharmacokinetic parameters, including Cmax, Tmax, and AUC0-xhrs were calculated for plasma concentration data of hydrocodone using non-compartmental methods.

The study utilized 2 cohorts. In the case of the initial Cohort 1, due to incorrect blood sampling processing, no PK data was obtained. However, Drug Liking VAS was conducted. A second group of subjects (Cohort 2) was assembled, consisting of 24

subjects who completed the study. Both PK data and Drug Liking VAS data were obtained from these 24 subjects.

Dr. Tolliver's Findings Regarding HAP Study KP201.A03

Pharmacokinetic data with respect to hydrocodone in plasma was evaluated using Cohort 2 (N=24 subjects). The Cmax for plasma hydrocodone following intranasal KP201 API was approximately 36% lower compared to that found following intranasal HB API. The time to achieve Cmax was also significantly delayed following intranasal KP201 API (median of 1.75 hours) compared to following intranasal HB API (median of 0.5 hours). Areas under the hydrocodone plasma concentration versus time curve (AUCs) at all intervals were significantly lower following KP201 API versus HB API. Although the study was not properly designed (see below), to evaluate Drug Liking VAS an exploratory analysis was conducted on Cohort 2 by the FDA, CDER Office of Biostatistics.

Their results revealed no statistically significant difference in mean maximum Drug Liking between intranasal KP201 API and intranasal HB API (p = 0.0615). Median time to maximum drug liking was 0.5 hours and 1.1 hours for HB API and KP201 API, respectively.

Study KP20 l.A03 had a number of design deficiencies listed below which precluded the use of the data in the abuse deterrent evaluation ofKP201/APAP Tablets.

- Study was primarily a pharmacokinetic study with Drug Liking added as an exploratory analysis.
- Study involved insufflation of KP201 API and hydrocodone bitartrate API, and not the products KP201/APAP and hydrocodone bitartrate/APAP. As such, this study did not take into account possible effects of either mass of powder to be insufflated or the effects of APAP on the insufflation experience as would occur following insufflation of the products.
- There was no Drug Discrimination (Qualification) Phase intended to select subjects having an appropriate placebo and active comparator response using the Drug Liking VAS.
- There was no placebo treatment in the Treatment Phase of the study. It is not known how subjects might have responded on the Drug Liking VAS when administering placebo intranasally. It also was not possible to validate the Drug Liking VAS.
- There were no additional subjective reinforcing measures (i.e., High VAS or Take Drug Again VAS) conducted, which could be used to support observed effects on the Drug Liking VAS.
- A pre-specified statistical analysis plan was not provided for the study.

SAFETY RESULTS

Study Disposition

A total of 54 subjects were randomized; and of these subjects 52 completed the study.

There were no deaths, SAEs or severe AEs reported for this study. No subjects were reported to have been discontinued from the study due to a TEAE. Treatment Emergent Adverse Events reported in at Least 3% of Subjects are summarized in Table 10

Table 10: Treatment-Emergent Adverse Events Reported in At Least 3% of Subjects

MedDRA System Organ Class Preferred Term	KP201 API N=52		HB API N=54		Any Treatment N=54	
	N (%)	AE Counts	N (%)	AE Counts	N (%)	AE Counts
Any Events	16 (30.8)	25	15 (27.8)	24	23 (42.6)	49
Gastrointestinal disorders						
Nausea	2 (3.8)	2	2 (3.7)	2	4 (7.4)	4
Vomiting	1 (1.9)	1	1 (1.9)	1	2 (3.7)	2
Nervous system disorders						
Dizziness	0	0	2 (3.7)	2	2 (3.7)	2
Headache	4 (7.7)	5	4 (7.4)	4	6 (11.1)	9
Respiratory, thoracic and mediastinal disorders						
Nasal congestion	1 (1.9)	1	1 (1.9)	1	2 (3.7)	2
Skin and subcutaneous tissue disorders						
Pruritus generalized	3 (5.8)	3	3 (5.6)	3	4 (7.4)	6

AE=adverse event; API=active pharmaceutical ingredient; HB=hydrocodone bitartrate.
Presentation is incidence (n [%] and frequency (AE counts).

Source: NDA208653, KP201/APAP, Clinical Study Report KP201.A03, Table 13, pg.77/211

Overall, the incidence of TEAEs reported for KP201 API and HB API treatment groups were similar. The most commonly reported TEAEs for both treatment groups included: headache, pruritus generalized, and nausea.

