FDA ADVISORY COMMITTEE BRIEFING DOCUMENT

Advisory Committee Briefing Materials: Available for Public Release

Apadaz™
(Benzhydrocodone HCl/Acetaminophen)

JOINT MEETING OF THE ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

MEETING DATE: May 5, 2016

Table of Contents

List of Tables

List of Figures

List of Abbreviations and Definition of Terms

ADF	abuse-deterrent formulation
AE	adverse event
APAP	acetaminophen
API	active pharmaceutical ingredient
ASI-MV	NAVIPPRO Addiction Severity Index – Multimedia Version
AQ	abuse quotient
AUC_{0-t}	Area under plasma concentration-time curve from zero (0) hours to time (t)
AUC_{last}	Area under plasma concentration-time curve up to the last measurable concentration
AUC_{inf}	Area under plasma concentration-time curve from zero (0) hours to infinity
BA	bioavailability
BE	bioequivalence/bioequivalent
BLQ	below limit of quantification
BMI	body mass index
CHAT	Comprehensive Health Assessment for Teens
CI	confidence interval
C_{max}	peak plasma concentration
CSS	Controlled Substances Staff
DEA	Drug Enforcement Administration
DEQ	Drug Effects Questionnaire
E_{max}	maximum effect
ER	extended-release
ER/LA	extended-release/long-acting
FDA	United States Food and Drug Administration
GM	geometric mean
GRAS	generally recognized as safe
HAP	human abuse potential

List of Abbreviations and Definition of Terms

HB	hydrocodone bitartrate
HC	hydrocodone free base
HCl	hydrochloride
HFHC	high-fat, high-calorie
IN	intranasal
IR	immediate-release
IV	intravenous
LS	least squares
NAVIPPRO	National Addictions Vigilance Intervention and Prevention Program
NDA	New Drug Application
NTX	naltrexone
NSAID	nonsteroidal anti-inflammatory drug
PAUC	partial area under the curve
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PSR	particle size reduction
REMS	Risk Evaluation and Mitigation Strategies
SD	standard deviation
T_{max}	time to maximum plasma concentration
TE_{max}	time to maximum effect
VAS	visual analog scale

1 EXECUTIVE SUMMARY

Apadaz™ is an immediate-release (IR) fixed-dose combination product, composed of benzhydrocodone HCl (also known as KP201), a prodrug of hydrocodone and benzoic acid, and acetaminophen (APAP). Apadaz has a proposed indication for the short-term management (no more than 14 days) of acute pain. KemPharm, Inc. (herein "KemPharm") submitted a New Drug Application (NDA) to the Food and Drug Administration (FDA) requesting approval of Apadaz on December 15, 2015.

The prodrug in Apadaz, benzhydrocodone, is a re-engineered form of hydrocodone that imparts its abuse-deterrent properties at the molecular level. Benzhydrocodone is a new molecular entity that is formed by covalently bonding hydrocodone to benzoic acid, a widely used food preservative. Benzhydrocodone, itself, is not pharmacologically active, but must be metabolized by into hydrocodone enzymes in the intestinal tract to deliver its pharmacologic effects. Therefore, unlike many other abuse-deterrent formulations (ADFs) on the market, crushing or grinding benzhydrocodone has no impact on its release profile.

Apadaz was developed to provide deterrence against the riskier, non-oral routes of abuse. Given that IR opioid products must deliver effective analgesia with a rapid onset for its intended route of administration, Apadaz was not designed to provide barriers against oral abuse. The potential abuse-deterrent properties of Apadaz were evaluated in laboratory-based in vitro studies, clinical pharmacokinetic (PK) studies, and human abuse potential (HAP) studies. These studies were conducted in accordance with the guidance on the development of abuse-deterrent opioid formulations issued by the Food and Drug Administration (FDA) (FDA, 2015) and with the input from the Controlled Substance Staff (CSS).

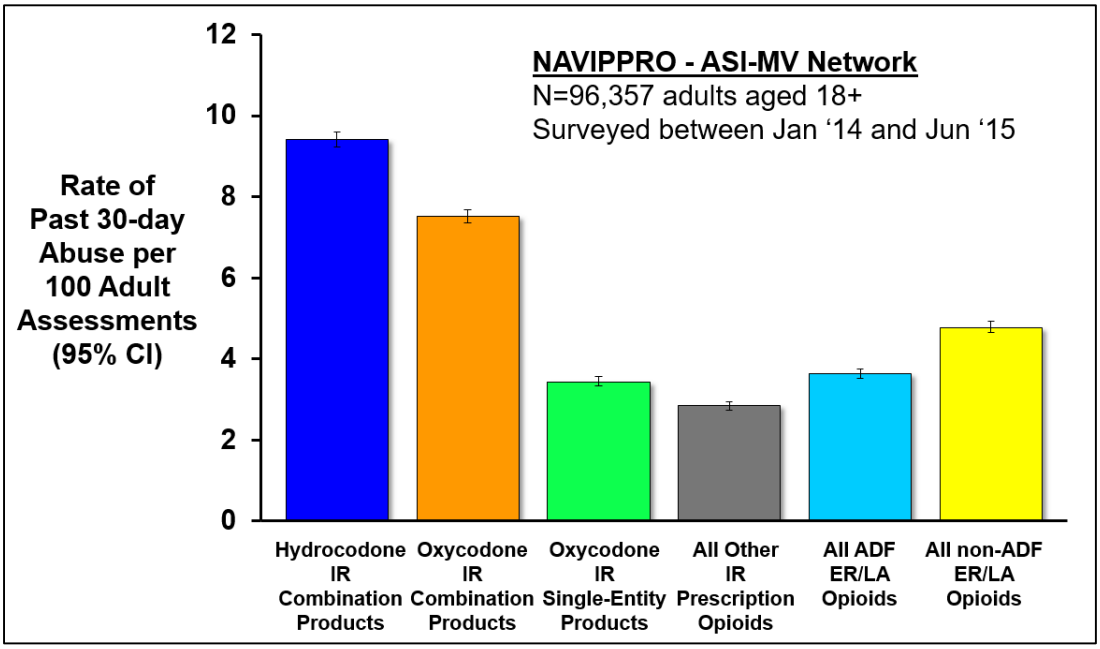
1.1 Unmet Public Health Need for Abuse-Deterrent Hydrocodone IR Combination Products

Hydrocodone IR combination products are the most frequently prescribed medication to treat pain in the United States, and were the second most commonly prescribed pharmaceutical in 2014 with over 119 million dispensed prescriptions (IMS Health, 2015).

Epidemiological studies were conducted to investigate the pattern of abuse and abuse potential of hydrocodone IR combination products in relation to other opioid products using data sources from the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO®) surveillance system. Two epidemiology reports and two internet surveys were generated by Inflexxion, Inc. (Newton, MA) to provide supportive information about the abuse profile of these products, including how they relate to patterns of abuse using non-oral alternate routes of administration such as snorting and the overall role that hydrocodone products play within the abuse landscape.

The rate of abuse of hydrocodone IR combination products is significantly greater than any other class of opioid products (Figure 1).

Figure 1: Rate of Abuse of Opioid Products in the ASI-MV Network between January 2014 and June 2015



In an effort to curb abuse and misuse, hydrocodone IR combination products were rescheduled in October of 2014 from Schedule III to Schedule II under the Controlled Substances Act. For this reason, the epidemiology studies also evaluated the rate of abuse of hydrocodone IR combination products prior to and after rescheduling. While rescheduling was associated with an overall reduction in the number of prescriptions dispensed by approximately 5 million prescriptions per quarter, it did not appear to result in a concomitant decrease in the rate of abuse of hydrocodone IR combination products.

Epidemiological data collected from the NAVIPPRO studies show that oral abuse is the most common route of hydrocodone IR combination products and snorting is the second most common. Twenty-three percent (23%) of adults and 43% of adolescents who abuse hydrocodone IR combination products have used snorting as a route of administration within the past 30 days. The number of individuals snorting these products, in absolute terms, is comparable to the number who snort ER opioids and IR oxycodone products.

In a survey of lifetime abusers of hydrocodone IR combination products, survey participants most frequently reported swallowing these products whole (96%). However, they also indicated chewing (45%), drinking in solution (36%), and snorting (34%) as common routes of administration. Nearly all forms of abuse included some form of manipulation (e.g., chewing, snorting, IV). The majority (97%) of those surveyed also recognized the dangers of liver toxicity associated with acetaminophen, and 23% reported using a common extraction technique to mitigate these dangers.

In another survey of lifetime abusers of hydrocodone IR combination products, 63% reported that their first abuse occurred between the ages of 10 and 18, and 74% reported that hydrocodone IR combination products were the first type of opioid that they abused. Among participants who believed that using hydrocodone IR combination products led them to abuse other prescription opioids, 75% reported snorting other opioids, 31% reporting smoking other opioids, and 31% reported injecting. Furthermore, the age at first abuse of hydrocodone IR combination products appeared to be an important factor in the progression of abuse of other drugs. Among abusers who abused hydrocodone IR combination products *before* 18 years old, 74% had abused 6 or more non-opioid prescription drugs or illicit drugs after their first abuse of hydrocodone IR combination products, compared to just 33% of those whose first abuse of hydrocodone IR combination products was *after* the age of 18.

The fact that so many lifetime abusers start abusing hydrocodone IR combination products in adolescence highlights the need for products with abuse deterrent features to discourage abuse of hydrocodone as a "gateway" to the abuse of more potent opioids and other illicit drugs, and to remove the reinforcement of achieving better "highs" with more dangerous routes of administration.

1.2 Clinical Pharmacology

The development program for Apadaz utilized the 505(b)(2) regulatory pathway, which allows for bridging to previous findings of safety and efficacy using data from currently marketed reference products based on pharmacokinetic assessments. Several studies were conducted and the following key points were documented:

- Apadaz is bioequivalent to the reference drugs needed for 505(b)(2) pathway (i.e., bioequivalent to Vicoprofen for the hydrocodone component and bioequivalent to Ultracet for the APAP component)
- Apadaz is bioequivalent to Norco, thereby demonstrating that it is not a novel drug-drug combination. Norco could not be used for bridging to prior efficacy and safety findings because it was approved through an Abbreviated NDA (ANDA).
- No clinically relevant effect of food was found with Apadaz. Fed C_{max} of hydrocodone and APAP were approximately 15% lower in the fed compared to the fasted state with similar overall exposure.
- Systemic exposure to the prodrug, benzhydrocodone, was not found in any oral PK study.
- A study of the safety and gastrointestinal effects of Apadaz compared to Norco found that the total digestive transit times and the incidence of gastrointestinal AEs of the two products were similar.

1.3 Category 1 Abuse Deterrence Studies: Laboratory-Based In Vitro Manipulation and Extraction Studies

Laboratory-based studies were conducted to evaluate the potential to extract benzhydrocodone and active hydrocodone from Apadaz tablets, convert benzhydrocodone to hydrocodone (hydrolysis), prepare IV formulations from Apadaz tablets, smoke benzhydrocodone or Apadaz, and to assess the risk of precipitation when injected into human blood. Hydrocodone/ acetaminophen tablets (referred to as Norco for the remainder of this document) were used as comparator in all studies.

Extraction of crushed and intact Apadaz tablets with 26 common ingestible and advanced non-ingestible solvents resulted primarily in dissolution of intact benzhydrocodone and no release of hydrocodone with very few exceptions. Hydrolysis of benzhydrocodone to hydrocodone only occurred under harsh acidic and basic conditions, with heat over an extended period of time. In contrast, several common ingestible solvents extracted >80% of hydrocodone from Norco tablets after only 5 minutes. Additionally, results showed that smoking of benzhydrocodone in any form (i.e., salt, free base, tablet formulation) is not possible, unlike hydrocodone bitartrate or Norco for which smoking appears plausible.

It is possible to prepare IV solutions from Apadaz with limited concentrations of inactive benzhydrocodone (up to about 3.8 mg/mL with no released hydrocodone). The same techniques extracted up to approximately 2.8 mg/mL of active hydrocodone from Norco. However, filtration of both Apadaz and Norco tablet extracts proved to be inefficient via the methods most commonly applied by abusers and resulted in hazy to cloudy solutions, which was likely due to undissolved excipients and APAP as both benzhydrocodone and hydrocodone were found to be soluble at those concentrations. Thus, IV abusers will have to make a conscious decision to inject a cloudy solution whether it is Apadaz or Norco.

The solubility of benzhydrocodone at physiological pH and salinity (2.3 mg/mL) is similar to the highest concentration (3.8 mg/mL) of mock IV formulations that can be achieved by extracting Apadaz tablets. Injections of these mock IV formulations into human plasma and whole blood did not produce any visible precipitate. Microscopic examination indicated the presence of solid particles in plasma which were most likely residual excipients and APAP not removed in the filtration process.

The combined data ultimately demonstrated that (1) even under optimal conditions the maximum concentration of benzhydrocodone that can be achieved by extracting Apadaz tablets is only about 3.8 mg/mL, (2) the microscopic particles observed in plasma after injecting IV preparations of Apadaz and Norco tablets were most likely excipients and APAP, and (3) the solid particles were already in the IV preparations of both tablet formulations before injection due to the inefficiency of clandestine filtration methods and no additional precipitate formed when the solutions were introduced into human blood.

Overall, Apadaz does not present any new or greater risk for injection than the currently marketed hydrocodone combination products but may actually limit the potential for IV abuse

due to the slow conversion of inactive benzhydrocodone to active hydrocodone in whole blood, as observed in an in vitro stability study.

1.4 Category 2 Abuse Deterrence Studies: Pharmacokinetic Clinical Trials

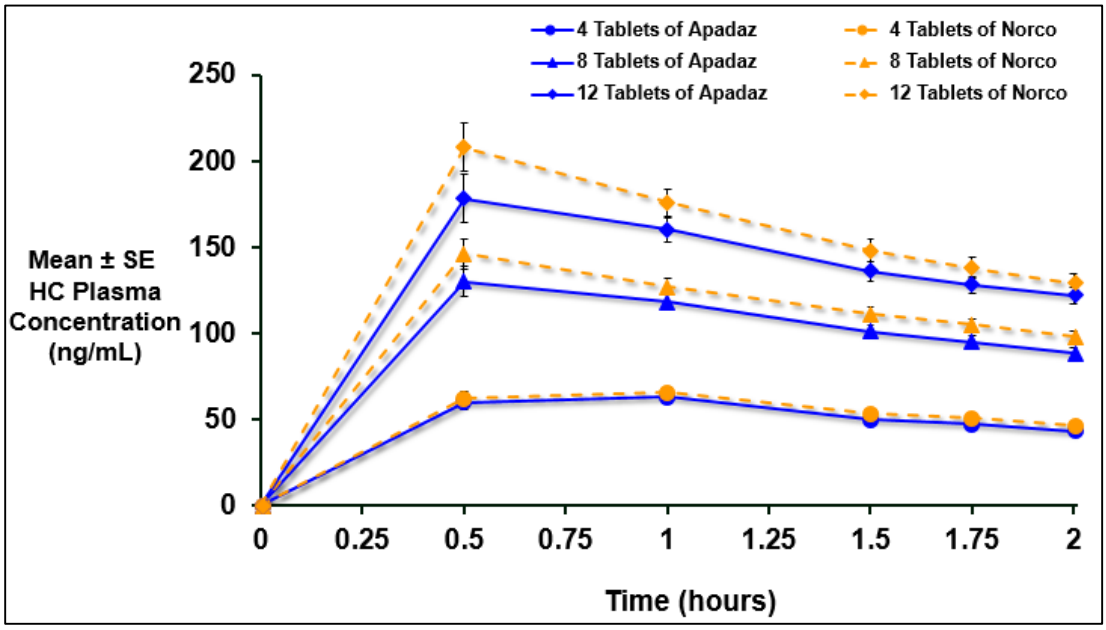
To assess the abuse potential of Apadaz via the oral route or intranasal route (either as crushed tablet or as benzhydrocodone isolated from the tablet formulation), three clinical studies were conducted including two human abuse potential (HAP) studies (A01 [oral] and A02 [intranasal]) and one intranasal (IN) bioavailability (BA) study of the active pharmaceutical ingredients (APIs) without acetaminophen (A03) in opioid-experienced, non-dependent recreational drug users.

It was not anticipated that Apadaz would provide any barriers to oral abuse. However, as benzhydrocodone is a prodrug that rapidly converts to hydrocodone in the intestinal tract, it was thought to have potential to decrease the bioavailability of hydrocodone if the product is snorted because conversion is much slower in whole blood. It should be noted that while benzhydrocodone is rapidly converted into hydrocodone in the intestinal tract, plasma hydrocodone levels will still be achieved with crushed Apadaz or benzhydrocodone via the IN route because an appreciable amount of the crushed powder will be swallowed after insufflation, particularly with large insufflation volumes (e.g., with APAP).

Study A01 – Oral HAP Study

Oral administration of supratherapeutic doses (4, 8 or 12 tablets) of Apadaz or Norco resulted in generally similar hydrocodone exposures at each respective dose level, though early exposure to hydrocodone was slightly lower at 8 and 12 tablets (Figure 2).

Figure 2: Hydrocodone Plasma Concentration-Time Profiles after Single Oral Doses of 4, 8 and 12 tablets of Apadaz and Norco (Study A01)

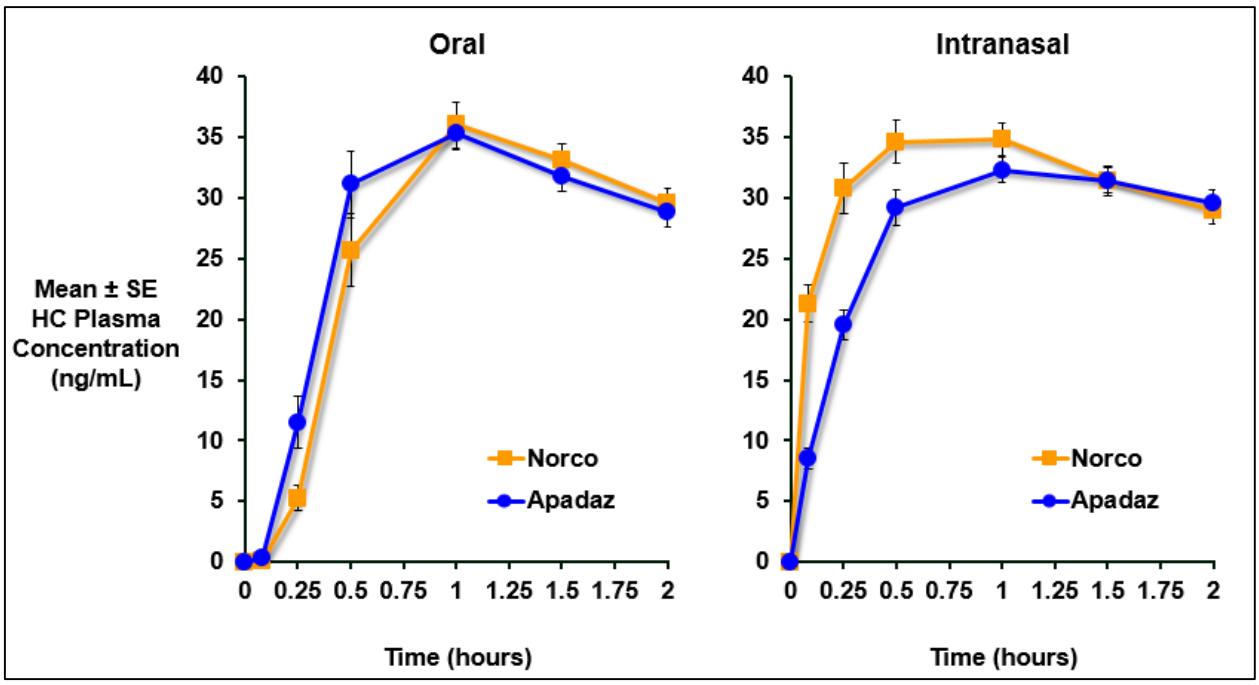


Study A02 – Intranasal HAP Study

The dose selection part of Study A02 (Part A) demonstrated that 2 tablets of Apadaz represents the maximum dose that can be reasonably snorted due to the bulk of the tablet. Higher doses lead to significant nasal adverse effects, and most of the insufflated material being swallowed and metabolized as an oral dose.

The main part of Study A02 (Part B) showed that IN administration of crushed Apadaz tablets results in lower peak exposure (i.e., approximately 11%) and lower cumulative exposure to hydrocodone at early time points compared to crushed Norco (50% lower at 30 minutes, 29% lower at 1 hour). Figure 3 illustrates how snorting crushed Norco led to a faster onset of hydrocodone concentrations compared to intact oral dosing at early time points, while Apadaz did not. Crushing and snorting Apadaz was associated with 11-13% lower peak exposures than a comparable oral dose of either Apadaz or Norco. Additionally, the median time to peak exposure (T_{max}) was similar after oral and IN administration of Apadaz. Thus, Apadaz removes the incentive for snorting by eliminating the more rapid onset of hydrocodone concentrations typically associated with snorting crushed hydrocodone IR combination tablets and providing lower peak exposures compared to oral dosing.

Figure 3: Hydrocodone Plasma Concentration-Time Profiles after IN and Oral Administration of Apadaz and Norco (Study A02)



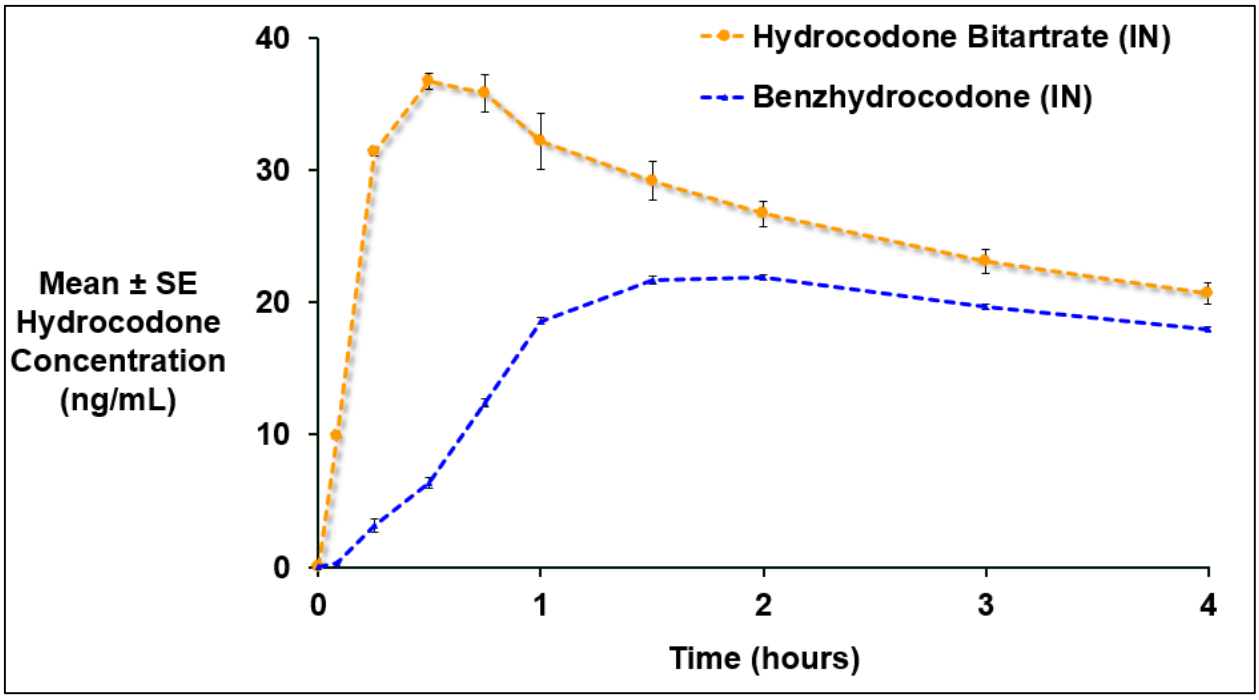
Study A03 – Intranasal BA Study of APIs

Study A03 was conducted in opioid-experienced, non-dependent recreational drug users and evaluated the IN BA of the Apadaz prodrug, benzhydrocodone, compared to the IN bioavailability of HB. The goal of this study was to provide clinical PK data for the scenario

where abusers attempt to extract and isolate the opioid component from combination products before snorting in order to reduce the insufflation volume.

IN administration of benzhydrocodone was associated with a lower peak (by about 36%) and overall hydrocodone exposure (by about 20%) compared to equimolar IN administration of HB (Figure 4). The differences were even more pronounced during the first two hours post-dose when the reduction in cumulative hydrocodone exposure after IN administration of benzhydrocodone ranged from 53% to 95% compared to an equimolar IN dose of HB. In addition, there was a significant delay of 1.25 hours in median time to peak hydrocodone exposure after IN administration of benzhydrocodone (1.75 hours) compared to HB (0.50 hours).

Figure 4: Hydrocodone Plasma Concentration-Time Profiles after IN Administration of Benzhydrocodone and Hydrocodone Bitartrate (Study A03)



Overall, results indicate that attempts to manipulate Apadaz tablets for IN abuse yield lower overall exposure to hydrocodone relative to manipulated Norco tablets and relative to intact Apadaz tablets. Accordingly, the risk of IN abuse to achieve desired subjective opioid-related effects may be decreased for Apadaz when compared to Norco.

1.5 Category 3 Abuse Deterrence Studies: Human Abuse Potential Clinical Trials

Abuse Quotient (AQ)

Clinical observations suggest that reducing the time to maximum plasma concentration (T_{max}) and increasing the peak plasma concentration (C_{max}) of an active opioid enhance euphoric effects (Webster 2009a). It has also become apparent that neither T_{max} nor C_{max} considered alone can precisely predict euphoria. Both parameters are important and need to be evaluated together.

The abuse quotient (AQ), calculated as C_{max}/T_{max}, allows for a numerical assessment of peak drug exposure relative to rate of rise in plasma concentration. AQ increases either by heightening C_{max} or shortening T_{max}. The faster opioid concentrations rise in the blood and brain, the greater the reward experience (Moorman-Li 2012). Consequently, the speed of onset and the extent of drug exposure appear to correlate with the reinforcing effect of the drug (Webster 2009b). For this reason, opioid abusers crush extended-release/long-acting (ER/LA) opioid tablets before oral consumption, or crush and snort tablets in order to enhance the positive subjective effects by shortening T_{max} and possibly increasing C_{max}. Thus, AQ higher scores suggest greater abuse potential.

The AQ values for all treatments assessed in studies A01, A02, and A03 have been calculated to allow comparison of their relative abuse potentials based on pharmacokinetics and hydrocodone exposure (Table 1). The results show that of all treatments IN Apadaz, either with or without APAP, has the lowest abuse potential compared to oral Apadaz and compared to all hydrocodone treatments (with or without APAP, oral or IN) when administered at an equimolar dose. Moreover, IN benzhydrocodone has the lowest AQ score of all conditions evaluated. This suggests that IN administration of crushed Apadaz does not increase the abuse potential compared to oral administration. Additionally, isolation and snorting of the prodrug, benzhydrocodone, from the tablet formulation does not only decrease its abuse potential compared to IN administration of crushed Apadaz and Norco tablets, but also decreases its abuse potential compared to IN HB and oral Norco tablets.

Table 1: Abuse Quotients for All Treatments Administered in Studies A01, A02, and A03

Rank[a]	Treatment	ROA	Dose Units (mg)	AQ[a] (ng/mL/hours)
1	Benzhydrocodone	IN	2 (13.34)	17.0
2	Apadaz	IN	2 (13.34/650)	31.9
3	Norco	PO	2 (15/650)	34.5
4	Apadaz	PO	2 (13.34/650)	38.6
5	Norco	IN	2 (15/650)	56.5
6	Hydrocodone bitartrate	IN	2 (15)	87.3
7	Apadaz	PO	4 (26.68/1300)	99.6
8	Norco	PO	4 (30/1300)	99.7
9	Apadaz	PO	8 (53.36/2600)	204.8
10	Norco	PO	8 (60/2600)	222.7
11	Apadaz	PO	12 (80.04/3900)	287.8
12	Norco	PO	12 (90/3900)	329.7

[a] All treatments from studies A01, A02 and A03 are ranked from smallest to largest abuse quotient (AQ)
[b] AQ (Abuse Quotient) = C_{max}/T_{max}
ROA = Route of Administration, IN = intranasal, PO = per os (oral)

Pharmacodynamic (PD) Measures

Per FDA Guidance, the primary endpoint in the HAP studies was Maximum Drug Liking (E_{max}). In the evaluation of abuse-deterrent properties of ER/LA opioids, the guidance recommends comparing a manipulated form of the putative abuse-deterrent ER opioid to a manipulated, non-abuse deterrent form of an IR or ER product containing the same opioid (FDA, 2015). Essentially, this evaluates whether the ER properties of the test formulation remain intact when manipulated, at least to a meaningful extent, and thus can prevent "dose dumping" and produce a lower drug liking score than the manipulated IR or ER product.

For a putative abuse-deterrent IR product, where the comparator is a non-abuse-deterrent IR product containing the same active moiety, the same primary objective of Drug Liking E_{max} falls short of describing the effects sought by abusers of IR opioids. The rationale of an abuser to use a non-oral route of administration with an IR opioid is to accelerate the onset of a high, however Drug Liking E_{max} does not account for reduced Drug Liking at early time points (i.e., Drug Liking E_{max} is calculated as the average of each subject's maximum Drug Liking score achieved at any point in time). Thus, Drug Liking E_{max} may not capture all of the formulation's characteristics that confer abuse potential. For example, FDA guidance notes that the rate of rise of drug onset should be considered in the overall assessment of abuse-deterrent properties. A more rapid onset of positive subjective effects has been associated with greater abuse potential. Accordingly, assessing Drug Liking at early time intervals (e.g., 30 minutes, 1 hour, 2 hours) may provide a more comprehensive understanding of the overall abuse potential of the intact and manipulated IR formulation.

Drug Liking E_{max} values were similar for Apadaz and Norco whether administered orally (in Study A01) or intranasally (in Study A02). There were statistically significant reductions in Drug Liking (by 3.0 to 11.9 points on a bipolar 100-point scale) in the first 2 hours post-dose after IN administration of two crushed tablets of Apadaz compared to two crushed tablets of Norco ($p \leq 0.0079$). No significant differences were seen in other PD measures such as positive effects, willingness to take again, and pupillometry with the exception of adverse nasal effects, which were significantly more severe with Apadaz than with Norco.

While Study A03 was designed primarily as a PK study of the insufflated APIs, data related to measures of abuse (e.g., drug liking, ease of insufflation) were also collected. No discrimination test was performed in Study A03 to confirm that subjects could discern the opioid-related effects from active drug versus placebo. In this study, Drug Liking through 2 hours was significantly lower for the snorted Apadaz prodrug, benzhydrocodone, than snorted HB. Drug Liking E_{max} was also significantly lower for benzhydrocodone ($p=0.0039$). Furthermore, the median time to E_{max} (TE_{max}) was longer for benzhydrocodone than HB (1.1 vs. 0.5 hours). Similar to Study A02, benzhydrocodone was reported to be more difficult to insufflate than HB based on Ease of Insufflation scores.

1.6 Conclusions

Currently, there are no marketed IR formulations of hydrocodone with abuse-deterrent properties. Based on the totality of evidence collected during the Apadaz development program, the abuse potential of Apadaz is reduced when compared to Norco based on the following results:

- Two tablets of Apadaz represents the maximum dose that can be reasonably snorted due to the bulk of the tablet. Higher doses lead to significant nasal adverse effects, and in the majority of the insufflated material being swallowed and metabolized as an oral dose.
- Similar peak and overall hydrocodone exposure after IN administration of crushed Apadaz tablets compared to equimolar oral doses of Apadaz and Norco. This result is supported by the lower but similar AQ for IN Apadaz compared to both Apadaz and Norco administered orally.
- Significantly reduced hydrocodone exposure at all time points and delayed T_{max} after IN administration of benzhydrocodone compared to HB supported by lower peak (E_{max}) and early Drug Liking scores up to 2 hours post-dose.
- Extraction and isolation of benzhydrocodone from the Apadaz tablet formulation enhances the IN abuse-deterrent properties. At equimolar does, the AQ for IN benzhydrocodone was significantly lower compared to all treatments tested in Studies A01, A02, and A03 regardless of route of administration.
- Subjects reported more difficulty in snorting benzhydrocodone and Apadaz than HB and Norco, respectively. In addition, more severe nasal adverse effects including increased nasal irritation, nasal burning, need to blow nose, runny nose, facial pain/pressure and nasal congestion were reported after insufflation of crushed Apadaz tablets versus crushed Norco tablets.
- The combined IN data, including AQ values, which indicate that snorting of benzhydrocodone or Apadaz does not increase exposure to hydrocodone or abuse potential when compared to an equivalent oral dose.
- In vitro testing demonstrated tamper-resistant properties under a wide range of conditions and an inability to smoke benzhydrocodone or Apadaz.
- There is no new or greater risk of injecting IV formulations prepared from Apadaz tablets. Instead, the IV abuse liability of Apadaz may be lower compared to Norco due to the delayed conversion of benzhydrocodone to hydrocodone as demonstrated by the relative stability of benzhydrocodone in human whole blood.

2 EPIDEMIOLOGY OF HYDROCODONE IR COMBINATION PRODUCT ABUSE AND UNMET PUBLIC HEALTH NEED

Summary

- Despite the rescheduling of hydrocodone combinations products in October 2014, the rate of abuse has not decreased.
- Although proportionally most individuals report oral abuse of hydrocodone IR combination products, snorting is the second most prevalent route of abuse despite the presence of non-psychoactive components (e.g., APAP) in the formulation.
- The frequency of abuse by snorting of hydrocodone IR combination products was greater in adolescents (42.7%) within the CHAT network compared to adults (23.1%) within the ASI-MV network.
- While the prevalence of snorting among adults who abuse hydrocodone IR combination products (23.3%) is lower than other prescription opioids, the total absolute number who report snorting of hydrocodone IR combination products is comparable to that reported for other prescription opioids with high relative rates of snorting.
- While the level of abuse of hydrocodone IR combination products by injection is similar across all ages (~1-2%), smoking is more prevalent among adolescents (5%) than adult abusers (1%).
- A survey of non-medical users of hydrocodone IR combination products found almost universal awareness of the issues related to acetaminophen exposure and report often limiting oral dose or utilizing common extraction methods to avoid liver toxicity. Tampering or manipulation appears to be prevalent with these products as abusers report using multiple techniques to improve drug function.
- Hydrocodone combination products may act as a "gateway" to other opioids and more extreme routes of administration and manipulation. In an internet survey of drug abusers, hydrocodone IR combination products were the first opioids used non-medically by approximately 74% of respondents.
- Another internet survey of abusers indicated that first abuse of hydrocodone IR combination products at a younger age may lead to more severe abuse behavior later on. The percentage of respondents who reported abusing 6 or more non-opioid prescription drugs or illicit drugs was 74% among respondents who first abused hydrocodone IR combination products before the age of 18 compared to 33% of those who first abused hydrocodone IR combination products after the age of 18.

2.1 Background

Misuse and abuse of prescription opioids is an enormous public health concern. Abuse is defined as the intentional, non-therapeutic use of a drug product or substance to achieve a desirable

psychological or physiological effect (FDA, 2010). However, the use of alternate routes of administration to achieve the desired effects more quickly or intensely is associated with risks, such as overdose and progression to dependence and addiction.

Prescription opioid abuse is most common via the oral route. However, alternate routes of administration such as IN and IV routes, are prevalent in more experienced users (Butler 2010; Katz 2011). Users often initially abuse the drug orally and progress to IN or other alternate routes of administration in order to achieve the desired drug-liking effects quickly. These alternate routes of administration are associated with increased risk of negative health outcomes (e.g., drug dependence/addiction, nasal/palatal necrosis and perforation, overdose, death) and therefore, are relevant targets in the development of ADFs (Katz 2011; Surratt 2011).

The patterns of abuse and abuse potential of IR hydrocodone combination products in relation to other opioid products were investigated using data sources from the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO®) surveillance system. Two epidemiology reports and two internet surveys were generated by Inflexxion, Inc. (Newton, MA) to provide supportive information about the abuse profile of these products, including how it relates to patterns of abuse using non-oral routes of administration and the overall relationship that hydrocodone products have within the abuse landscape. In addition, data was collected on how abuse progresses and what kind of negative life problems may result from abuse of IR hydrocodone combination products.

- The first epidemiology report evaluated the rate of abuse of opioid medications in adults and adolescents in the time period prior to the rescheduling of hydrocodone IR combination products.
- The second epidemiology report more closely examined the abuse of opioids for the 3 quarters before and after the rescheduling of hydrocodone IR combination products.
- The first internet survey collected data on the use and misuse of hydrocodone IR combination products among recreational opioid users who visit drug-discussion forums online (i.e., Bluelight.org).
- The second internet survey collected data on the progression of abuse after initiation with hydrocodone IR combination products among recreational opioid users who visit drug-discussion forums online (i.e., Bluelight.org).

2.2 Drug Abuse Surveillance of Data for Hydrocodone Combination Products (Jan 2012 to June 2015)

The baseline analysis of abuse was assessed in adults (18 years old and older) using data from the NAVIPPRO Addiction Severity Index – Multimedia Version (ASI-MV®) and in adolescents (i.e., individuals 18 years old and younger) using data from the NAVIPPRO Comprehensive Health Assessment for Teens (CHAT®). Abuse and specific route of administration for hydrocodone IR combination products and other prescription opioids were captured via self-report during the ASI-MV and CHAT interviews. Abuse was defined as any non-medical use of a prescription opioid product within the past 30 days prior to assessment.

The ASI-MV is a validated proprietary data stream of the NAVIPPRO surveillance system that collects data on substances used and abused by individuals assessed for or entering in treatment for substance use disorders. Data from a total of 151,704 adults across 743 sites located in 42 states were collected during the reporting period Jan 2012 through Sep 2014 using a self-administered and structured computerized interview from adults within a network of substance abuse treatment centers and other assessment settings. A summary of the characteristics of ASI-MV participants who abused prescription opioids in the past 30 days is shown in Table 2. The ASI-MV assessment captured product-specific data related to past 30-day use and abuse for over 60 brand and generic prescription opioid products, including information on routes of administration used and sources of procurement for each product.

Table 2: Characteristics of Respondents Reporting Any Past 30-Day Prescription Opioid Abuse in ASI-MV (1/1/2012 – 6/30/2015)

Characteristic		% of Respondents (N = 51,116)
Chronic medical problem	Yes	39.5
	No	60.3
	Unknown/no response	<1.0
ASI-MV Severity Score[a]	0-1	9.9
	2-3	6.3
	4-5	12.3
	6-7	37.1
	8-9	31.0
	Unknown/no response	3.4

[a] ASI-MV severity score category definitions include 0-1: No real problem, treatment not indicated; 2-3: Slight problem, treatment probably not indicated; 4-5: Moderate problem, some treatment indicated; 6-7: Considerable problem, treatment necessary; 8-9: Extreme problem, treatment absolutely necessary.

CHAT is a validated proprietary data source of the NAVIPPRO surveillance system that is used to monitor substance abuse patterns within a sentinel population of adolescents entering treatment for substance abuse within a network of participating centers and other facilities such as alternative schools and mental health programs throughout the United States. Data from a total of 9,847 adolescents across 152 sites located in 23 states were collected during the reporting period Jan 2012 through Sep 2014. A summary of the characteristics of CHAT respondents is shown in Table 3. Data from CHAT was collected at a product-specific level, including data on routes of administration and source of the drug, allowing for the comparison of abuse among similar products and compounds.

Table 3: Characteristics of CHAT Participants (1/1/2012 – 6/30/2015)

Characteristic		% of Respondents (N=14,812)
Past 30 days in a controlled environment (juvenile justice center, substance abuse treatment, etc.)	Yes	35.0
	No	64.9
	Unknown/no response	<1.0
Currently taking medication for emotional, behavioral, or learning problems	Yes	32.2%
	No	67.6%
	Unknown/no response	<1.0
Current physical problems or illnesses	Yes	28.4%
	No	71.6%
	Unknown/no response	0.0%
Current pain problem	Yes	19.4%
	No	80.4%
	Unknown/no response	<1.0

2.2.1 Prevalence of Abuse Before Hydrocodone Rescheduling (Jan 2012 to Sep 2014)

The prevalence of abuse across different opioid compounds including hydrocodone IR combination products was evaluated for the reporting period in both adults (ASI-MV) and adolescents (CHAT) (Table 4). Hydrocodone IR combination products had the highest number of associated abuse cases in both adults and adolescents of all the different classes of opioid products. Hydrocodone IR combination products were also associated with the greatest number of prescriptions dispensed and morphine-equivalent milligrams dispensed.