6 Review of Efficacy

Efficacy Summary

The Applicant is relying on the Agency's findings of efficacy and safety of two listed drugs, Vicoprofen® (7.5 mg hydrocodone bitartrate/ 200 mg ibuprofen oral tablet; NDA 20716) for the hydrocodone component and Ultracet® (37.5 mg tramadol hydrochloride/325 mg APAP oral tablet; NDA 21123) for the APAP component. To establish the scientific bridge with each listed drug, two bioequivalence studies were conducted in the fasted state comparing KP201/APAP with Vicoprofen for hydrocodone component (Study KP201.105, n=28) and Ultracet for APAP component (study KP201.106, n=27). The proposed KP201/APAP product met the bioequivalence criteria for AUC and Cmax for the hydrocodone component compared to Vicoprofen; and for the APAP component compared to Ultracet. In addition, KP201/APAP was compared to Norco (hydrocodone and APAP) to show that the former was not a "novel" combination.

No additional efficacy studies were required.

6.1 Indication

The Applicant has proposed the indication, "for the short-term (no more than 14 days) management of acute pain."

6.1.1 Methods

This section is non-applicable.

6.1.2 Demographics

This section is non-applicable.

6.1.3 Subject Disposition

This section is non-applicable.

6.1.4 Analysis of Primary Endpoint(s)

This section is non-applicable.

6.1.5 Analysis of Secondary Endpoints(s)

This section is non-applicable.

6.1.6 Other Endpoints

This section is non-applicable.

6.1.7 Subpopulations

This section is non-applicable.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

This section is non-applicable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

This section is non-applicable.

6.1.10 Additional Efficacy Issues/Analyses

This section is non-applicable.

7 Review of Safety

Safety Summary

The assessment of the safety of APADAZ relies on the clinical data provided from the Applicant's studies and the Agency's prior findings of safety for the listed drugs, Vicoprofen and Ultracet. No additional data was required to assess the safety of the benzhydrocodone because there was no detectable systemic exposure, indicating that hydrolysis to hydrocodone was rapid and complete. The safety profile of APADAZ was assessed in 418 healthy subjects who received at least one dose of KP201/APAP and 245 healthy subjects who received multiple doses of KP201/APAP across ten clinical studies. Overall, the safety data submitted in the application indicate that APADAZ has a similar safety profile to existing hydrocodone/APAP formulations and no new safety concerns were identified with this product.

There were no deaths or other serious adverse events reported during clinical development of APADAZ. Other significant adverse events were reported for a total of 14 subjects in five of the clinical studies, of which seven were KP201/APAP treated subjects.

For subjects in the APADAZ treatment groups, three subjects were discontinued from studies because they met the vital sign criteria for treatment discontinuation and experienced clinically significant adverse events of hypotension, two subjects were discontinued due to nausea and vomiting, and one subject was discontinued because of

presyncope and hypotension. One subject was discontinued due to supraventricular extrasystoles and ventricular extrasystoles, but, as systemic exposure to KP201 is minimal, and these are not adverse events known to occur with hydrocodone or acetaminophen, they are unlikely to be related to study participation

Naltrexone block was used in Study KP201.103 only and this may have affected the AEs reported during this study which included: abdominal distention, abdominal pain, and nausea. Otherwise, the most frequently reported AEs associated with KP201 treatment were abdominal pain, constipation, nausea, and vomiting.

In the intranasal human abuse liability studies, there were more subjects who reported nasal discomfort, rhinorrhea, and throat irritation after insufflation of crushed KP201/APAP compared to insufflation of crushed hydrocodone/APAP.

7.1 Methods

A total of ten studies were reviewed for safety. Refer to Section 7.1.1 for a listing and a summary discussion of each study included in the submission.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The Applicant conducted six pharmacokinetic/BA studies in healthy adult volunteers (one study using an early formulation of KP201 capsules and five studies with the final dosage form, KP201/APAP tablet). Three additional studies evaluated the abuse potential and relative BA of KP201/APAP and one motility study was conducted as well. Naltrexone block was used in Study KP201.103 only, and this may have affected the AEs reported during this study. Table 11 displays the list of clinical studies used to evaluate safety in this NDA.