Table 4: Prevalence of Past 30-day Abuse for Hydrocodone Immediate-release Combination Products and Comparator Opioids within the ASI-MV or CHAT Networks (Jan 2012 to Sep 2014)

	Addiction Severity Index – Multimedia Version (ASI-MV®)			Comprehensive Health Assessment for Teens (CHAT®)		
Opioid Product/ Compound Category	Total abuse cases	Total prescriptions dispensed	Total morphine equivalent milligrams dispensed	Total abuse cases	Total prescriptions dispensed	Total morphine equivalent milligrams dispensed
Hydrocodone IR combination products[a]	14,871	314,681,245	148,457,159,524	393	216,923,599	105,567,132,872
Oxycodone IR combination products[a]	12,319	80,230,772	60,694,582,586	329	53,067,177	40,516,815,219
Oxycodone IR single-entity products	5,699	45,063,417	118,561,444,902	78	28,456,422	82,390,437,528
All other IR prescription opioids[b]	4,206	14,360,755	26,538,807,431	71	10,434,219	20,055,894,621
All ER/LA opioids[c]	9,986	33,852,484	117,416,287,634	195	23,770,572	85,108,565,450
All ADF ER/LA opioids	5,401	15,148,330	60,145,651,217	95	10,540,208	43,149,024,938
All non-ADF ER/LA opioids[d]	7,877	18,704,154	57,270,636,418	148	13,230,364	41,959,540,513

[a] Represents brand and generic formulations
[b] Represents single entity and combination formulations excluding Schedule III products
[c] Represents abuse-deterrent formulations and non-abuse-deterrent products excluding patch and buprenorphine products.
[d] Excludes patch and buprenorphine products
A list of the comparator products in each opioid product/compound category is provided in the Appendix (Table 17).
Total prescriptions dispensed include states with sites that contributed assessments to the ASI-MV or CHAT datasets during the reporting period in order to provide a more accurate estimate of the potential availability of products in the areas monitored.

Among the total population of adults assessed for substance abuse treatment during the period January 2012 through September 2014, the prevalence of past 30-day abuse was greatest for hydrocodone IR combination products (9.80 cases per 100 assessments) and oxycodone IR combination products (8.12 cases per 100 assessments) (Table 5). Prevalence of past 30-day abuse for ER/LA opioids was 6.58 cases per 100 assessments with a lower abuse prevalence among this substance abuse treatment population for ADF ER/LA opioids (3.56 cases per 100 assessments) than observed for non-ADF ER/LA opioids (5.19 cases per 100 assessments).

Similar to patterns observed among adults, the prevalence of past 30-day abuse of hydrocodone IR combination products was higher among adolescents assessed via CHAT compared to other prescription opioid categories (3.99 cases per 100 CHAT assessments) followed by abuse of oxycodone IR combination products (3.34 cases per 100 assessments) and all ER/LA opioids (1.98 cases per 100 assessments). Among adolescents within the CHAT network, a lower prevalence of abuse was observed for ADF ER/LA opioids (0.96 cases per 100 assessments), oxycodone IR single-entity products (0.79 cases per 100 assessments) and all other IR prescription opioid products (0.72 cases per 100 assessments).

Table 5: Past 30-day Abuse per 100 assessments for Hydrocodone Immediate-release Combination Products and Comparator Opioids within the ASI-MV and CHAT Networks (Jan 2012 to Sep 2014)

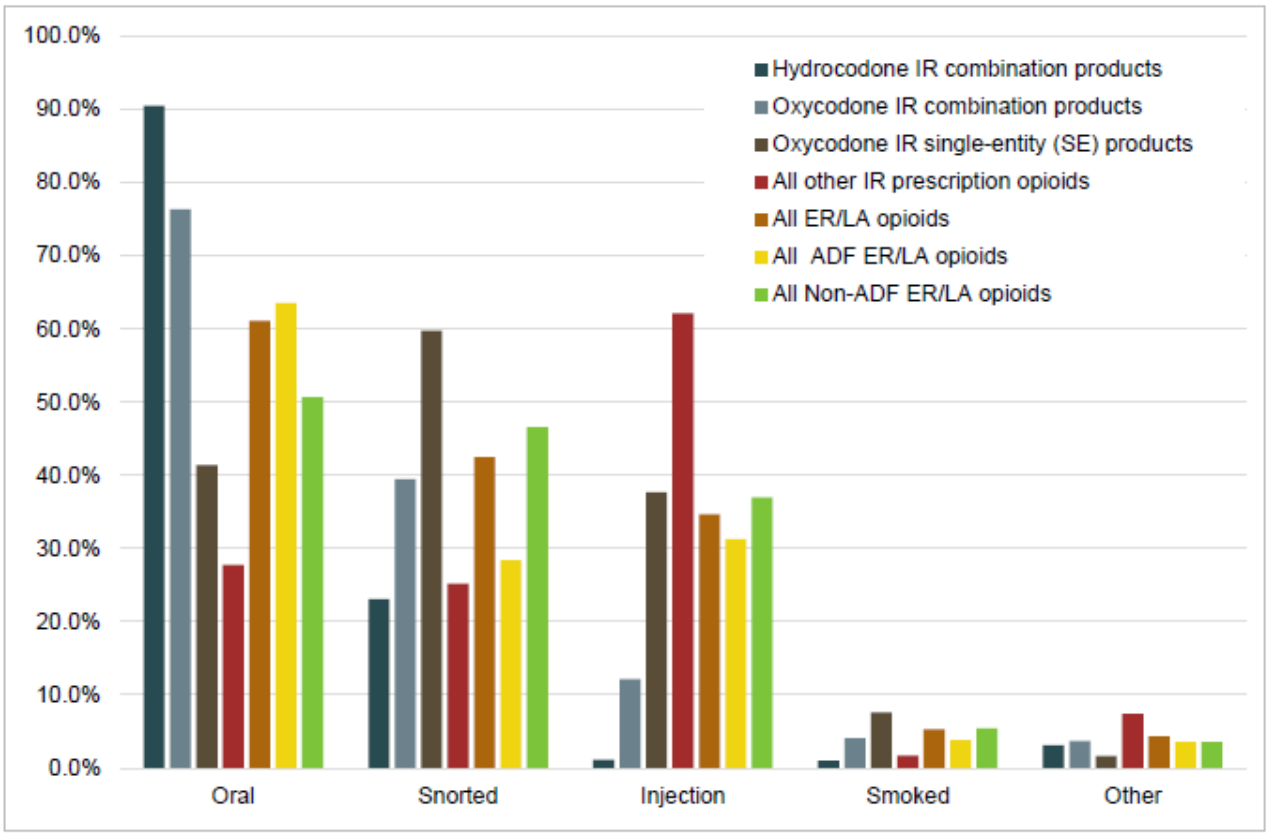
Opioid Product/ Compound Category	Cases per 100 ASI-MV assessments		Cases per 100 CHAT assessments	
	Rate	95% CI	Rate	95% CI
Hydrocodone IR combination products[a]	9.80	9.65, 9.95	3.99	3.60, 4.38
Oxycodone IR combination products [a]	8.12	7.98, 8.26	3.34	2.99, 3.70
Oxycodone IR single-entity products	3.76	3.66, 3.85	0.79	0.62, 0.97
All other IR prescription opioids[b]	2.77	2.69, 2.86	0.72	0.55, 0.89
All ER/LA opioids[c]	6.58	6.46, 6.71	1.98	1.71, 2.26
All ADF ER/LA opioids	3.56	3.47, 3.65	0.96	0.77, 1.16
All non-ADF ER/LA opioids[d]	5.19	5.08, 5.30	1.50	1.26, 1.74

[a] Represents brand and generic formulations
[b] Represents single entity and combination formulations excluding Schedule III products
[c] Represents abuse-deterrent formulations and non-abuse-deterrent products excluding patch and buprenorphine products.
[d] Excludes patch and buprenorphine products
A list of the comparator products in each opioid product/compound category is provided in the Appendix (Table 17).
95% CIs for each rate were calculated as a two-sided CI for a single population proportion and when appropriate (i.e. when the numerator, n, is less than 30) with use of CIs based on a Poisson distribution.

2.2.2 Abuse by Route of Administration before Hydrocodone Rescheduling (Jan 2012 to Sep 2014)

In general, oral routes, snorting, and injection were the most frequently reported routes of administration for all of the opioid categories reviewed during the reporting period in the ASI-MV network (Figure 5). Among adults who reported past 30-day abuse of hydrocodone IR combination products, approximately 90% reported abuse of these products via the oral route, which was the highest percentage among all opioid categories evaluated, and 23.1% reported snorting as a route of administration. A markedly lower percentage reported abuse of hydrocodone IR combination products by use of injection (1.1%) or via smoking (1.0%).

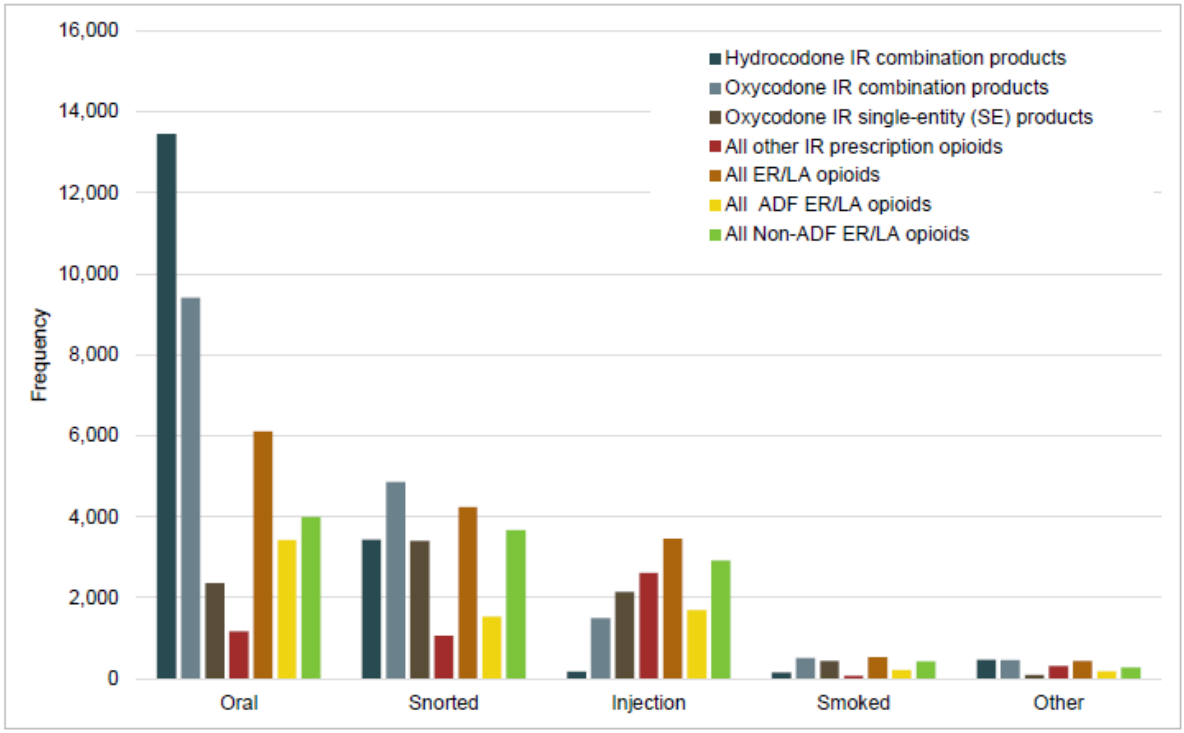
Figure 5: Percentage Reporting Past 30-day Abuse by Route of Administration for Hydrocodone Immediate-release Combination Products and Comparator Opioids within the ASI-MV Network (Jan 2012 to Sep 2014)



Data represent the percent of individuals who reported abuse via 1 or more specific routes of administration among individuals who reported past 30-day abuse for an opioid category. Therefore, percentages do not sum to 100 across the various routes of administration within a particular drug category.

In absolute terms of the frequency of individuals who abused, the number of IN abusers of hydrocodone IR combination products was comparable to that reported for other prescription opioids typically associated with high levels of snorting (i.e., oxycodone and ER products) (Figure 6).

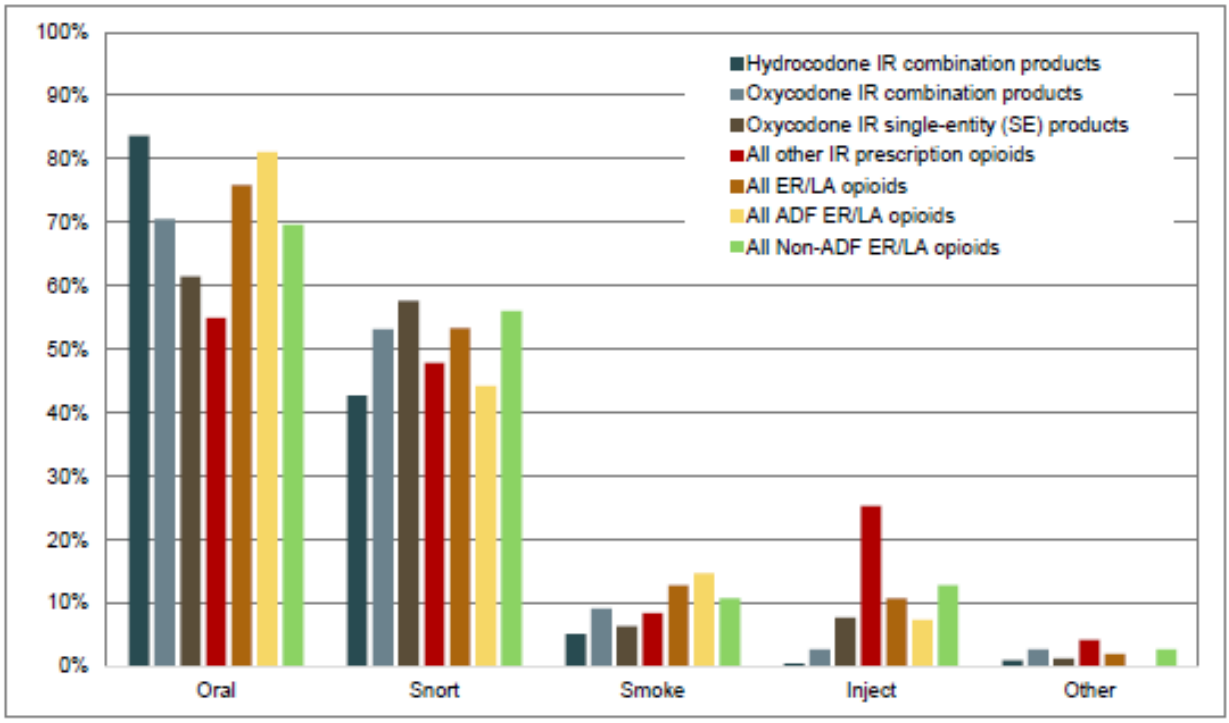
Figure 6: Frequency of Past 30-day Abuse by Route of Administration for Hydrocodone Immediate-release Combination Products and Comparator Opioids within the ASI-MV Network (Jan 2012 to Sep 2014)



Data represent the number of individuals who reported abuse via 1 or more specific routes of administration among individuals who reported past 30-day abuse for an individual opioid category.

In adolescents who reported past 30-day abuse, the oral route was the most common route of abuse of all opioid products followed closely by snorting (Figure 7). Compared to adults within the ASI-MV network, a greater percentage of adolescents within the CHAT network reported past 30-day abuse of hydrocodone IR combination products by snorting (43% of adolescents compared to 23% of adults). The percentage of adolescents who abused hydrocodone IR combination products via smoking was greater than the number who abused the product via injection (5% versus <1.0%, respectively), which contrasts the similar percentage in adults of approximately 1% for either smoking or injection. Across all opioid categories, adolescents reported smoking more often than injection, with the exceptions of oxycodone IR single-entity products, all other IR prescription opioids, and all non-ADF ER/LA opioids.

Figure 7: Percentage Reporting Past 30-day Abuse by Route of Administration for Hydrocodone Immediate-release Combination Products and Comparator Opioids within the CHAT Network (Jan 2012 to Sep 2014)

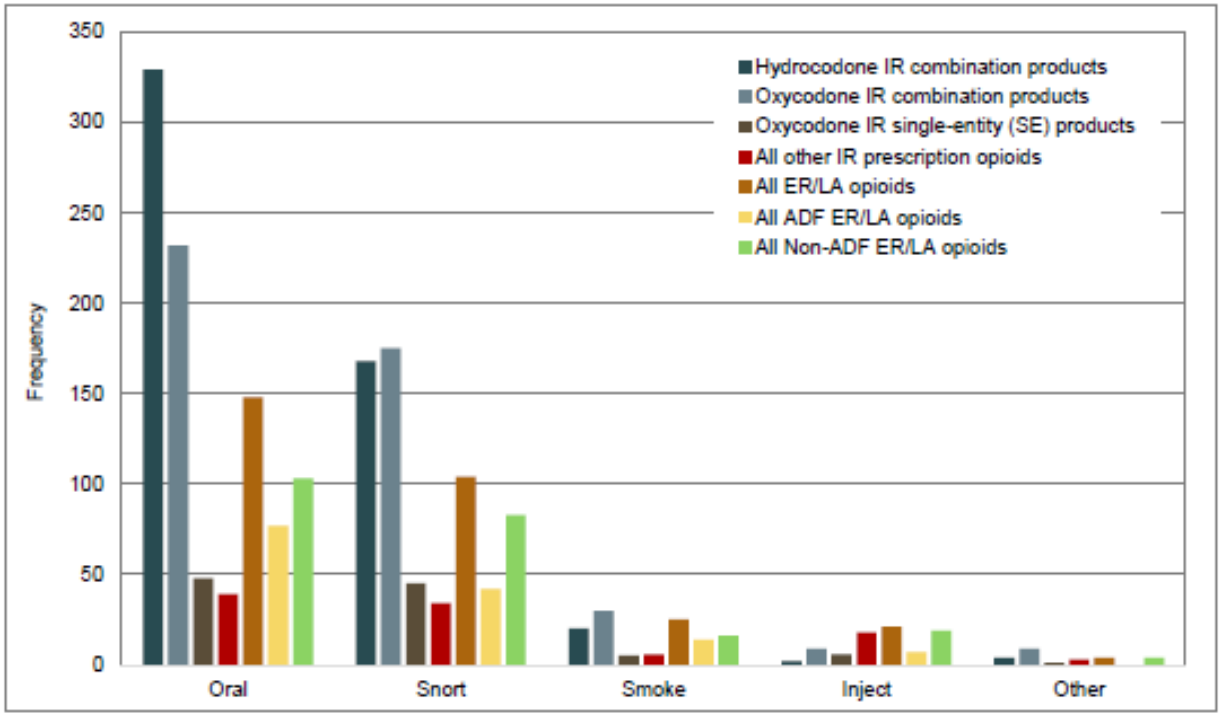


Data represent the percent of individuals who reported abuse via 1 or more specific routes of administration among individuals who reported past 30-day abuse for an opioid product/compound category. Therefore, percentages do not sum to 100 across the various routes of administration within a particular drug category.

In terms of frequency of past 30-day abuse by route of administration, the greatest absolute number of adolescents reported abuse via the oral route for hydrocodone IR combination products (329 adolescents) followed by oxycodone IR combination products (232 adolescents) and all ER/LA opioids (148 adolescents) (Figure 8). The absolute number of adolescents who reported snorting these products (168 adolescents) as well as oxycodone IR combination products (175 adolescents) was similar to that for all ER/LA opioids (104 adolescents). Furthermore, the absolute number of 168 adolescents was greater than the number observed for opioid categories with higher percentages of snorting, such as oxycodone IR single-entity

products (snorting = 57.7%, 45 adolescents) and all non-ADF ER/LA opioids (snorting = 56.1%, 83 adolescents).

Figure 8: Frequency of Past 30-day Abuse by Route of Administration for Hydrocodone Immediate-release Combination Products and Comparator Opioids within the CHAT Network (Jan 2012 to Sep 2014)



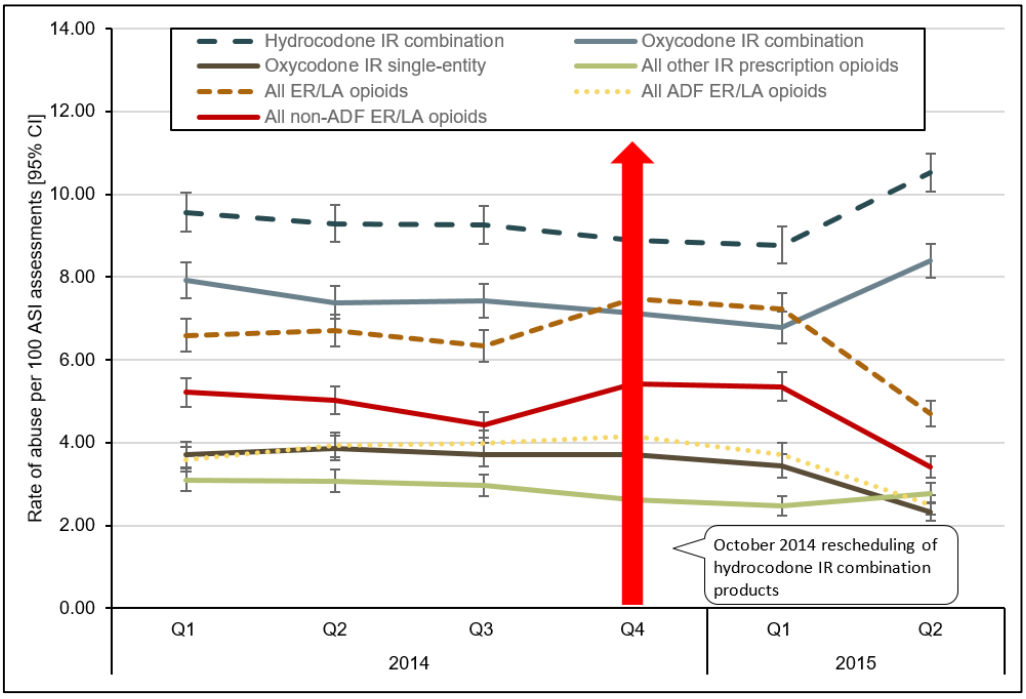
Data represent the number of individuals who reported abuse via 1 or more specific routes of administration among individuals who reported past 30-day abuse for an individual opioid category.

2.2.3 Drug Abuse Surveillance Report of Rates of Abuse Prior to and After Rescheduling of Hydrocodone IR Combination Products

In October 2014, the Drug Enforcement Administration (DEA) rescheduled hydrocodone IR combination products from Schedule III to Schedule II resulting in certain restrictions in prescribing and dispensing of these opioid medications (DOJ, 2014). It is important to understand and characterize the pattern of abuse of these products to be able to examine the possible impact of this change. Data from both ASI-MV and CHAT networks were analyzed to evaluate abuse of hydrocodone IR combination products before (Jan 2012 through Sep 2014) and after (Oct 2014 through Jun 2015) rescheduling.

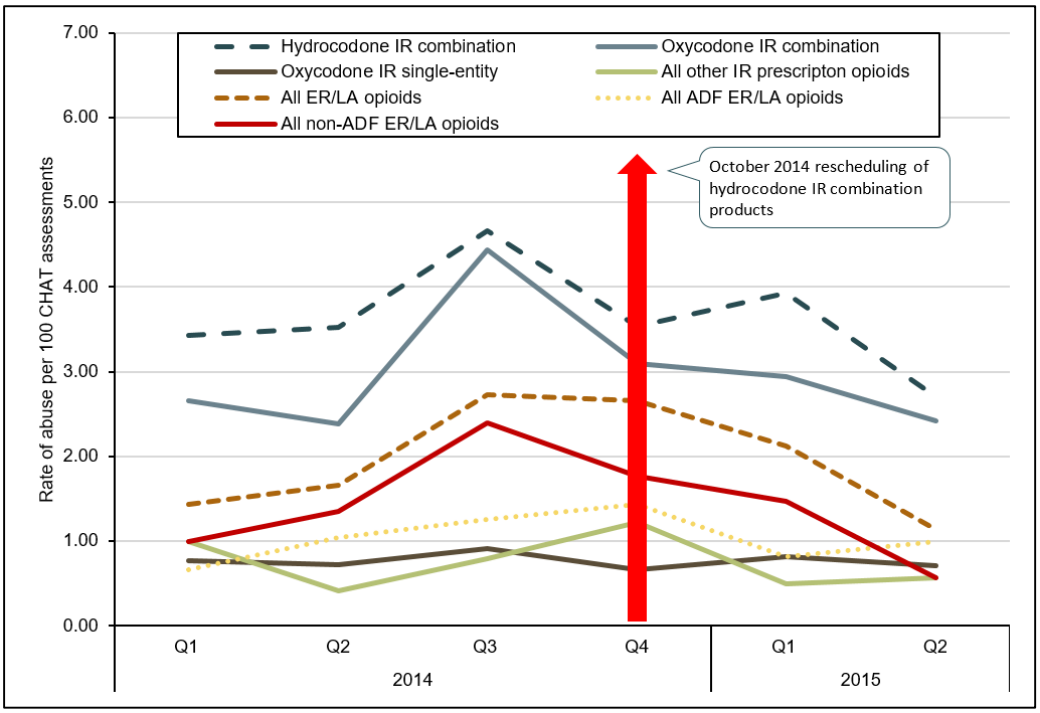
While the average number of quarterly prescriptions for IR hydrocodone combination products decreased significantly (by approximately 5 million or 20%) after the rescheduling of hydrocodone IR combination products in Q4 2014, prevalence of past 30-day abuse of hydrocodone IR combination products did not appear to decline (Figure 9). It is possible that the change of higher abuse in more recent quarters among adults assessed for substance abuse problems within the ASI-MV reflects a larger overall change in the pattern abuse of IR opioid formulations. While data presented in this summary indicate a change of higher abuse of IR hydrocodone combination products in more recent quarters, this change also coincided with a change to some of the screens that present opioid product options within the ASI-MV assessment which may also have influenced the difference in estimates of abuse observed during this time. However, the size and direction of the changes suggest that rescheduling has not, to date, been associated with a meaningful decrease in abuse rates of hydrocodone IR combination products.

Figure 9: Past 30-day Abuse per 100 Assessments for Hydrocodone IR Combination Products and Comparator Opioids within ASI-MV (Jan 2014 – Jun 2015)



The prevalence of abuse of hydrocodone IR combination products among adolescents assessed within the CHAT varied during the six quarters before and after hydrocodone rescheduling, and the pattern for hydrocodone and oxycodone combination products was different from that observed among adults within the ASI-MV. While recent (Q2 2015) increases in abuse prevalence for these opioid compounds were noted among adults, prevalence of abuse for hydrocodone and oxycodone combination products among adolescents within the CHAT network, was lower in Q2 2015 compared to previous quarters (Figure 10).

Figure 10: Past 30-day Abuse per 100 Assessments for Hydrocodone IR Combination Products and Comparator Opioids within CHAT (Jan 2014 – Jun 2015)



2.3 Internet Survey on Use and Abuse of Hydrocodone Combination Products

The use and abuse of hydrocodone IR combination products was evaluated by administering the Use and Abuse of Hydrocodone Combination Products Internet Survey 2014 to individuals ≥18 years old who visited drug-related discussion forums online (i.e., Bluelight.org). Data from individuals who visited the site for the purpose of taking this survey were included in the analysis. Participants were recruited between December 2014 and March 2015.

The purpose of the survey was to provide data on non-medical use of hydrocodone IR combination products among a subgroup of abusers. The internet survey focused on drug abuse history of individuals who reported abuse of hydrocodone IR combination products including progression of abuse, progression of abuse regarding certain opioid products and routes of administration, as well as reasons and motivation for abuse of certain products.

In order to be eligible to participate in the survey, individuals must have met the following criteria: (1) ability to read and understand the English language; (2) visit Bluelight.org or been directed to Bluelight.org for the purposes of taking the survey; (3) willing to "Agree" to participate in the survey; and (4) be at least 18 years of age.

Data from 304 participants who met eligibility criteria and completed the survey were included in the analysis. The survey participants were characterized as prescription opioid users who had used at least one opioid in their lifetime. It is important to note that the online survey was advertised specifically to users of hydrocodone IR combination products, meaning that the prevalence of use and abuse of these products in the survey sample may be different from that of the general population.

2.3.1 Use and Abuse/Misuse of Prescription Opioids

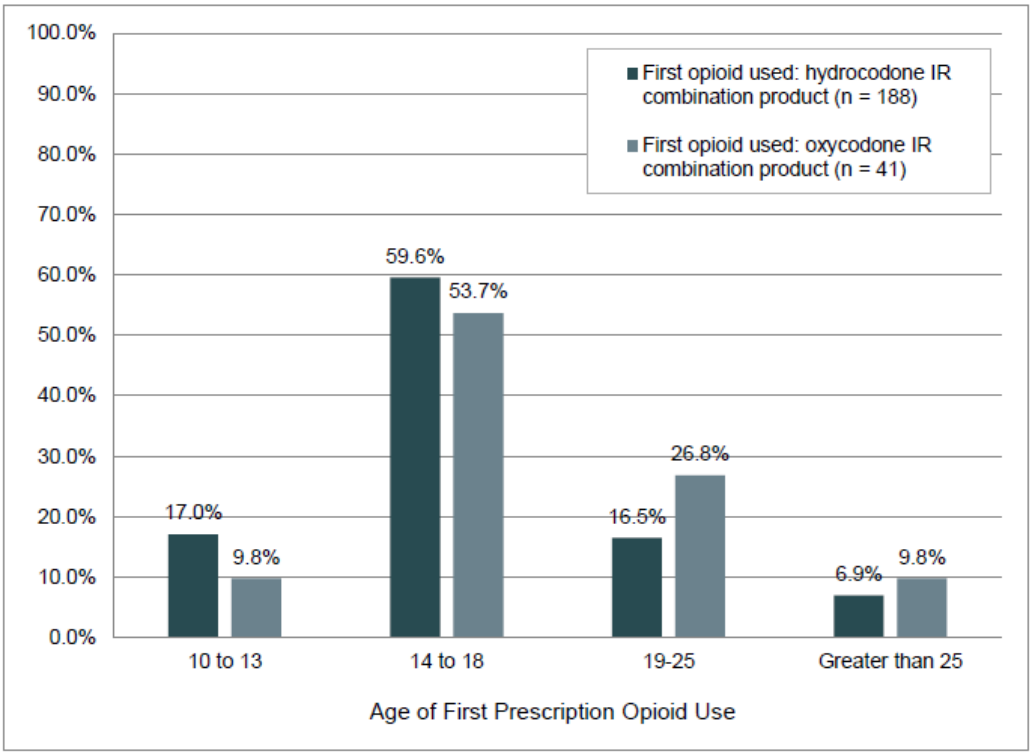
Participants were presented with a series of questions that examined both first-time use and lifetime use of prescription opioids to evaluate the progression of use of hydrocodone IR combination products, regardless of whether or not these products were the first prescription opioid product the participants used in their lifetime.

Of the 304 participants, 95% (288 participants) indicated use of hydrocodone IR combination products in their lifetime, and approximately 59% indicated their first-time use was non-medical use; however, the target recruitment of the online survey was users of hydrocodone IR combination products and this should be considered in the interpretation of these results. Of the total 288 lifetime users of hydrocodone IR combination products, 73% abused or misused these products at one point in their lifetime. Of the 288 lifetime users of hydrocodone IR combination products, 39% identified as current users. Current users of these products indicated their current frequency of use was less than a few times a month (46%), followed by a few times a month (24%). The reasons for using these products included getting high, such as enjoying how the product makes them feel (73%) and the positive quality of their high (42%). Participants also indicated response options related to obtaining these products, such as the drug is easy to obtain (36%) and the drug is not expensive compared to other prescription opioids (27%).

The most frequent first-opioid product used in a respondent's lifetime was hydrocodone IR combination products (62%), followed by oxycodone IR combination products (13.5%). Of the 188 participants who indicated first-opioid used in a lifetime was a hydrocodone IR combination product, 52% indicated non-medical use of the product during that first use. It is noteworthy that the majority of lifetime users of prescription hydrocodone IR combination products or oxycodone IR combination products indicated the age of first use occurred during adolescence (14 to 18 years old) (Figure 11).

Most (97%) of the 188 participants who used hydrocodone IR combination products in their lifetime indicated awareness of the potential risks with APAP. When asked how participants have attempted to avoid the risks, the majority (56%) limited the amount used orally, while others used common methods of manipulation to extract APAP (23%) or simply ignored the risks and did not address them (17%).

Figure 11: Age at First Prescription Opioid Use Among Lifetime Users of a Hydrocodone Immediate-release Combination Product or an Oxycodone Immediate-release Combination Product – Internet Survey 2014

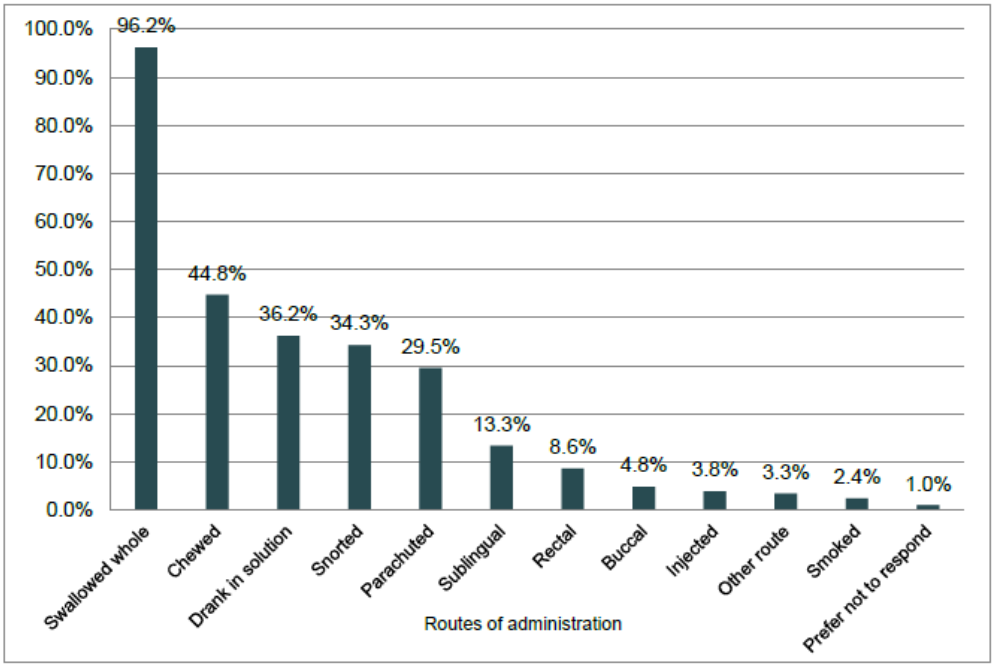


2.3.2 Abuse by Route of Administration

Lifetime non-medical users of hydrocodone IR combination products, survey participants most frequently reported swallowing these products whole. However, they also indicated chewing, drinking in solution, and snorting as common routes of administration (Figure 12). Nearly all forms of abuse included some form of manipulation (chewing, snorting, IV, etc.).

In addition, these illicit routes of administration, such as chewing, drinking in solution, and snorting, were more frequently selected as lifetime-preferred routes compared to those selected as first routes of administration, suggesting a possible progression among lifetime users of hydrocodone combination products from swallowing whole to alternate or illicit routes.

Figure 12: Lifetime Routes of Administration of Hydrocodone Immediate-release Combination Products – Internet Survey 2014



Survey responses from 304 participants; results are not mutually exclusive.

2.4 Internet Survey on the Progression of Abuse with Hydrocodone Combination Products

The progression of abuse of hydrocodone IR combination products was evaluated by administering the Progression of Hydrocodone Combination Product Use Internet Survey to individuals ≥18 years old who visited drug-related discussion forums online (i.e., Bluelight.org). Data from individuals who visited the site for the purpose of taking this survey were included in the analysis. Participants were recruited between September 2015 and December 2015.

The purpose of the survey was to understand the progression of non-medical use of hydrocodone IR combination products and the potential for these products to serve as a gateway to use other prescription opioids and illicit drugs or to use opioids via more dangerous illicit routes of administration such as snorting or injection among a sample of adults who visit drug-related Internet forums. Survey respondents were asked about their first, continued, and most recent non-medical use of hydrocodone IR combination products as a way to assess and evaluate their progression in use of these products. Respondents were also asked about the socioeconomic, behavioral, and physical impact the non-medical use of both hydrocodone IR combination products and other prescription opioid products had on their personal lives.

In order to be eligible to participate in the survey, individuals must have met the following criteria: (1) ability to read and understand the English language; (2) visit Bluelight.org or been directed to Bluelight.org for the purposes of taking the survey; (3) willing to "Agree" to participate in the survey; and (4) be at least 18 years of age.

Data from 472 participants who met eligibility criteria and completed the survey were included in the analysis. The survey participants were characterized as prescription opioid users who had used at least one opioid in their lifetime. It is important to note that the online survey was advertised specifically to users of hydrocodone IR combination products, meaning that the prevalence of use and abuse of these products in the survey sample may be different from that of the general population.

2.4.1 History of Use and Abuse/Misuse of Prescription Opioids

Most participants reported that their first non-medical use of any prescription opioid products was between the ages of 14 to 18 years (62%), followed by between the ages of 19 to 25 years (21%). The age of first non-medical use of hydrocodone IR combination products was similar; 58% reported their first non-medical use between the ages of 14 and 18, and 24% reported their first non-medical use between the ages of 19 and 25.

Among those whose first non-medical use of hydrocodone IR combination products was before the age of 18, 77% reported that their first non-medical use of hydrocodone IR combination products was swallowing the product whole. Only 7% reported snorting and none reported injecting at their first use. The routes of administration during first non-medical use was similar among those whose first non-medical use was after the age of 18.

2.4.2 Progression of Abuse/Misuse of Prescription Opioids from Hydrocodone IR Combination Products

Approximately half of all respondents (49%, n = 235) believed that non-medical use of hydrocodone IR combination products led them to use other prescription opioids non-medically in the future. Specifically, 86.4% of these respondents believed their use of hydrocodone IR combination products led them to use oxycodone IR combination products non-medically. Additionally, greater than 50% of respondents believed that using hydrocodone IR combination products non-medically led them to non-medical use of oxycodone IR (76.2%), oxycodone ER (63.0%), hydromorphone IR (54.9%), morphine ER (53.2%), and buprenorphine (51.5%).

Among those who believed hydrocodone IR combination products had led them to abuse other prescription opioids, age was an important factor in the progression of the routes of administration (Table 6). Of those respondents whose first abuse of hydrocodone IR combination products was before the age of 18, 75% reported snorting other prescription opioids compared to 47% of those whose first abuse of hydrocodone IR combination products was after the age of 18. Similarly, the rates of smoking (31% vs. 23%) and injecting (31% vs. 19%) other opioid products was higher among those whose first abuse of hydrocodone IR combination products was before the age of 18.

Table 6: Routes of Administration Used with Other Prescription Opioids Among Respondents Who Believed Using Hydrocodone IR Combination Products (HCPs) Non-Medically Led Them to Use Other Prescription Opioids Non-Medically, by Age at First Use

Route of Administration	First used HCPs non-medically when ≤18 years of age (%) (n = 157)	First used HCPs non-medically when >18 years of age (%) (n = 78)
Swallowed whole	86	83
Snorted	75	47
Chewed	48	42
Sublingual	41	40
Drank in solution	42	29
Parachuted	36	15
Smoked	31	23
Injected	31	19
Rectal (plugging)	24	23
Buccal (in cheek)	16	9
Other route	3	1

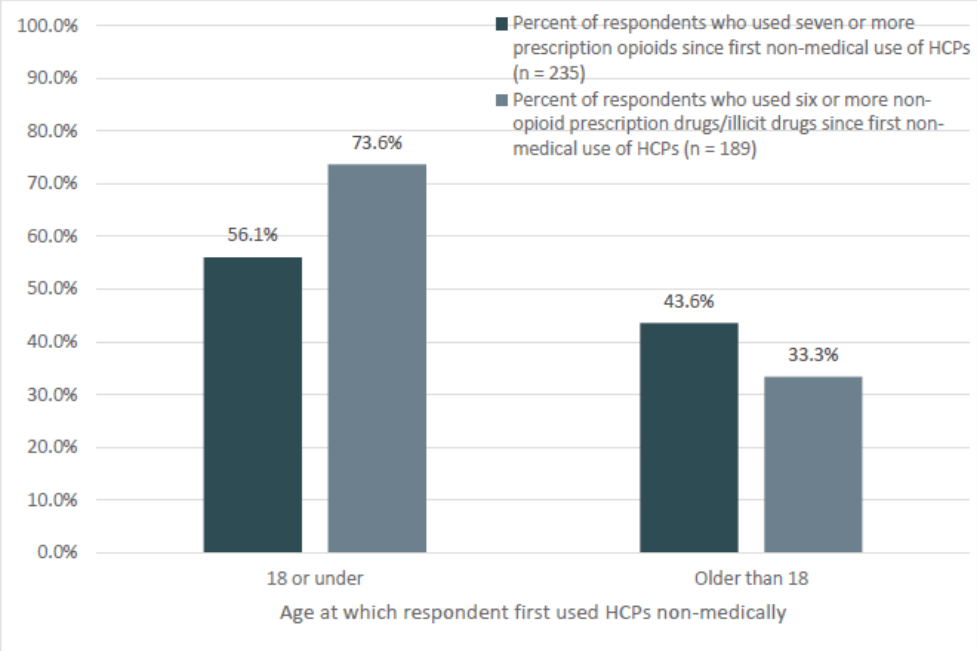
* Parachuted = rolled powdered or crushed tablet in a piece of toilet paper to ingest.

Approximately 74% of respondents provided the same age when asked about their age at first non-medical use of any prescription opioid and age at first non-medical use of hydrocodone IR combination products, indicating hydrocodone IR combination products may have been the first opioids used non-medically by the majority of respondents.

Respondents who started using hydrocodone IR combination products non-medically before the age of 18 used a greater number of prescription opioids subsequently during their lifetime. Of those who first used hydrocodone IR combination products before 18 years old, 56% used the sample median of seven or more prescription opioid products since their first use of hydrocodone IR combination products, compared to 44% of those who first used hydrocodone IR combination products when they were older than 18.

Those who first used hydrocodone IR combination products before 18 years old were significantly more likely to use the median of six or more non-opioid prescription drugs/illicit drugs in their lifetime (74%) after their first use of hydrocodone IR combination products compared to those who first used these products when they were older than 18 (33%). This finding illustrates that individuals first using hydrocodone IR combination products non-medically at an early age may lead to non-medical use of a greater number of non-opioid prescription drugs/illicit drugs and thus more severe progression of drug abuse.