Table 11: Table of Clinical Studies

Study	Study Population	N	KP201 Dosage/Formula	Study Design
KP201.101	Healthy adult subjects; fasting	24	Single oral dose: 5 mg KP201 capsule (5 and 10 mg administered	Open-label, single-dose, 3-treatment, 3-period, 6-sequence, randomized, crossover, Phase 1 bioavailability study.
KP201.102	Healthy adult subjects; fasting	30	Single oral dose: 6.67 mg KP201/325 mg APAP Tablet	Open-label, single-dose, randomized, 2-treatment, 2-period, 2-sequence, crossover bioequivalence study
KP201.104	Healthy adult subjects; fed	42	Single oral dose: 6.67 mg KP201/325 mg APAP Tablet	Single-dose, 3-period, 3-treatment, 6-sequence study of the effect of food on the bioavailability and of PK hydrocodone and APAP from KP201/APAP
KP201.103	Healthy adult subjects; fasting	26	Single and repeat oral doses: 6.67 mg KP201/325 mg APAP Tablet	Open-label, single-period, single- and multiple-dose study
KP201.105	Healthy adult subjects; fasting	30	Single oral dose: 6.67 mg KP201/325 mg APAP Tablet	Open-label, single-dose, randomized, 2-treatment, 2-period, 2-sequence crossover relative bioequivalence study
KP201.106	Healthy adult subjects; fasting	30	Single oral dose: 6.67 mg KP201/325 mg APAP Tablet	Open-label, single-dose, randomized, 2-treatment, 2-period, 2-sequence crossover relative bioequivalence study
KP201.A01	Healthy adult subjects; opioid-experienced; nondependent	151	Single oral dose of 6.67 mg KP201/325 mg APAP Tablet (12, 8, or 4 tablets)	Randomized, double-blind, placebo-controlled, single-dose, 7-way crossover study
KP201.A02	Healthy adult subjects; opioid-experienced; nondependent	Part A 110 Part B 80	Part A: Escalating intranasal doses (1 to 4 tablets, crushed); Part B: intranasal dose (2 tablets, crushed) and oral dose (2 tablets), 6.67 mg KP201/325 mg APAP Tablet	Randomized, double-blind, double-dummy, placebo-controlled, single-dose, 2-part, 5-way crossover study
KP201.A03	Healthy adult subjects; opioid-experienced; nondependent	66	Single intranasal dose: 13.34 mg KP201 API	Randomized, double-blind, single-dose, 2-way crossover study
KP201.S01	Healthy adult subjects	50	Oral dose of 6.67mg KP201/325 mg APAP Tablet (1 tablet every 4 hours for 72 hours)	Randomized, 2-way, crossover study to assess the gastrointestinal effect of KP201/APAP compared with Norco

Source: NDA 208653, KP201/APAP, SCS, Table 2.7.4.1.2, pg. 11/42

7.1.2 Categorization of Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA).

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

No pooling of data across studies was performed.

7.2 Adequacy of Safety Assessments

This section is non-applicable

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported during clinical studies.

7.3.2 Nonfatal Serious Adverse

There were no serious adverse events reported during clinical studies.

7.3.3 Dropouts and/or Discontinuations

Table 12 displays the list of subjects treated with KP201-APAP that were reportedly discontinued from studies and the reason for the discontinuation.

Table 12: List of Subjects Treated with KP201-APAP Discontinued from Studies

Study	Subject #	Treatment Arm	Reason for Discontinuation
KP201.102	(b) (6)	KP201/APAP	Presyncope/hypotension
KP201.104		KP201/APAP fed	Hypotension
KP201.104		KP201/APAP fed	Hypotension
KP201.104		KP201/APAP fed	Hypotension
KP201.S01		KP201/APAP	Nausea & Vomiting
KP201.S01		KP201/APAP	Nausea & Vomiting
KP201.A02		KP201/APAP IN	Supraventricular extrasystoles & ventricular extrasystoles

Source: NDA 208653, KP201/APAP, Summary of Clinical Safety

Subject # (b) (6)

Subject (b) (6) was a black 50-year old male enrolled in Study KP201.A02 who was reportedly withdrawn in Part B, Treatment Period 2 (IN crushed KP201/APAP) following TEAEs of mild supraventricular extrasystoles and ventricular extrasystoles. The subject had no reported cardiac history, however reported outputs assessed at the screening visit, Part A Visit 2 (Day -1), and Part B check-in (Treatment Periods 1 and 2) showed left ventricular hypertrophy. Onset of both TEAEs reportedly occurred one hour after dosing was completed; and both events were reported to have resolved approximately

nine hours after onset without therapy. The study drug, KP201/APAP was discontinued after these events. ECG assessments performed one week later (Day -1, Treatment Period 3) showed left ventricular hypertrophy and premature ventricular complex. The subject returned for the final follow-up visit three weeks after these events and the ECG assessment included high voltage criteria for left ventricular hypertrophy.