Figure 13: Percentage of Respondents Using 7 or More Prescription Opioids or 6 or More Non-opioid Prescription Drugs/Illicit Drugs Non-medically by Age at First Non-Medical Use of Hydrocodone IR Combination Products



2.5 Conclusion

The totality of the epidemiologic and survey data highlight the magnitude and the seriousness of the role hydrocodone IR combination products play in the opioid abuse epidemic. While oral administration is the most common route of abuse for hydrocodone IR combination products, tampering and alternative non-oral routes are prevalent. Specifically, the number of abusers who snort hydrocodone IR combination products is similar to the number who snort ER opioid products and IR oxycodone products, which are known to have high rates of IN abuse.

Hydrocodone IR combination products account for the preponderance of cases of abuse in both adults and adolescents and is typically the first opioid product abused among lifetime abusers. The findings regarding abuse among adolescents is particularly concerning given that abuse of hydrocodone IR combination products in adolescence is associated with progression of abuse to riskier, non-oral routes (e.g., intranasal, IV) and more frequent abuse of other prescription opioids or illicit drugs.

Overall, the data highlight the unmet public health need for hydrocodone IR combination products with abuse-deterrent properties to discourage the escalation of abuse to more potent opioids and to eliminate the reinforcement of more rapid highs associated with riskier non-oral routes of administration.

3 OVERVIEW OF CLINICAL PHARMACOLOGY AND DEVELOPMENT PROGRAM

Summary

- Apadaz is an IR benzhydrocodone-APAP combination product for the short-term management (no more than 14 days) of acute pain
- The Section 505(b)(2) application for Apadaz was supported by clinical PK studies and extensive evaluations of the drug's abuse-deterrent characteristics.
- The hydrocodone component of Apadaz was bridged using Vicoprofen (HB/ibuprofen combination product).
- The APAP component of Apadaz was bridged using Ultracet (tramadol/APAP combination product).
- There was no clinically significant effect of food with Apadaz on the bioavailability of hydrocodone or APAP.
- There was no systemic exposure to the benzhydrocodone which is very rapidly converted into hydrocodone in the intestinal tract. Due to this rapid conversion, pre-systemic exposure is also low and transient.
- A gastrointestinal safety study confirmed that Apadaz does not pose any additional safety risk compared to Norco.

3.1 Clinical Development Overview

The Apadaz tablet consists of a prodrug composed of hydrocodone and benzoic acid, benzhydrocodone HCl (KP201), in a fixed-dose combination with APAP for treatment of short-term (no more than 14 days) management of acute pain. KemPharm is relying on the FDA's determination of efficacy and safety for NDA-listed drugs Vicoprofen® (7.5 mg hydrocodone bitartrate/200 mg ibuprofen oral tablet) for the hydrocodone component and Ultracet® (37.5 mg tramadol hydrochloride/325 mg acetaminophen (APAP) oral tablet) for the APAP component of Apadaz. In addition, Norco®, an ANDA-listed approved combination of hydrocodone and APAP, was used to show that the combination of Apadaz is not novel.

The development program for Apadaz focused primarily on investigating whether the intact prodrug, benzhydrocodone, results in any pharmacological and/or toxicological differences to hydrocodone that could pose new safety risks not associated with other IR hydrocodone products. Benzhydrocodone is rapidly converted to hydrocodone in the intestine after oral administration and any exposure to intact prodrug is low, limited to the intestinal tract, and of very short duration.

The clinical pharmacology program comprised of seven (7) Phase 1 studies in healthy volunteers: one (1) PK/BA study with an early formulation of neat-filled benzhydrocodone

capsules, five (5) PK/BA studies with the final dosage form, Apadaz tablet, 6.67 mg/325 mg, and a one (1) gastrointestinal (GI) motility study (Table 7).

Table 7: Overview of Clinical Pharmacology Studies

Study Number	Subjects	Comparator	Conditions	Purpose
105	28	Vicoprofen (HB/Ibuprofen)	• Cross-over • Healthy volunteers • Single dose • Fasted	Bioequivalence to Vicoprofen for regulatory purposes
106	27	Ultracet (tramadol/APAP)	• Cross-over • Healthy volunteers • Single dose • Fasted	Bioequivalence to Ultracet for regulatory purposes
102	24	Norco (HB/APAP)	• Cross-over • Healthy volunteers • Single dose • Fasted	Bioequivalence to approved HB/APAP product, Norco
104	38	Norco (HB/APAP)	• Cross-over • Single dose • Healthy volunteers • Fed and fasted	Food effect of Apadaz
103	24	None	• Single and multiple doses • Naltrexone block • Healthy volunteers	Evaluate Apadaz at steady state
101[a]	21	Norco (HB/APAP)	• Cross-over • Single dose • Healthy volunteers • Fasted	Relative bioavailability of non-final formulation to HB/APAP product, Norco
S01	41	Norco (HB/APAP)	• Cross-over • Multiple dose • Healthy volunteers	Evaluate GI motility

[a] Pilot PK study with early formulation of neat-filled benzhydrocodone capsules

3.1.1 Bioequivalence Studies with Vicoprofen and Ultracet

Two studies were conducted to compare Apadaz to listed drugs. Study 105 was conducted to compare the relative bioavailability (BA) of Apadaz to Vicoprofen. Study 106 was conducted to compare the relative BA of Apadaz to Ultracet. The design of the studies was as follows:

- **Study 105** was an open-label, single-dose, randomized, 2-treatment, 2-period, 2-sequence crossover relative bioequivalence study in which 30 healthy adult subjects were enrolled,

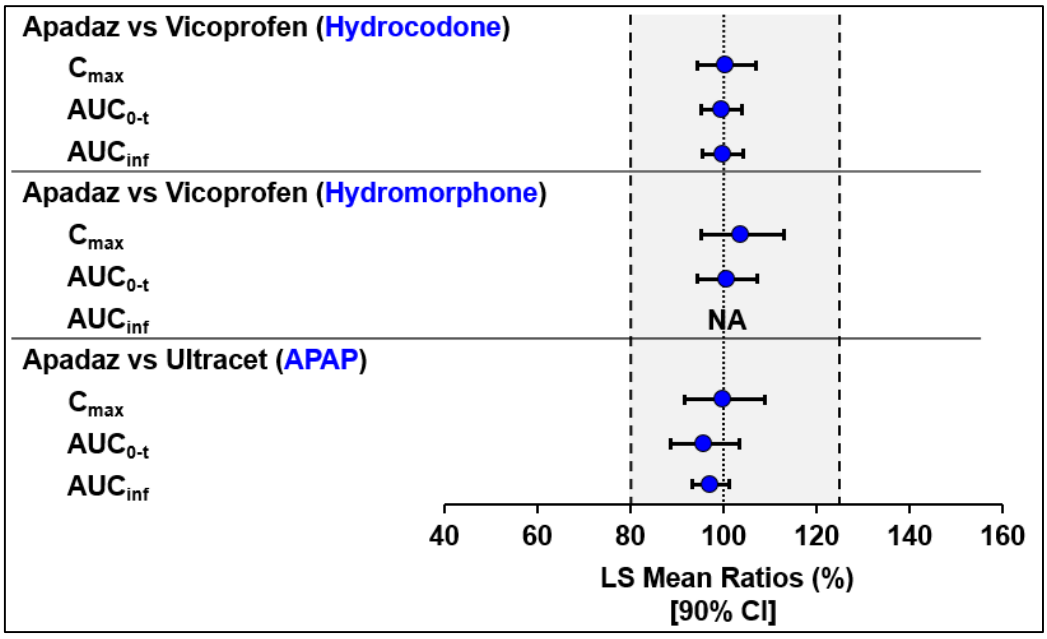
and 28 subjects completed the study. In a randomized fashion, subjects received a single-dose of Apadaz or Vicoprofen (7.5 mg hydrocodone/ 200 mg ibuprofen) on 2 separate occasions separated by a 7-day washout period. All study doses were administered after a standard overnight fast (approximately 10 hours).

- **Study 106** was an open-label, single-dose, randomized, 2-treatment, 2-period, 2-sequence crossover relative bioequivalence study in which 30 healthy adult subjects were enrolled, and 27 subjects completed the study. In a randomized fashion, subjects received a single dose of Apadaz or Ultracet tablet, 37.5 mg tramadol/325 mg APAP, on 2 separate occasions separated by a 7-day washout period. All study doses were administered after a standard overnight fast (approximately 10 hours).

Figure 14 presents results for hydrocodone and hydromorphone (the active metabolite of hydrocodone) when Apadaz was compared with Vicoprofen and results for APAP when Apadaz was compared with Ultracet. Taken together, the results of both studies demonstrated equivalence in exposure to hydrocodone, hydromorphone, and APAP as measured by C_{max}, AUC_{0-t}, and AUC_{inf} after oral administration of Apadaz and the relative reference product.

Note that the FDA definition of bioequivalence is that the 90% confidence intervals (CI) for the Least Squares (LS) Mean ratio of the C_{max}, AUC_{0-t}, and AUC_{inf} are within the range of 80% to 125% (shown by the gray shading in the figure below).

Figure 14: Summary of Bioequivalence Assessments in Study 105 and 106



Note: Gray shaded area reflects bioequivalence range of LS Mean Ratio of 80% to 125%.
NA = Lack of log-linear decay for many hydromorphone datasets resulted in insufficient calculable AUC_{inf} values. As a result, the 90% CI does not provide a reliable estimate for bioequivalence.

3.1.2 Bioequivalence Study with Norco

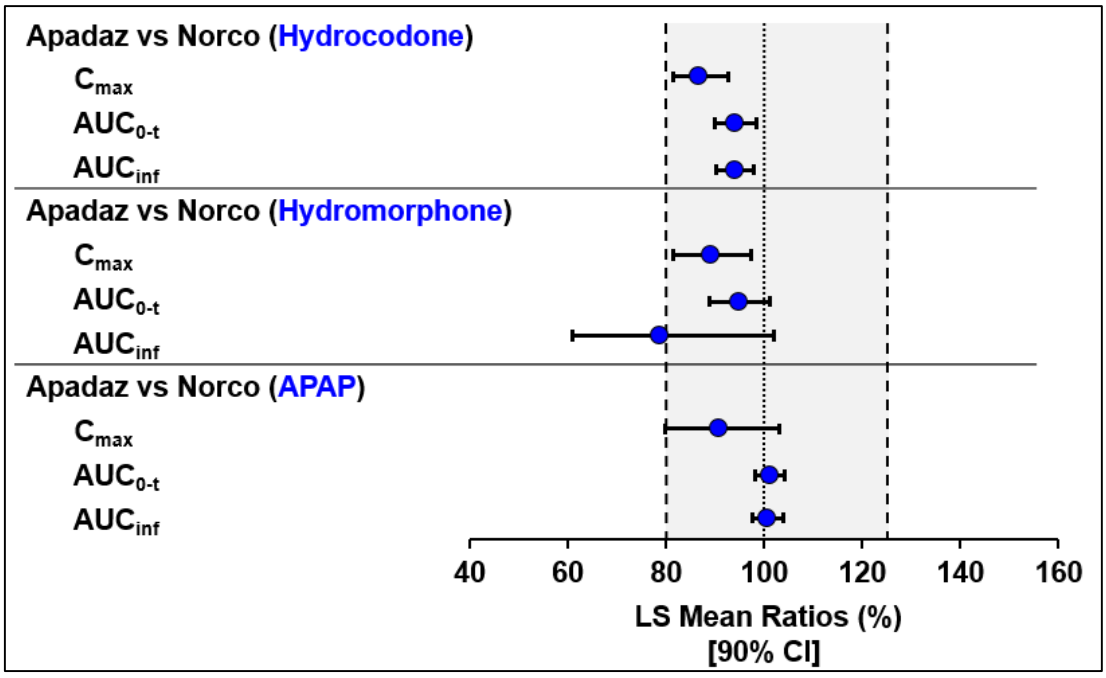
Study 102 compared the rate and extent of absorption of hydrocodone, hydromorphone, and APAP from a single dose of Apadaz relative to a single dose of Norco tablet, 7.5 mg hydrocodone/325 mg APAP, in 24 healthy subjects when administered orally under fasted conditions.

Figure 15 provides an overview of the bioequivalence assessments in Study 102. Apadaz was bioequivalent to Norco on all PK parameters for hydrocodone.

For hydromorphone, geometric means for C_{max} and AUC_{0-t} were bioequivalent. AUC_{inf} could only be calculated for 14 subjects for Apadaz and 8 subjects for Norco due to the lack of a log-linear decay for many of the hydromorphone datasets, and only 4 subjects had a value for both treatments. Consequently, the geometric mean ratio and 90% CI for AUC_{inf} for hydromorphone, in this study, do not provide a reliable estimate for bioequivalence.

For APAP, geometric means for all PK parameters were similar between the two products. For C_{max}, the lower limit of the 90% CI was 79.8%, slightly under the 80% threshold. When taken together with the fact that C_{max} for APAP was bioequivalent in the assessment with Ultracet, as well, we conclude that this finding is unlikely to have a clinical impact on the safety or efficacy of Apadaz.

Figure 15: Summary of Bioequivalence Assessments in Study 102



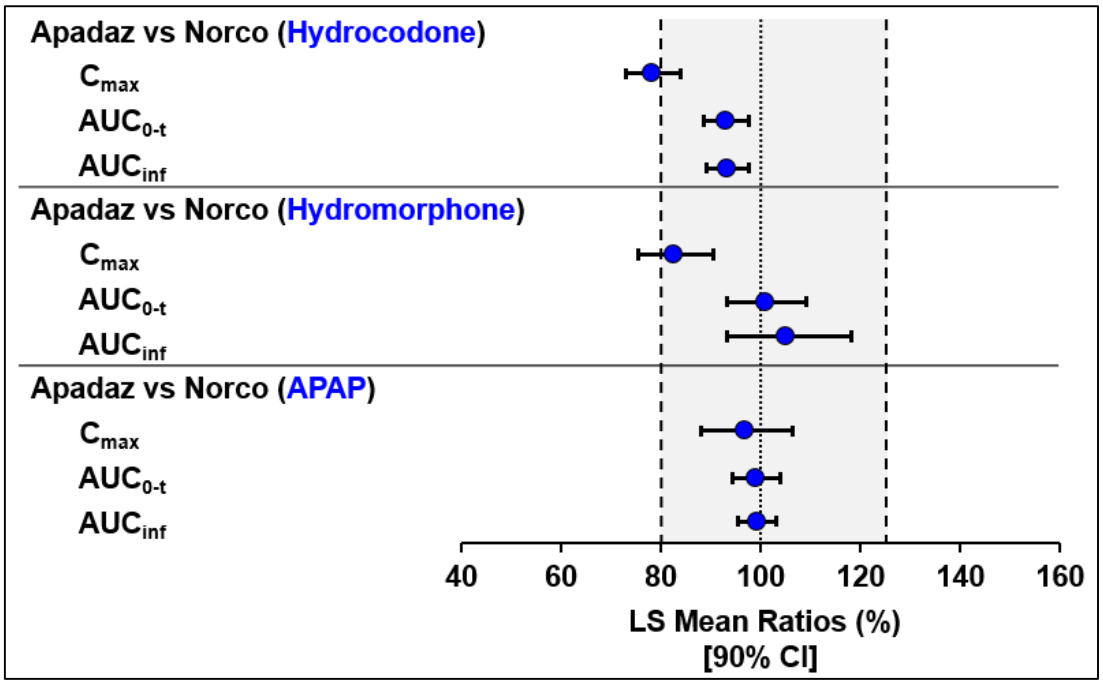
Note: Gray shaded area reflects bioequivalence range of LS Mean Ratio of 80% to 125%.

3.1.3 Effect of Food on PK of Apadaz

Study 104 was a single-dose study that characterized the effect of food on the oral bioavailability and PK of Apadaz (6.67 mg/325 mg tablet) in 38 healthy subjects. Apadaz was dosed in fasted and fed (FDA standard high-fat, high-calorie breakfast) conditions. Norco was dosed in the fed condition as a comparator. (Note: Norco is dosed without regard to food.)

Dosing Apadaz and Norco in the fed state led to comparable median times to maximum exposure (T_{max}) for hydrocodone (2.5 and 1.9 hours, respectively) with identical T_{max} ranges for all individuals that were contained within the minimum recommended dosing interval of 4 hours (0.5 to 4 hours for both products). While the data demonstrated a small decrease in the exposure rate (LSM ratio of C_{max} = 78.4%), the overall exposure to hydrocodone (AUC_{last} and AUC_{inf}) was similar after oral administration of a single dose of Apadaz compared with Norco when both were administered with food (Figure 16). Additionally, there was no difference in APAP exposure for both fed treatments. Considering the similar overall exposure to hydrocodone with identical median T_{max} ranges and the lack of food effect observed for APAP with both treatments, the relatively small difference in peak and rate of hydrocodone exposure does not suggest any safety concerns or impact on efficacy when comparing Apadaz and Norco in the fed state.

Figure 16: Summary of Bioequivalence Assessments in Study 104 Comparing Apadaz to Norco in a Fed State

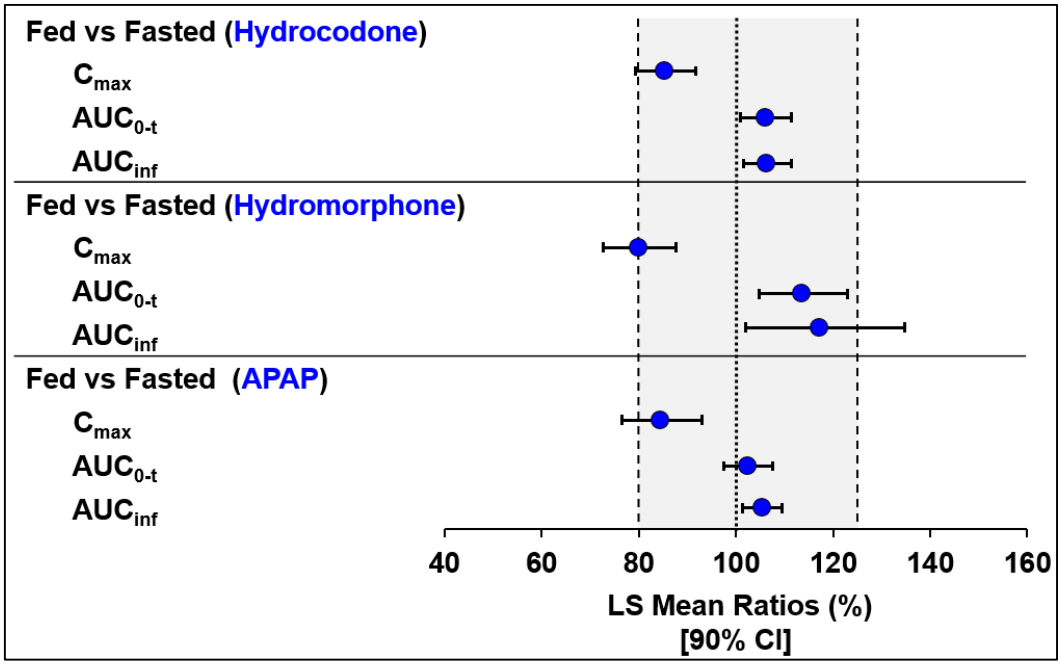


Note: Gray shaded area reflects bioequivalence range of LS Mean Ratio of 80% to 125%.

For Apadaz in the fed and fasted condition, the overall extent of exposure (AUC_{last} and AUC_{inf}) to hydrocodone and APAP were equivalent. While peak exposure (C_{max}) was somewhat lower for Apadaz dosed in the fed state compared to the fasted state (LSM ratio = 85.3%).

Overall, these data support the conclusion that Apadaz may be administered without regard to food.

Figure 17: Summary of Bioequivalence Assessments in Study 104 Comparing Apadaz in Fed versus Fasted States



Note: Gray shaded area reflects bioequivalence range of LS Mean Ratio of 80% to 125%.

3.1.4 Single- and Multi-Dose Study with Apadaz

Study 103 was an open-label, single-period, single- and multiple-dose, naltrexone-blocked study in which 26 healthy adult subjects were enrolled; 24 subjects completed the study. After an overnight fast (10 hours), subjects received a single dose (Dose 1, Day 1) of Apadaz (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 Apadaz tablets (Dose 2 through Dose 14) every 4 hours for a total of 12 doses over a 24 hour period.

Under multiple-dose administration of Apadaz, hydrocodone concentrations reached steady-state at approximately 48 hours and APAP concentrations reached steady state between 48 and 60 hours, which is consistent with the half-life of the two drugs. The calculated hydrocodone mean C_{max} and exposure were consistent with the predicted accumulation of plasma hydrocodone at steady-state, while mean C_{max} and exposure values were slightly lower than the predicted accumulation of APAP. There was no measurable systemic exposure to the prodrug, benzhydrocodone, at any time during the study, even after administration of the maximum daily dose of 2 tablets taken every 4 hours.

Overall, the pharmacokinetics of hydrocodone and APAP were linear and predictable after administration of single and multiple doses of Apadaz.

3.1.5 Gastrointestinal Motility Study

Study S01 was a randomized, double-blind crossover study to assess the GI effects of administration of an Apadaz tablet (6.67 mg/325 mg) compared to a Norco tablet (7.5 mg/325 mg) among healthy volunteers in which 50 subjects were enrolled and 41 completed the study. Several key points were demonstrated:

- There was no difference in the GI transit times between the two drugs.
- Benzhydrocodone was rapidly converted to hydrocodone before any systemic exposure and before the prodrug reached μ-opioid receptors in the enteric nervous system of the intestinal tract. This suggests that any exposure to benzhydrocodone is limited to the GI tract for a very short time after oral administration.
- The incidence of gastrointestinal AEs was similar between Apadaz and Norco.
- The most frequently reported AEs (i.e., somnolence, nausea, constipation, and vomiting) were consistent with the known safety profile of hydrocodone, and the vast majority of the AEs were mild or moderate in severity.

Based on the points above, it was concluded that Apadaz poses no additional GI safety risk compared with Norco when administered orally.

4 OVERVIEW OF ABUSE DETERRENT EVALUATION

Summary

- The abuse-deterrent evaluation of Apadaz was conducted in accordance with FDA's Final Guidance on Evaluation and Labeling of Abuse-Deterrent Opioids.
- Category 1 (Laboratory Manipulation and Extraction)
  - As a prodrug, the release properties of Apadaz, an IR formulation, are not impacted by physical manipulations such as crushing or grinding.
  - More than 90% of all analyzed extraction samples for Apadaz were BLQ (< 5%) for hydrocodone. All of the common ingestible solvents extracted significant amounts of hydrocodone from Norco, but none were able to extract any hydrocodone from Apadaz at any time point through 24 hours.
  - Hydrolysis of benzhydrocodone to hydrocodone only occurred under harsh conditions with heat over an extended period of time, and would require additional steps to obtain abusable hydrocodone.
  - Injection of mock IV formulations prepared from Apadaz tablet extracts into human plasma and whole blood did not show any evidence of benzhydrocodone precipitating.
  - Benzhydrocodone cannot be smoked in any form (i.e., salt, free base, tablet formulation).
- Category 2 (Pharmacokinetics [PK])
  - Overall hydrocodone exposures were similar for Apadaz and Norco at supratherapeutic oral doses. Early exposure to hydrocodone was slightly lower with Apadaz at the 8- and 12-tablet doses.
  - IN Apadaz did not result in a more rapid onset of hydrocodone exposure than oral dosing, with an overall similar PK profile to both Apadaz and Norco taken orally. IN Apadaz had significantly lower C_{max} than IN Norco.
  - IN benzhydrocodone was associated with a significantly lower (36%) hydrocodone C_{max} compared to IN HB, with a shorter median T_{max} (0.5 hour vs. 1.75 hours).
- Category 3 (Human Abuse Potential [HAP])
  - Results do not support a lower oral abuse potential for Apadaz than Norco.
  - Abuse quotient (AQ) comparisons suggested lower abuse potential for insufflated Apadaz and benzhydrocodone compared to Norco and HB, respectively.
  - Drug Liking E_{max} was similar for IN Apadaz and IN Norco, though Drug Liking through peak effect (2 hours) was significantly lower for Apadaz.
  - Subjects reported that insufflating Apadaz or benzhydrocodone was not as easy as insufflating Norco or HB, respectively, based on adverse nasal effects and Ease of Insufflation scores.

4.1 Category 1: Tampering

In April 2015, the FDA released a final guidance on the assessment of abuse-deterrent opioids and included recommended methodology for in vitro testing that is required in the assessment of abuse-deterrent properties (e.g., mechanical manipulation, extractability, syringeability, and solubility) (FDA, 2015). However, standardized methods for evaluating and reporting potential product manipulation techniques have not yet been established and may not provide guidance on methodology related to prodrugs (Goliber, 2005; Katz, 2007; Cone, 2013).

Three laboratory-based studies were conducted to evaluate the amount of hydrocodone that could be extracted using various solvents and conditions using both Apadaz and Norco tablets.

4.1.1 Extraction and Hydrolysis

The goal of extraction and hydrolysis studies was to determine the amount of hydrocodone that could be released from benzhydrocodone through chemical hydrolysis relative to the amount of hydrocodone that could be readily extracted from Norco tablets. Apadaz tablets (intact or crushed) were evaluated for the possibility and potential for individuals to extract benzhydrocodone from the formulation and then convert extracted benzhydrocodone to hydrocodone. Norco tablets (intact or crushed) were evaluated under the same conditions for the potential to extract hydrocodone.

A combination of extraction and hydrolysis procedures were used to assess the feasibility and efficiency of such tampering methods. Both intact and crushed Apadaz and Norco tablets were extracted using various conditions. These extractions examined the relative amount of either benzhydrocodone or hydrocodone that could be removed from the formulated tablets. Once appropriate extractions were identified, these conditions were used to determine to what extent benzhydrocodone could be hydrolyzed to hydrocodone from whole and crushed tablets.

4.1.1.1 Extraction with Various Solvents

A total of 26 solvents were tested on crushed and intact Apadaz and Norco tablets. Five solvents were common ingestible solvents; 14 were advanced non-ingestible solvents, and 7 were advanced buffers at various pH levels. Up to 6 time points at up to 24 hours were assessed for a total of 306 samples for each tablet formulation, with each condition evaluated in triplicate.

Extraction of Apadaz tablets mostly yielded no active hydrocodone (Table 6). Of the 26 solvents tested, 23 solvents extracted no hydrocodone from the Apadaz tablets and 22 solvents extracted hydrocodone from Norco. Of the 3 solvents that released a limited amount of hydrocodone from Apadaz tablets, Solvent X released 10.6% and Solvent Y released 8.8% of hydrocodone from crushed Apadaz tablets at 24 hours (1440 minutes). All prior time points were below the limit of quantification (BLQ). Solvent Z released from 6.4% (at 15 minutes) to 37.1% (at 6 hours) of hydrocodone from crushed Apadaz tablets.

Overall, crushed and intact Apadaz tablets produced similar results for all analytes. Generally, more hydrocodone was extracted from crushed Norco tablets compared to intact. Hydrocodone was efficiently extracted from Norco by all aqueous solvents (>72%). Further, the three solvents

that released at least some hydrocodone from Apadaz also extracted large amounts of APAP (>67%).

Table 8: Maximum Amounts of Hydrocodone Extracted from Either Crushed or Intact Apadaz and Norco Tablets with 26 Solvents

Solvent	Apadaz (intact or crushed)		Norco (intact or crushed)	
	T_{max} (min)	Hydrocodone (%)	T_{max} (min)	Hydrocodone (%)
Common Ingestible Solvents				
A	NA	0	180	86.9
B	NA	0	1440	92.8
C	NA	0	360	63.2
D	NA	0	180	92.1
E	NA	0	60	93.8
Advanced Non-Ingestible Solvents				
F	NA	0	1440	86.8
G	NA	0	60	96.7
H	NA	0	60	62.0
I	NA	0	5	93.2
J	NA	0	360	82.9
K	NA	0	180	63.0
L	NA	0	180	54.5
M	NA	0	180	37.6
N	NA	0	180	11.7
O	NA	0	180	33.0
P	NA	0	NA	0
Q	NA	0	NA	0
R	NA	0	NA	0
S	NA	0	NA	0
Advanced Buffers				
T	NA	0	45	99.6
U	NA	0	45	95.0
V	NA	0	180	95.4
W	NA	0	1440	93.9
X	1440	10.6	360	90.2
Y	1440	8.8	360	94.1
Z	360	37.1	15	72.2

NA (not applicable): concentrations at all time points were below the limit of quantification (< 5%)
Values that were below the limit of quantification (< 5%) were set to 0.

4.1.1.2 Extraction at Various Temperatures and Continued Agitation

The effects of various temperatures and continued agitation were evaluated on the extraction potential and solubility of benzhydrocodone, hydrocodone, and APAP from Apadaz and Norco tablets. A total of 20 solvents were tested on crushed and intact Apadaz and Norco tablets at various temperatures (i.e., Temperature A, Temperature B, and Temperature E) with continuous agitation (Table 9). Under at least one condition, all 20 solvents extracted hydrocodone from Norco. Similar total amounts (% label claim) of APAP were extracted from both tablet formulations.

Solvent A, a common ingestible solvent, extracted >80% of active hydrocodone from crushed Norco tablets after 5 minutes at Temperature B. The maximum amount of hydrocodone extracted from Norco was similar at all temperatures (81.5%-86.9%) regardless whether tablets were crushed or intact. Solvent A, however, did not release any hydrocodone from Apadaz at any temperature at any time point.

More than 90% of all samples were BLQ (<5%) for hydrocodone from Apadaz compared to only 8% for hydrocodone from Norco. Only four solvents released any hydrocodone from Apadaz while all 20 solvents extracted hydrocodone from Norco. Compared to the previous extraction results (Table 8) performed at Temperature B, similar amounts of hydrocodone were released from Apadaz with Solvents X, Y, and Z at Temperature B under continuous agitation, indicating that agitation had little effect on the amount of hydrocodone released from Apadaz or on the time to maximum extraction.

The maximum amount of hydrocodone released from crushed Apadaz tablets with Solvent Z was comparable at all temperatures but Temperature E decreased T_{max}, which was 24 hours, 6 hours and 0.5 hours for Temperatures A, B, and E, respectively. Temperature E also increased the amount of hydrocodone released from Apadaz with Solvents X and Y, both of which released up to about 60% at 4 and 6 hours, respectively. At Temperature B, solvents X and Y released only 10-15% of hydrocodone from Apadaz at 24 hours but at no prior time point. Solvent W released about 61% of hydrocodone from Apadaz only at 24 hours at Temperature E, but none at any time point at either Temperatures A or B.

Although Solvents W, X, Y and Z released ≥46% of hydrocodone from Apadaz under some conditions, the same conditions also seemed to decompose hydrocodone. For example, no sample treated with Solvent Z contained any benzhydrocodone even though the maximum amount of hydrocodone released from Apadaz was always ≤46% of the total label claim. Similar results were seen with the other three solvents where the amount of benzhydrocodone extracted typically remained <10% and often BLQ (<5%). Hydrocodone decomposition was also indicated by notable changes in the color of the solutions. Colors included shades of orange, brown, purple and black, typically adopting darker shades with harsher solvents and longer extraction times. The four solvents that released at least some hydrocodone from Apadaz also extracted large amounts of APAP (about 80% and higher). The three solvents that released >50% hydrocodone (only at Temperature E) from Apadaz also extracted >95% of APAP under the same conditions. No condition released hydrocodone from Apadaz with a hydrocodone:APAP ratio greater than 0.64:1.

Hydrocodone was efficiently dissolved from Norco by all aqueous solvents (two-thirds of the conditions tested extracted >90%). The same solvents were also efficient in extracting APAP (>65%). While hydrocodone was effectively extracted by aqueous solvents from Norco at all temperatures, APAP solubility dropped significantly at Temperature A (typically <50% of the solubility at Temperature E).

Importantly, none of the resulting solutions that were able to release hydrocodone from Apadaz were in an abusable form. All would require additional back-extraction steps prior to being able to obtain abusable hydrocodone.

Table 9: Maximum Amounts of Hydrocodone Extracted from Apadaz and Norco with 20 Solvents under Various Temperature Conditions and Continuous Agitation

Solvent	Apadaz		Norco	
	T_{max} (min.)	Hydrocodone (%)	T_{max} (min.)	Hydrocodone (%)
Common Ingestible Solvents				
A	NA	0	45	86.9
B	NA	0	60	93.9
C	NA	0	1440	76.4
D	NA	0	45	90.8
E	NA	0	30	96.6
Advanced Non-Ingestible Solvents				
F	NA	0	15	90.5
G	NA	0	180	96.9
J	NA	0	1440	84.5
K	NA	0	15	63.3
L	NA	0	1440	71.3
N	NA	0	1440	80.3
O	NA	0	180	72.9
R	NA	0	1440	49.1
Advanced Buffers				
T	NA	0	60	98.3
U	NA	0	45	97.7
V	NA	0	45	94.7
W	1440	60.9	1440	95.3
X	240	59.6	360	92.4
Y	360	62.7	1440	93.5
Z	1440	46.0	240	92.2

[a] NA (not applicable): concentrations at all time points were below the limit of quantification (< 5%)
[b] Values that were below the limit of quantification (< 5%) were set to 0.

4.1.1.3 Hydrolysis of Benzhydrocodone

The covalent bond between benzoic acid and hydrocodone has to be broken to release hydrocodone from benzhydrocodone. Since only a few solvents at Temperature E were able to release any hydrocodone, the hydrolysis experiments focused on the evaluation of strong acids and weak to strong bases at Temperatures B and E. No comparator was used in this hydrolysis study since the extra step of chemically cleaving the API is only applicable to a prodrug and is not necessary for chemically unmodified hydrocodone as found in Norco.

An abuser who intends to obtain hydrocodone from Apadaz may either attempt to first extract the prodrug from the tablet formulation or perform hydrolytic experiments directly with crushed or intact tablets. To simulate each method, three sets of Apadaz tablets were evaluated under hydrolytic conditions. One set of tablets (the equivalent of three tablets per sample) was crushed in a mortar and pestle before the hydrolysis evaluation. The second set of tablets (three tablets per sample) was used intact and unaltered. The third set of tablets was first subjected to extraction methods that were selected based on three criteria: (1) benzhydrocodone extraction efficiency; (2) benzhydrocodone:APAP ratio; (3) sufficient variation between all selected extraction procedures.

Twenty (20) and 24 combinations of hydrolysis solvent combinations were tested with crushed/intact tablets and with extracted samples, respectively. A total 484 samples were evaluated, each in triplicate. Results from the hydrolysis experiments for Apadaz intact or crushed tablets as well as extracted samples are presented in Table 10.

More than 50% of all samples tested were BLQ (<5%) for hydrocodone and <20% of all samples resulted in >50% of hydrocodone released from Apadaz. The highest release of hydrocodone (98.5%) was observed with HS10 for crushed tablets at Temperature E for 4 hours. Only three hydrolysis solvents released >50% hydrocodone before the 6 hour time point: HS10, HS12, and HS13. While Temperature E improved hydrolysis with some hydrolysis solvents, it reduced the effectiveness of other hydrolysis solvents. These results suggest that Temperature E decomposed at least a portion of hydrocodone, which was consistent with data collected during extractions at various temperatures and with continuous agitation.

Table 10: Maximum Amounts of Hydrocodone Released from Apadaz Crushed or Intact Tablets with Each Hydrolysis Solvent at Temperatures B and E

	Temperature B				Temperature E			
	Crushed		Intact		Crushed		Intact	
Hydrolysis Solvent (HS)	Time (min.)	HC (%)	Time (min.)	HC (%)	Time (min.)	HC (%)	Time (min.)	HC (%)
Tablet Hydrolysis								
HS1	NA	0	NA	0	NA	0	NA	0
HS2	NA	0	NA	0	NA	0	NA	0
HS3	NA	0	NA	0	NA	0	NA	0
HS4	NA	0	NA	0	NA	0	NA	0

	Temperature B				Temperature E			
	Crushed		Intact		Crushed		Intact	
Hydrolysis Solvent (HS)	Time (min.)	HC (%)	Time (min.)	HC (%)	Time (min.)	HC (%)	Time (min.)	HC (%)
HS5	NA	0	NA	0	NA	0	NA	0
HS6	NA	0	NA	0	360	7.3	360	7.3
HS7	NA	0	NA	0	360	21.2	360	20.8
HS8	1440	9.9	1440	9.1	360	55.9	360	56.8
HS9	NA	0	NA	0	360	62.6	360	62.4
HS10	1440	13.6	1440	14.2	240	98.5	240	94.4
HS11	NA	0	NA	0	360	58.9	360	60.7
HS12	1440	13.1	1440	12.6	240	94.2	240	90.2
HS13	1440	46.9	1440	47.5	30	64.2	30	65.6
HS14	360	83.8	1440	83.7	60	38.4	240	21.1
HS15	360	85.9	1440	81.1	30	49	60	32.9
HS16	360	86	360	76.4	NA	ND	NA	ND
HS17	NA	0	15	36.5	60	23.4	360	17.9
HS18	1440	16.3	1440	14.6	60	11.4	360	9.2
HS19	NA	0	NA	0	NA	ND	NA	ND
Extract Hydrolysis								
Solvent A/HS8	NA	ND	NA	ND	360	58.3	NA	ND
Solvent A/HS10	NA	ND	NA	ND	240	84.8	NA	ND
Solvent A/HS12	NA	ND	NA	ND	360	84.5	NA	ND
Solvent A/HS15	360	79.2	NA	ND	NA	ND	NA	ND
Solvent A/HS18	1440	15.5	NA	ND	NA	ND	NA	ND
Solvent A/HS19	15	8.1	NA	ND	NA	ND	NA	ND
Solvent E/HS8	NA	ND	NA	ND	NA	ND	360	57.7
Solvent E/HS10	NA	ND	NA	ND	NA	ND	240	83.5
Solvent E/HS12	NA	ND	NA	ND	NA	ND	240	78.2
Solvent E/HS15	NA	ND	60	83.8	NA	ND	NA	ND
Solvent E/HS18	NA	ND	NA	0	NA	ND	NA	ND
Solvent E/HS19	NA	ND	15	47.4	NA	ND	NA	ND
Solvent C/HS8	NA	ND	NA	ND	360	35	NA	ND
Solvent C/HS10	NA	ND	NA	ND	240	94.3	NA	ND
Solvent C/HS12	NA	ND	NA	ND	240	95	NA	ND
Solvent C/HS15	360	94.9	NA	ND	NA	ND	NA	ND
Solvent C/HS18	1440	74	NA	ND	NA	ND	NA	ND
Solvent C/HS19	1440	0	NA	ND	NA	ND	NA	ND
Solvent L/HS8	NA	ND	NA	ND	240	71.1	NA	ND
Solvent L/HS10	NA	ND	NA	ND	360	12.5	NA	ND
Solvent L/HS12	NA	ND	NA	ND	360	74.4	NA	ND

	Temperature B				Temperature E			
	Crushed		Intact		Crushed		Intact	
Hydrolysis Solvent (HS)	Time (min.)	HC (%)	Time (min.)	HC (%)	Time (min.)	HC (%)	Time (min.)	HC (%)
Solvent L/HS15	1440	72.6	NA	ND	NA	ND	NA	ND
Solvent L/HS18	1440	9.5	NA	ND	NA	ND	NA	ND
Solvent L/HS19	1440	0	NA	ND	NA	ND	NA	ND

NA=not applicable; ND=no data (condition not tested)

Release of >90% of hydrocodone required a very strong hydrolysis solvent and Temperature E for at least 4 hours, with the exception of samples extracted with Solvent C. Extraction of crushed tablets with Solvent C, followed by treatment with HS15 at room temperature yielded 92.3% of hydrocodone at 15 minutes. However, the released hydrocodone was not isolated from the resulting hydrolysis mixture.

Hydrolysis was generally more effective after extraction with Solvent C compared to direct treatment of crushed and intact tablets. Less hydrocodone, however, was released when extractions with Solvent A and solvent E were treated with hydrolysis solvents compared to crushed and intact tablets. At Temperature B, hydrolysis with HS15 and HS19 was more effective after extraction with solvent E compared to direct treatment of tablets. Similarly, HS8 at Temperature E resulted in more hydrocodone after extraction with Solvent L compared to crushed and intact tablets.

All conditions took at least 30 minutes to maximum release of hydrocodone. The T_{max} for more than 75% of the conditions was 6 hours or longer, and 42% of all tested conditions took at least 24 hours to maximum release of hydrocodone.

4.1.2 Benzhydrocodone Solubility and IV Injection

An in vitro study was designed and conducted to understand the potential risks associated with the injection of Norco and Apadaz. Conditions typically used to prepare a sample for injection, the injectability, and the resulting injected products were all examined.

The goals of this study were: to assess the solubility profiles of benzhydrocodone and HB in aqueous solutions of varying pH and salinity that bracket physiological conditions; to evaluate the feasibility of creating aqueous solutions from Apadaz tablets (i.e., "extracts") suitable for IV abuse compared with Norco tablets; and to evaluate the potential for precipitation of benzhydrocodone or hydrocodone after simulated injections of extracts from both Apadaz and Norco tablets into human plasma and blood.