Reviewer's Comments – Subject [redacted] experienced AEs of supraventricular extrasystoles and ventricular extrasystoles that required him to be discontinued from study drug, KP201/APAP and from the study. It appears that his ECG from screening was abnormal showing left ventricular hypertrophy, and this abnormality continued after discharge from the study and on follow-up, which in this reviewer's opinion did not make him and ideal candidate for this study. It is unlikely that the AEs of supraventricular extrasystoles and ventricular extrasystoles were due to KP201 drug treatment.

Subject [redacted] (b) (6)
This subject was a 26-year-old white male enrolled in Study KP201.S01 who was reportedly in good general health upon study enrollment and received the first dose of study drug (KP201) of Period 2 [redacted] (b) (6) The subject experienced severe nausea and vomiting [redacted] (b) (6) His study medication was stopped at that time. His vomiting resolved later [redacted] (b) (6) and his nausea resolved [redacted] (b) (6) [redacted] (b) (6)

Subject [redacted] (b) (6)
This subject was a 48-year-old black female enrolled in Study KP201.S01 who was reportedly in good general health upon study enrollment and received her first dose of study drug (KP201) [redacted] (b) (6) The subject began experiencing mild nausea [redacted] (b) (6) and moderate constipation [redacted] (b) (6) Her study medication was stopped at that time [redacted] (b) (6) Her constipation resolved one day after discontinuing study medication, [redacted] (b) (6) and her nausea resolved two days later after discontinuing study medication [redacted] (b) (6) [redacted] (b) (6)

7.3.4 Significant Adverse Events

Subject [redacted] (b) (4)
This subject was a 22-year-old, White, Hispanic female, enrolled in Study KP201.102 who reportedly experienced significant AEs of hypotension and presyncope after dosing with Treatment A (KP201/APAP) in Period 1. For her symptoms related to presyncope, the subject was placed in Trendelenburg position and given a cold pack. The AEs were resolved. The AE hypotension was judged by the Investigator to be probably related to the study treatment, while the AE presyncope was judged to be possibly related to the study treatment. The subject was withdrawn from the study by the Sponsor due to meeting the vital sign criteria for withdrawal.

7.3.5 Submission Specific Primary Safety Concerns

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In Phase 1, single-dose, clinical studies, the most frequently reported AEs in KP201/APAP treated subjects were nausea, dizziness, and headache.

The most common adverse events reported for APADAZ-treated subjects were consistent with the opioid safety profile and include constipation, nausea, somnolence, fatigue, headache and dizziness.

7.4.2 Laboratory Findings

Generally, clinical laboratory tests (chemistry, hematology, and urinalysis) were performed at screening and at the end of the study. In study KP201.A01, six subjects (4 – KP201 and 2- HB) reportedly had clinically significant events of hemoglobin decreases that were recorded as TEAEs, related to the significant volume of blood that was obtained during the study, and all of which resolved with concomitant oral ferrous sulfate. None of the other studies reported safety events related to clinical laboratory values.

7.4.3 Vital Signs

In Studies #102, and #104, several subjects were withdrawn by the sponsor because they met the vital sign criteria for withdrawal; these subjects had experienced AEs (hypotension) that were considered clinically significant by the investigator

7.4.4 Electrocardiograms (ECGs)

No clinically significant abnormalities in ECGs were reported during clinical studies.

7.4.5 Special Safety Studies/Clinical Trials

This section is non-applicable.

7.4.6 Immunogenicity

This section is non-applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

This section is non-applicable.

7.5.2 Time Dependency for Adverse Events

This section is non-applicable.

1.5.3 Drug-Demographic Interactions

This section is non-applicable.

7.5.4 Drug-Disease Interactions

This section is non-applicable.

7.5.5 Drug-Drug Interactions

This section is non-applicable.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

This section is non-applicable.

7.6.2 Human Reproduction and Pregnancy Data

This section is non-applicable.

7.6.3 Pediatrics and Assessment of Effects on Growth

This section is non-applicable.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no cases of reported overdose in clinical studies.

7.7 Additional Submissions / Safety Issues

This section is non-applicable

8 Postmarket Experience

APADAZ has not previously been marketed in the United States or in any other countries.

9 Appendices

9.1 Literature Review/References

This section is non-applicable.