Because any extraction from Apadaz tablets using aqueous solutions suitable for IV abuse will yield only inactive benzhydrocodone, the physicochemical properties of benzhydrocodone may play a role in its 'injectability'. Therefore, in addition to the assessment of 'extractability' (defined herein as the efficiency of extracting benzhydrocodone, hydrocodone [if applicable], or APAP from the tablet formulation) and 'syringeability' (defined as the concentration that can be achieved in an extracted formulation and its ability to pass through various needle gauges),

Apadaz tablet extracts suitable for IV abuse was also evaluated for their effects during a simulated 'injection' into human plasma and whole blood. Visual observations, photographs, and analytical characterization of the particulates and appearance of the plasma and blood were reported.

4.1.2.1 Solubility Profiles of Benzhydrocodone and Hydrocodone Bitartrate

The solubility of benzhydrocodone and HB was tested at Temperatures B and C at various buffered pH and salt concentrations. Buffers were prepared at the required pH and then salinity was adjusted by adding NaCl. At Salinity C, D, and E and pH I, benzhydrocodone was practically insoluble. All HC concentrations in benzhydrocodone samples were BLQ (< 5%). The solubility data for benzhydrocodone is summarized in Table 11.

Table 11: Solubility of Benzhydrocodone at Various pH and Salinities

pH	Benzhydrocodone Free Base Concentration (mg/mL)				
	Salinity A	Salinity B	Salinity C	Salinity D	Salinity E
A	16.659	6.718	4.028	2.646	2.018
B	20.462	8.141	4.417	2.720	2.096
C	15.489	8.604	3.800	2.703	2.011
D	14.550	10.242	3.538	2.339	1.714
E	12.497	5.623	3.454	2.320	1.685
F	20.632	11.234	0.530	2.273	1.657
G	5.271	3.607	1.820	0.770	1.319
H	10.494	ND	ND	ND	ND
I	7.544	3.291	BLQ	BLQ	BLQ

ND = Benzhydrocodone Not Detected
BLQ = Benzhydrocodone below the limit of quantitation (<5% of label claim)

4.1.2.2 Extraction and Preparation of Mock IV Formulations

The feasibility of creating aqueous solutions from Apadaz tablets (i.e., 'extracts') suitable for IV abuse was evaluated and compared with Norco tablets. A total of 160 combinations of solvents, crushed/intact tablets and temperatures were each tested for Apadaz and Norco. Three different solvents were evaluated, either unadjusted or at various pH levels, for a total of 12 solvent combinations. For each solvent, Table 12 and Table 13 show the maximum percentage of benzhydrocodone and hydrocodone extracted from Apadaz and Norco, respectively.

Table 12: Highest Percent of Label Claim of Benzhydrocodone Extracted from Apadaz Tablets with Each Solvent and Associated Test Condition

Solvent & pH Adjustment	Crushed/ Intact	Tablet:Solvent Volume Ratio	Temperature	Highest % of Benzhydrocodone Extracted from Apadaz
IV Solvent CB	intact	Ratio AA	Temperature CC	71.6
IV Solvent BB	intact	Ratio AA	Temperature AA	69.8
IV Solvent AB	crushed	Ratio AA	Temperature AA	66.2
IV Solvent CA	crushed	Ratio AA	Temperature CC	64.6
IV Solvent CC	crushed	Ratio AA	Temperature AA	59.4
IV Solvent BA	intact	Ratio AA	Temperature CC	59.4
IV Solvent BC	crushed	Ratio AA	Temperature AA	58.2
IV Solvent AA	crushed	Ratio AA	Temperature AA	57.9
IV Solvent AC	crushed	Ratio AA	Temperature AA	54.9
IV Solvent CD	crushed	Ratio AA	Temperature CC	24.2
IV Solvent BD	crushed	Ratio AA	Temperature BB	16.5
IV Solvent AD	crushed	Ratio AA	Temperature BB	12.6

Table 13: Highest Percent of Label Claim of Hydrocodone Extracted from Norco Tablets with Each Solvent and Associated Test Condition

Solvent & pH Adjustment	Crushed/ Intact	Tablet:Solvent Volume Ratio	Temperature	Highest % of Hydrocodone Extracted from Norco
IV Solvent BD	crushed	Ratio BB	Temperature AA	78.9
IV Solvent BC	crushed	Ratio BB	Temperature AA	78.8
IV Solvent BB	intact	Ratio AA	Temperature CC	77.6
IV Solvent CD	crushed	Ratio AA	Temperature BB	75.1
IV Solvent CA	intact	Ratio AA	Temperature AA	74.2
IV Solvent BA	crushed	Ratio AA	Temperature CC	73.8
IV Solvent CC	crushed	Ratio AA	Temperature AA	73.5
IV Solvent CB	intact	Ratio AA	Temperature AA	73.3
IV Solvent AC	crushed	Ratio AA	Temperature BB	72
IV Solvent AD	crushed	Ratio AA	Temperature BB	71.4
IV Solvent AB	crushed	Ratio AA	Temperature BB	70
IV Solvent AA	crushed	Ratio AA	Temperature BB	67.1

In addition, the Common Extraction Technique demonstrated that >80% of APAP can be efficiently removed from Norco tablets while retaining about 25% to 75% of the hydrocodone dose. Only small amounts of inactive benzhydrocodone were extracted from Apadaz with this same method ranging from 2.4 mg to 5.0 mg (Table 14). Changing the Tablet:Volume ratio from AA to BB only resulted in an approximately 2-fold increase in total amount of benzhydrocodone recovered. No hydrocodone was present in any extractions of Apadaz with this extraction method. The amount of hydrocodone extracted from Norco with the Common Extraction Technique ranged from 5.1 mg to 9.3 mg. Similarly, the amount of hydrocodone recovered did not change proportionally when the Tablet:Volume ratio was adjusted. The amount of APAP extracted with the Common Extraction Method from Apadaz and Norco were comparable at Ratio AA (55.9 mg to 63.7 mg).

Table 14: Amounts of Benzhydrocodone, Hydrocodone, and APAP Extracted from Apadaz and Norco Tablets using Common Extraction Technique

Tablet:Water Volume Ratio	Crushed/ Intact	Extracted from Apadaz			Extracted from Norco	
		Benzhydrocodone (mg)	HC (mg)	APAP (mg)	HC (mg)	APAP (mg)
Ratio AA	crushed	2.4	BLQ	62.1	5.1	55.9
	intact	2.6	BLQ	63.7	5.3	57.9
Ratio BB	crushed	5.0	BLQ	BLQ	9.3	BLQ
	intact	4.5	BLQ	BLQ	7.8	BLQ

BLQ = below level of quantitation (< 5% of % label claim)

4.1.2.3 Syringeability

For this assessment, the three most efficient (i.e., highest benzhydrocodone and highest hydrocodone concentrations) and three least efficient (i.e., lowest benzhydrocodone and lowest hydrocodone concentrations) IV formulations obtained each from Apadaz tablets and Norco tablets, as outlined above were used.

The extracts (1 mL) were filled into 3-mL syringes fitted with a 0.5 inch 30G needle or a 0.62 inch 25G needle. This size range brackets the needle gauge most commonly discussed/used for IV use among drug abuse forums (e.g., drugs-forum.com, harmreduction.org). Samples were prepared in triplicate for each condition.

Visual observations and a semi-quantitative measure of the force required to simulate an injection (i.e., push the extract solutions through each needle) for each extract were recorded. Each 1 mL aliquot of solution was "injected" and the force measured with a QCS, Inc. model M5-10 compressibility/force gauge, in conjunction with an ES30 test stand and G1089 syringe fixture, connected to a laptop computer. The force gauge had a NIST-traceable factory calibration and was used as supplied without any additional qualification. The laptop was supplied by ABC Labs IT department and used the software from QCS, Inc. to acquire the data needed for the determination of "break-free" force and "glide force". The force needed to inject water from the same needle/syringe combinations was measured in triplicate as well.

The "break-free" and "glide" forces were approximately 4-6 times higher with the 0.5 inch 30G needle than with the 0.62 inch 25G needle for both Apadaz and Norco. Extractions consisting of IV Solvent C* required the most force for both tablet types. All other extraction solutions from Norco required an injection force comparable to IV Solvent AA. The injection of nearly all Apadaz solutions required more force than IV Solvent AA. Overall, the syringe injection forces for Apadaz and Norco mock IV formulations were comparable. These results were expected since Apadaz tablets are not formulated with any gelling properties.

4.1.2.4 Precipitation Risk after IV Injection

Abusers seeking to inject opioid tablet formulations commonly prepare IV solutions by adding suitable extraction solvents to the tablet and filtering off the majority of unwanted byproducts such as excipients and APAP.

Preliminary in vitro testing showed that a highly concentrated solution of benzhydrocodone (6.7 mg/mL) in water became cloudy when added to samples of blood and plasma. KemPharm subsequently designed a series of GLP experiments with the to-be-marketed formulation of Apadaz to evaluate the precipitation potential of both Apadaz and Norco in human blood.

Identical preparations of the three most efficient (i.e., highest benzhydrocodone and highest hydrocodone concentrations) and three least efficient (i.e., lowest benzhydrocodone and lowest hydrocodone concentrations) IV formulations obtained each from Apadaz tablets and Norco tablets as determined for syringeability (see Section 4.1.2.3) were used to evaluate the potential for forming precipitate when injected into human plasma and blood.

To simulate an injection, the IV formulations (~1 mL total, at room temperature) were introduced, in 0.2 mL increments, into plasma samples (1 mL) held at Temperature C for visual observation until a 1:1 volume ratio had been reached. After each addition of a 0.2 mL formulation aliquot, the plasma sample was inverted to mix and all observations such as visual appearance (turbidity, cloudiness, visible particles, etc.) of the resulting mixture were recorded and documented with photographs. After the complete volume of the IV formulation was added to the plasma or blood, a sample was removed for microscopy.

Any particulates formed after "injection" of benzhydrocodone or hydrocodone into plasma or blood in the above experiments were captured by microscopy in the sub-visible/visible range. Three microscope fields at 20× magnification were photographed for each sample.

The results obtained in the extraction experiments (see Section 4.1.2.2) demonstrated that it is possible to prepare IV solutions from Apadaz with limited concentrations of inactive benzhydrocodone (up to about 3.8 mg/mL with no released hydrocodone). The same techniques extracted up to approximately 2.8 mg/mL of active hydrocodone from Norco. However, filtration of both Apadaz and Norco tablet extracts proved to be inefficient via the methods most commonly applied by abusers (i.e., through cotton ball or coffee filter) and resulted in hazy to cloudy solutions (likely undissolved excipients and APAP as both benzhydrocodone and hydrocodone were found to be soluble at those concentrations). Thus, IV abusers will have to make a conscious decision to inject a cloudy solution whether it is Apadaz or Norco.

The solubility of benzhydrocodone (2.3 mg/mL) at physiological pH and salinity was found to be similar to the highest concentration (3.8 mg/mL) of mock IV formulations that could be achieved by extracting for Apadaz tablets. Considering venous flow rates and venous capacities, the injected volume would almost instantly be mixed with a large enough blood volume, even if a tourniquet was applied, to make precipitation of benzhydrocodone highly unlikely (i.e., only about 1 mL of additional blood is needed to solubilize benzhydrocodone). As suggested by the solubility data, injections of these mock IV formulations into human plasma and whole blood did not produce any visible precipitate. Microscopic evaluation indicated the presence of solid particles in plasma, which were most likely residual excipients and APAP not removed in the filtration process as both benzhydrocodone and hydrocodone, are soluble under these test conditions.

4.1.2.5 Conclusion

The benzhydrocodone solutions evaluated in the preliminary in vitro experiments were determined to be not representative of actual IV preparations that abusers can obtain from the to-be-marketed Apadaz tablet formulation. It was ultimately demonstrated that: (1) even under optimal conditions only about half the concentration (3.8 mg/mL) of benzhydrocodone can be achieved by extracting Apadaz tablets when compared to the solutions injected in the preliminary tests (6.7 mg/mL), (2) the microscopic particles observed in plasma after injecting IV preparations of Apadaz and Norco tablets were most likely excipients and APAP, and (3) the solid particles were already in the IV preparations of both tablet formulations before injection due to the inefficiency of clandestine filtration methods and no any additional precipitate formed when the solutions were introduced into human blood.

Overall, Apadaz does not present any new or greater risk for injection than the currently marketed hydrocodone IR combination products, but may actually limit the potential for IV abuse due to the slow conversion of inactive benzhydrocodone to active hydrocodone in blood, as demonstrated in an in vitro study.

4.1.3 Apadaz Abuse Potential by Smoking

The design of the smoking simulation study was based on the Laboratory Manipulation and Extraction Studies (Category 1) described in the recent FDA Guidance Abuse-Deterrent Opioids – Evaluation and Labeling (April 2015) and comments received from FDA CSS in the Pre-NDA meeting minutes.

The goal of the study was to determine to what extent Apadaz, benzhydrocodone, benzhydrocodone free base, Norco, HB, and hydrocodone free base could be smoked. The feasibility and efficiency of smoking crushed Apadaz tablets, the need to extract benzhydrocodone from the tablets, and the need to freebase benzhydrocodone for possibly easier vaporization were investigated and directly compared with hydrocodone and Norco tablets.

As outlined in the FDA Guidance, vaporization temperature of salt and free base of both benzhydrocodone and hydrocodone were determined. Further, to assess the chemical stability of benzhydrocodone and hydrocodone under heat, the melting and decomposition temperatures of the salt and free base of benzhydrocodone and hydrocodone were determined. Since both

benzhydrocodone and hydrocodone are present as salts in their respective formulations, the ease of converting the salts to free base was also investigated. The smoking experiments were designed to mimic real world applicability. Smoking studies were conducted with the API, API free base, and final tablet formulations (crushed) of both benzhydrocodone and hydrocodone. Each sample was placed in an enclosed tube and heated with a Bunsen burner. The resulting vapors were collected and analyzed for benzhydrocodone and hydrocodone (and in the case of tablets, APAP). The temperature at which visible volatilization occurred was recorded for each sample. In addition, the appearance of the samples after smoking was recorded and photos taken to document the observations. The amount of benzhydrocodone, APAP, and hydrocodone detected in the "smoked" samples was quantified.

Appropriate temperature ranges for smoking experiments were determined by thermo-gravimetric analysis for the following six samples: salt and free base forms of benzhydrocodone and hydrocodone; as well as Apadaz and Norco tablets.

Overall, the results show that benzhydrocodone is not suitable for smoking in any form (i.e., salt, free base, tablet formulation). Small amounts of benzhydrocodone are vaporized when heated up to 500 °C but no benzhydrocodone broke down to hydrocodone at any temperature. Smoking of Norco appears to be plausible given that small amounts of hydrocodone were released.

4.2 Category 2: Pharmacokinetics

4.2.1 Oral Administration of Supratherapeutic Doses of Apadaz and Norco

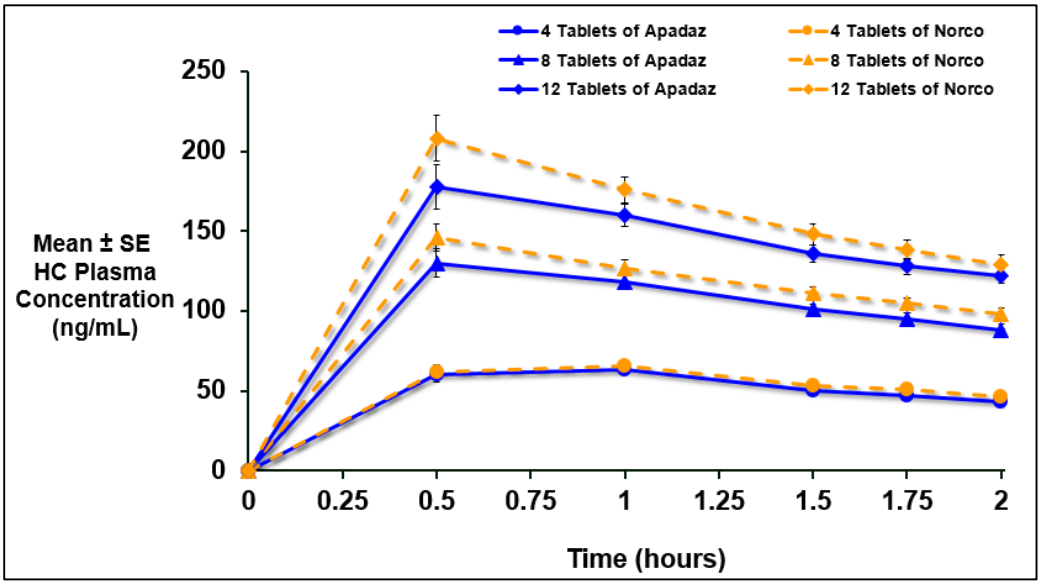
Study A01 was a randomized, double-blind, placebo-controlled, single-dose, 7-way crossover study of Apadaz administered orally to opioid-experienced nondependent subjects. The study included a Screening Phase, Qualification Phase, Treatment Phase, and Follow-up.

The Qualification Phase consisted of a Naloxone Challenge Test to confirm that subjects were not physically dependent on opioids and a Drug Discrimination Test to ensure that subjects were able to differentiate between the psychoactive effects of a single dose of Norco (45/1950 mg; 6 over-encapsulated tablets of 7.5 mg/325 mg HB/APAP) and placebo. Each dose was separated by at least 24 hours. Subjects who passed both the Naloxone Challenge Test and the Drug Discrimination Test proceeded into the Treatment Phase.

Treatments comprised placebo, 4-tablet, 8-tablet, and 12-tablet doses of Apadaz and Norco. Single oral doses were separated by a minimum 72-hour washout period. Serial blood samples were collected during the Treatment Phase for PK analysis before each dose and up to 24 hours after each dosing for the measurement of benzhydrocodone, hydrocodone, and hydromorphone in plasma.

At each of the respective dose levels, the overall exposure to hydrocodone was comparable for Apadaz and Norco at each respective dose level (Figure 18). Early exposure to hydrocodone was slightly lower for Apadaz than Norco at the 8- and 12-tablet dose levels. For T_{max} of hydrocodone, the *P* values from the Wilcoxon signed rank test were not statistically significant ($p > 0.6550$) for any dose comparison.

Figure 18: Mean Plasma Hydrocodone Concentration-time Profiles Following Single Oral Doses of Apadaz or Norco in Opioid-experienced, Non-dependent Recreational Users



4.2.2 Intranasal Administration of Apadaz and Norco

Study A02 was a single-center, randomized, double-blind, double-dummy, 2-part study to assess the abuse potential of IN crushed Apadaz tablets in opioid-experienced, non-dependent recreational users.

Study Part A consisted of a Screening Visit, a Qualification Phase, and a Dose Selection Phase. The Qualification Phase consisted of a Naloxone Challenge Test to confirm that subjects were not physically dependent on opioids and a Drug Discrimination Test to ensure that subjects were able to differentiate between the psychoactive effects of a single IN dose of 40 mg hydrocodone API versus weight-matched microcrystalline cellulose placebo powder. The Dose Selection Phase was designed to identify the maximum tolerated dose (MTD) of both Apadaz and Norco after IN administration.

Study Part B (Main Study) was a randomized, double-blind, double-dummy, active- and placebo-controlled, 5-period crossover study that assessed the abuse potential of crushed Apadaz and Norco tablets administered intranasally in non-dependent, recreational opioid users. The Main Study consisted of a Screening Visit, a Qualification Phase, a Treatment Phase, and a Follow-up Visit. The Qualification Phase consisted of a Naloxone Challenge Test to confirm that subjects were not physically dependent on opioids and a Drug Discrimination Test to ensure that subjects were able to differentiate between the psychoactive effects of a single IN dose of 2 crushed tablets of Norco versus placebo.

Each treatment included an IN dose and an intact (oral) dose of study drug in a double-blind, double-dummy manner. Placebo for IN administration consisted of microcrystalline cellulose powder and placebo for oral administration consisted of over-encapsulated lactose tablets. The 2-

tablet doses of Apadaz and Norco administered in Part B of the study were determined from the results obtained in Part A. Study assessments included serial PK blood draws for measurement of benzhydrocodone, hydrocodone, hydromorphone, and APAP during the Dose Selection Phase and Main Study Treatment Phase.

Part A

Due to the IN irritation observed at the highest dose tested (i.e., 4-tablet dose) for both Apadaz and Norco, with Apadaz producing more severe adverse nasal effects compared to Norco, as well as the nature of AEs related to nasal irritation, it was concluded that a 4-tablet dose administered intranasally would not have been well tolerated in the Main Study (Part B). The 3-tablet dose was not considered for evaluation in Part B because the active control (Norco) did not produce reliable significant Drug Liking effects at this dose level. Additionally, the 1-tablet dose did not provide reliable separation in Drug Liking from placebo for Norco or Apadaz.

Therefore, in accordance with the protocol, two-tablet IN doses of Apadaz (13.34/650 mg) and Norco (15/650 mg) were selected, resulting in a single equivalent dose of both drugs in the Main Study Treatment Phase (Part B).