9.2 Labeling Recommendations

1. Dr. James Tolliver from the Controlled Substance Staff has recommended that Section 9.0 of the Product Insert (PI) receive no labeling with respect to abuse-deterrent properties.
2. In April 2014, the product labeling of the class of extended-release and long-acting (ER/LA) opioid analgesics was updated to add more prominent warnings about the risks of misuse, abuse, addiction, overdose, death, and neonatal opioid withdrawal syndrome (NOWS). These products' indications were changed to better convey the patient population for whom the benefits of ER/LA opioid analgesics outweigh the risks. The Agency has determined that similar changes are needed for immediate-release (IR) opioids. A class-wide safety related labeling change letter was issued for all IR opioids. Among the changes, the Agency has required the addition of a boxed warning to include information about Risk of Medication Errors (for oral solutions only), Addiction, Abuse, and Misuse, Life Threatening Respiratory Depression, Accidental Ingestion (or Exposure) (for non-parenterals only), Neonatal Opioid Withdrawal Syndrome, and as appropriate, significant drug product-specific interactions that would potentiate the opioid adverse effects. These safety related changes were incorporated into the APADAZ label during the review cycle.

9.3 Advisory Committee Meeting

An advisory committee (AC) meeting was held on May 5, 2016 to discuss APADAZ and its purported abuse-deterrent characteristics.

Question #1 Discuss whether the data presented for hydrocodone and APAP combination drug products support that the nasal route of abuse is relevant for KP201?

Members of the AC thought the data presented for HC and APAP combination drug products supported that the nasal route of abuse may be relevant for KP201. Data from the Commonwealth of Kentucky demonstrated that a large amount of rural residents reported snorting hydrocodone/APAP prescription products before using marijuana and other "street drugs". The nasal route of abuse for HC/APAP combination drug products was associated with indicators of more severe abuse and of abuse of multiple drugs such as marijuana, cocaine and heroin, though it is not clear what the causal relationship is between these observations.

Question #2 Please discuss whether there are sufficient data to support a finding that KP201 has properties that can be expected to deter abuse for each of these possible routes of abuse:

a. Oral – (No) The majority of committee members stated that KP201 has no properties to deter oral abuse which is the most common form of abuse.
b. Nasal - (No)The effect was small; failed 2/3 studies and the design of 3rd study was flawed
c. IV – (No) Appears you can overcome the chemistry very easily, Sponsor took 1-step instead of 2-3 step processes in *in vitro* testing and manipulation studies

Question #3 Should KP201 be approved for the proposed indication?
Yes -16 No - 4 Abstain -0
Reasons why KP201 should not be approved for the proposed indication

- KP201 did not meet the Category 1 and 3 requirements per the abuse-deterrent guidance
- In oral HAP study similar drug liking and in particular in first 30 minutes compared to reference drug
- Ability to manipulate KP201 very easily in i*n vitro* studies
- KP201 did not show improvement over reference product

Question #4 If approved, should KP201 be labeled as an abuse-deterrent product?
Yes-2 No-18
Reasons for No answers include the following:

- Lack of evidence of abuse-deterrence in intranasal study compared to IR Norco
- For category 1 and 3 reasons
- Could lead to unintended consequences
- Data from study A02 failed to show abuse deterrent properties when compared to Norco
- Send message to providers and patients that this product is abuse deterrent that this is safe and unintentionally prescribe more pills,

Clinical Review
Jacqueline Spaulding MD, MPH
NDA #208653
APADAZ (Benzhydrocodone hydrochloride tablet)

Clinical Investigator Financial Disclosure
Review Template

Application Number: **208653**

Submission Date(s): **12/09/2015**

Applicant: **KemPharm**

Product: **APADAZ**

Reviewer: **Jacqueline A. Spaulding**

Date of Review: **5/1/16**

Covered Clinical Study (Name and/or Number): **KP201.101, KP201.102, KP201.103, KP201.104, KP201.105, KP201.106 KP201.S01, KP201.A01, KP201.A02, KP201.A03**

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: **52**		
Number of investigators who are sponsor employees (including both full-time and part-time employees): **0**		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): **0**		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: **0** Significant payments of other sorts: **0** Proprietary interest in the product tested held by investigator: **0** Significant equity interest held by investigator in sponsor of covered study: **0**		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure By Clinical Investigators.*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JACQUELINE A SPAULDING
05/20/2016

PAMELA J HORN
05/20/2016