Part B

Mean hydrocodone plasma concentrations following single 2-tablet oral and IN doses of Apadaz and Norco are shown in Figure 19. Following IN administration, C_{max} and partial systemic exposures ($AUC_{0-0.5}$, AUC_{0-1}, AUC_{0-2} and AUC_{0-4}) were statistically lower for Apadaz (P = 0.0053 or less) compared to an equimolar IN dose of Norco (Figure 20). C_{max} of hydrocodone was reduced by approximately 11% and early systemic hydrocodone exposures were reduced by approximately 50% for the comparison of IN crushed Apadaz versus IN crushed Norco.

Peak hydrocodone exposure (C_{max}) following an IN dose of crushed Apadaz was reduced by approximately 12.8% (P =0.0004) and 10.8% (P =0.0024) when compared to oral doses of Apadaz and Norco, respectively. Median time to peak exposure (T_{max}) to hydrocodone was 1.23 hours for all three treatments with comparable T_{max} ranges (IN Apadaz: 0.52 - 2.23 hours; oral Apadaz: 0.72 - 2.23 hours; oral Norco: 0.72 - 3.27 hours).

Figure 19: Hydrocodone Plasma Concentration-Time Profiles after IN and Oral Administration of Apadaz and Norco

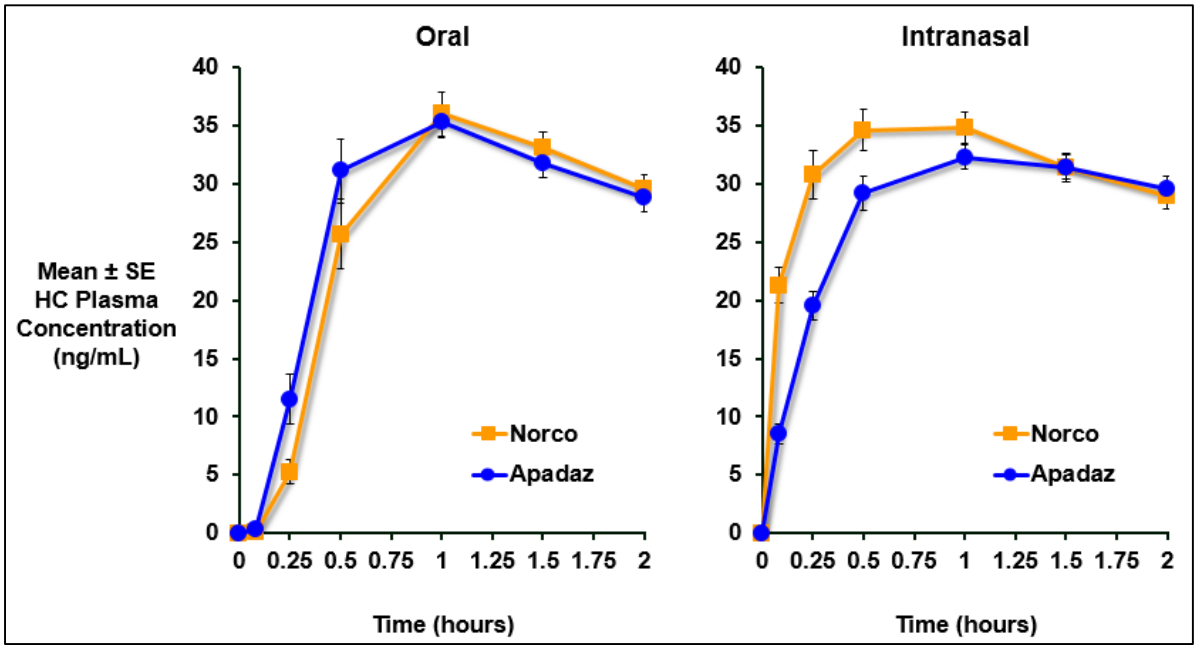
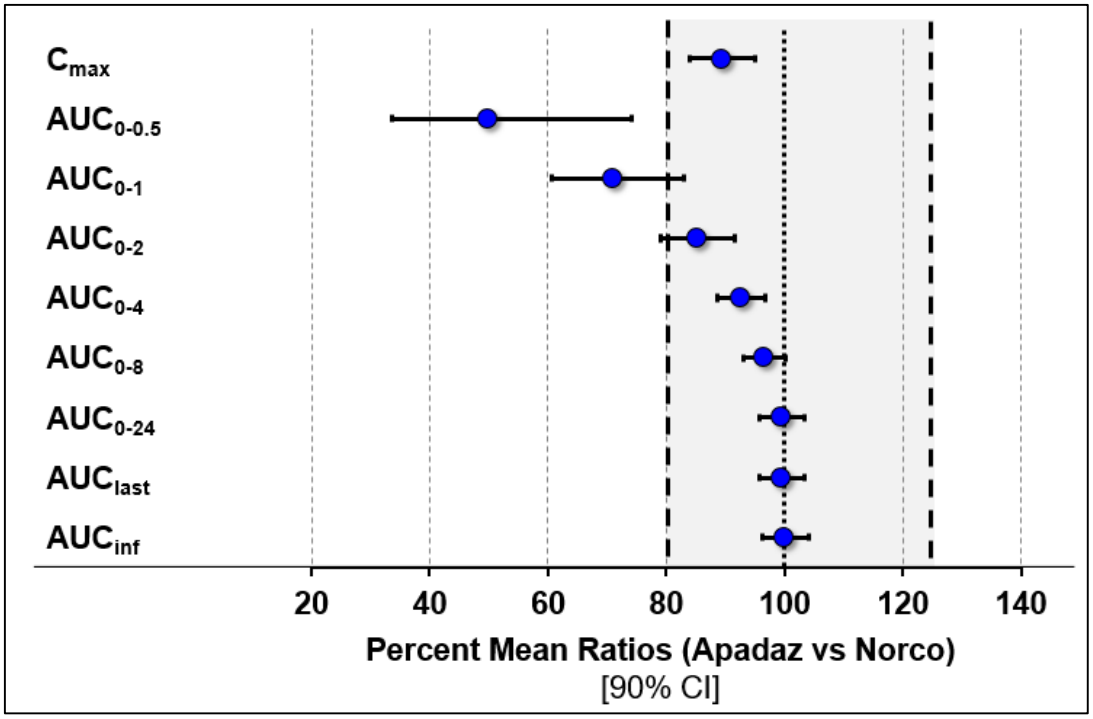


Figure 20: Forest Plot of Geometric Mean Ratios and 90% Confidence Intervals of the PK Parameters of Hydrocodone after Intranasal Administration of Apadaz versus Norco in Opioid-experienced, Non-dependent Recreational Users



Note: Gray shaded area reflects bioequivalence range of LS Mean Ratio of 80% to 125%.

While all subjects were able to insufflate the complete dose of 2 crushed tablets of Norco, only 84.6% of the subjects were able to do so with Apadaz. This is consistent with the data collected for Ease of Insufflation and Nasal Effects, which showed that crushed Apadaz tablets are more difficult to snort and cause more severe effects in the nasopharyngeal area.

4.2.3 Intranasal Administration of Benzhydrocodone and Hydrocodone Bitartrate

Study A03 was a randomized, double-blind, single-dose, 2-way crossover, single-center study to assess the relative PK of benzhydrocodone HCl (i.e., the Apadaz prodrug without a tablet formulation or APAP) compared to hydrocodone bitartrate (i.e., without a tablet formulation or APAP) after IN administration in recreational, nondependent drug users.

This study was designed to compare the PK of hydrocodone after IN administration of 13.34 mg benzhydrocodone compared to 15 mg HB. Drug liking, safety and tolerability were also assessed as secondary endpoints. Compared to IN administration of crushed opioid combination products, which include excipients and another active compound (e.g., APAP), insufflation of unformulated APIs was expected to minimize the amount of product swallowed and therefore, maximize the amount available for insufflation. The purpose of this study was to mimic a common real-world scenario in which abusers extract the opioid from the tablet formulation to maximize the drug effect and to reduce the volume of powder for snorting, minimize the amount of APAP ingested (to mitigate the risk of liver toxicity), and to decrease the amount of excipients with potentially unknown properties. It was expected that insufflation of benzhydrocodone without other formulation components would allow for a more robust characterization of the PK properties of benzhydrocodone after IN administration, especially in the situation in which benzhydrocodone is extracted from the Apadaz formulation.

The first post-dose quantifiable concentrations for hydrocodone were observed at the 5-minute post-dose sample time for both benzhydrocodone and HB. Mean peak plasma hydrocodone concentrations from benzhydrocodone were notably delayed (2 hours post-dose) and markedly lower than observed with HB. Review of individual concentration-time profiles supported the mean concentration-time profile, with the majority of subjects exhibiting a lower and delayed peak plasma hydrocodone concentration following IN administration of benzhydrocodone relative to HB (Figure 21).

Maximum (C_{max}), total and partial AUCs of hydrocodone were substantially lower for benzhydrocodone compared to HB (Figure 22). C_{max}, AUC_{last} and AUC_{inf} for benzhydrocodone were approximately 36%, 10% and 9% lower (all $p<0.0001$) and median T_{max} was significantly delayed (by 1.25 hours) compared with HB (Wilcoxon signed rank test, $p<0.0001$). The IN administration of benzhydrocodone resulted in an approximately 53% (AUC_{0-2} [$p<0.0001$]) to 95% ($AUC_{0-0.083}$ [$p<0.0001$]) reduction in early systemic hydrocodone exposure compared to HB, depending on the time interval (with consistently greater reduction in exposure at earlier time points). Exposure to hydrocodone remained lower overall for benzhydrocodone compared to HB as shown by later partial and total AUCs. At 10 hours post-dose, systemic exposure to hydrocodone after IN administration of benzhydrocodone was still approximately 25% lower ($p<0.0001$) compared to HB.

Figure 21: Mean Plasma Hydrocodone Concentration-Time Profiles after IN Administration of Benzhydrocodone (Apadaz Prodrug) and Hydrocodone Bitartrate

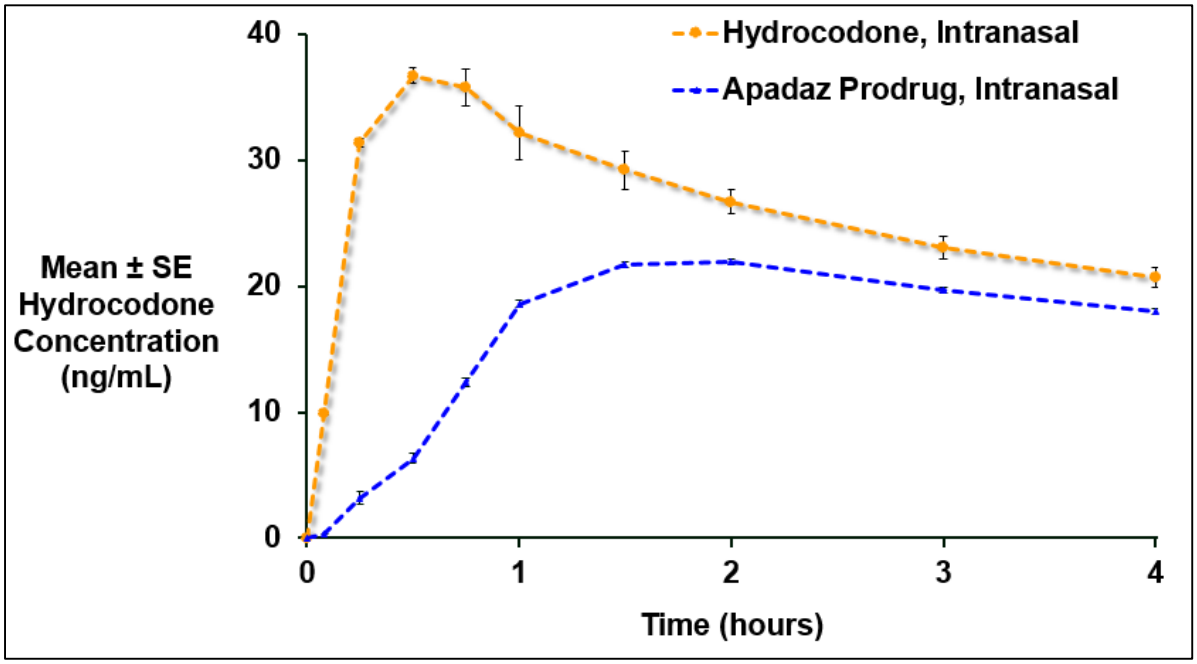
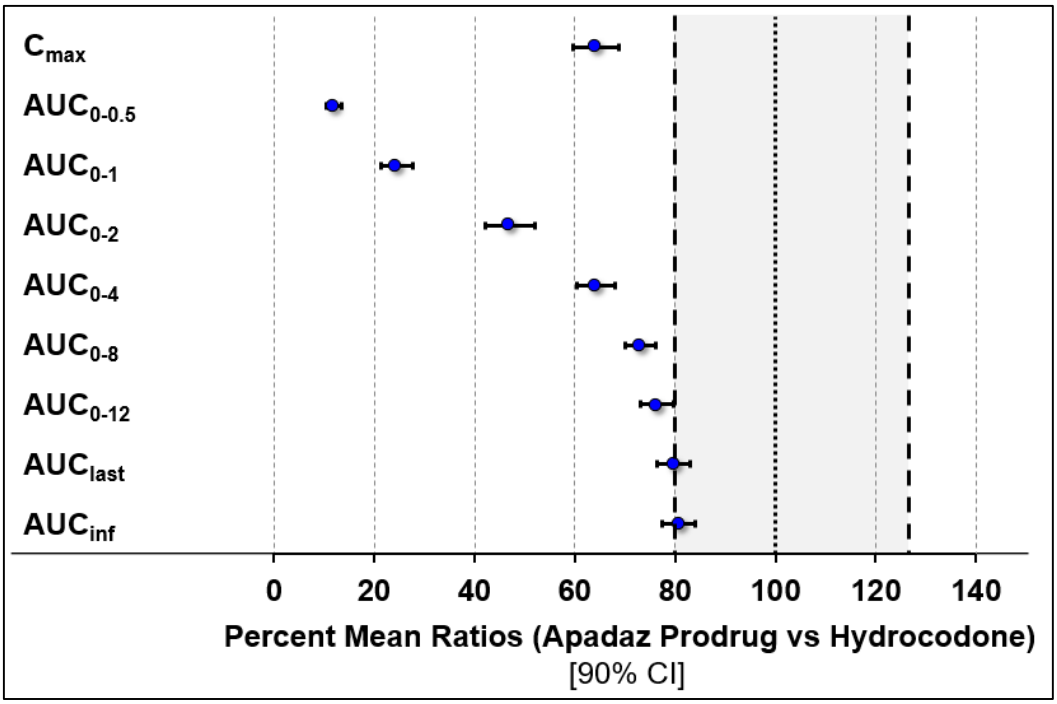


Figure 22: Forest Plot of Geometric Mean Ratios and 90% Confidence Intervals of the PK Parameters of Hydrocodone after IN Administration of Benzhydrocodone versus Hydrocodone Bitartrate in Opioid-experienced, Non-dependent Recreational Users



Note: Gray shaded area reflects bioequivalence range of LS Mean Ratio of 80% to 125%.

4.3 Category 3: Abuse Potential

The primary endpoint in the oral (A01) and IN (A02) HAP studies was Maximum Drug Liking (E_{max}), per FDA Guidance. In order to evaluate the abuse-deterrent properties of ER/LA opioids, the guidance recommends comparing a manipulated form of the putative abuse-deterrent ER opioid to a manipulated, non-abuse deterrent form of an IR or ER product containing the same opioid (FDA, 2015). This evaluation determines whether the ER properties of the test formulation remain intact when manipulated to prevent "dose dumping" and to produce lower Drug Liking scores than the manipulated IR or ER product.

For a putative abuse-deterrent IR product, where the comparator is a non-abuse-deterrent IR product containing the same active moiety, Drug Liking E_{max} falls short of describing the effects sought by abusers of IR opioids. By manipulating an IR opioid product, an abuser is attempting to accelerate the onset of opioid concentrations in the brain, and thus, the drug's euphoric effects. However, Drug Liking E_{max} does not account for reduced Drug Liking at early time points and does not capture the concept of "accelerated drug onset" that abusers are seeking.

FDA Guidance notes that the rate of rise of drug onset should be considered in the overall assessment of abuse-deterrent properties (FDA, 2015), because it is thought to contribute to differential abuse potential among drugs, formulations, and routes of administration. Therefore, a more comprehensive assessment of an IR opioid's abuse potential can be assessed by comparing the abuse-deterrent product to another IR formulation in two ways:

- Pharmacokinetically: Abuse Quotient (AQ), a quantitative summary of the rate of rise of drug concentrations in blood defined as the ratio of C_{max}/T_{max}
- Pharmacodynamically: Drug Liking at early time points

4.3.1 Abuse Quotient

Pharmacokinetic parameters, such as C_{max} and T_{max}, are important contributors to the abuse potential of opioid formulations (Webster 2009a; Katz 2011; Kirsh 2012; Moorman-Li 2012). Clinical observations suggest that an opioid drug that produces high plasma concentrations rapidly will likely result in greater reinforcing effects, and consequently, have greater abuse potential compared to an opioid with a slower onset of effect. The faster opioid concentrations rise in the blood and brain, the greater the reward experience (Moorman-Li 2012; Webster 2009b).

It has also become apparent that neither T_{max} nor C_{max} considered alone can precisely predict euphoria. Both parameters are important and need to be evaluated together. Thus, a ratio called the Abuse Quotient (C_{max}/T_{max}) has been introduced as a common numerical assessment of the abuse potential of an opioid drug. A higher AQ scores suggests greater abuse potential.

The AQ can potentially have significant implications for abusers taking drugs via oral and non-oral routes. For example, opioid abusers may crush ER tablets before oral consumption, or crush and snort tablets in order to enhance the euphoric high by shortening T_{max} and possibly increasing C_{max}. The AQ values for all treatments assessed in studies A01, A02, and A03 were calculated and are summarized in Table 15. The AQ values were then ranked from lowest to

highest to allow comparison of the relative abuse potentials for each dose and route of administration (Table 16).

Table 15: Abuse Quotient for Hydrocodone by Study

Study	Dose (ROA)	Treatment	Abuse Quotient (ng/mL/hours)
Study A01 (N=58)	4 Tablets (PO)	Apadaz	99.6
		Norco	99.7
	8 Tablets (PO)	Apadaz	204.8
		Norco	222.7
	12 Tablets (PO)	Apadaz	287.8
		Norco	329.7
Study A02 (N=41)	2 Tablets (PO)	Apadaz	31.9
		Norco	56.5
	2 Tablets (PO)	Apadaz	38.6
		Norco	34.5
Study A03 (N=24)	13.34 mg (IN)[a]	Benzhydrocodone	17.0
	15 mg (IN)[a]	HB	87.3

[a] 13.34 mg benzhydrocodone and 15 mg HB represent the amounts of benzhydrocodone in 2 Apadaz and HB in 2 Norco tablets, respectively. ROA = Route of Administration, IN = intranasal, PO = per os (oral)

Table 16: Abuse Quotient Values Ranked from Smallest to Largest

Rank[a]	Treatment	ROA	Dose Units (mg)	Abuse Quotient (ng/mL/hours)
1	Benzhydrocodone	IN	2 (13.34)	17.0
2	Apadaz	IN	2 (13.34/650)	31.9
3	Norco	PO	2 (15/650)	34.5
4	Apadaz	PO	2 (13.34/650)	38.6
5	Norco	IN	2 (15/650)	56.5
6	HB	IN	2 (15)	87.3
7	Apadaz	PO	4 (26.68/1300)	99.6
8	Norco	PO	4 (30/1300)	99.7
9	Apadaz	PO	8 (53.36/2600)	204.8
10	Norco	PO	8 (60/2600)	222.7
11	Apadaz	PO	12 (80.04/3900)	287.8
12	Norco	PO	12 (90/3900)	329.7

ROA = Route of Administration, IN = intranasal, PO = per os (oral)

4.3.2 Clinical Abuse Potential Studies

The oral and IN abuse potential of Apadaz was evaluated in two randomized, double-blind, double-dummy, placebo and active controlled human abuse potential (HAP) studies in opioid-experienced, non-dependent recreational users (Studies A01 and A02). In addition, data related to subjective measures of abuse (e.g., drug liking) were collected as a secondary objective in a relative IN bioavailability study of benzhydrocodone (Study A03) that was conducted in opioid-experienced, non-dependent recreational users.

4.3.2.1 Oral Human Abuse Potential Study of Apadaz – Study A01

As expected, the oral abuse potential of Apadaz was similar to that of Norco in opioid-experienced, non-dependent recreational users at each respective dose level (i.e., 4 tablets, 8 tablets, or 12 tablets), which mirrored the study's PK findings. Differences between Apadaz and Norco in Drug Liking E_{max} were not significant at any dosage level. Results for the other secondary objective and subjective measures were similar to those observed for the primary endpoint Drug Liking.

Drug Liking curves in the first two hours are shown in Figure 23. AQ values for Apadaz and Norco at each dosage level are shown in Figure 24.

Figure 23: Mean Drug Liking in First Two Hours of Oral HAP Study A01

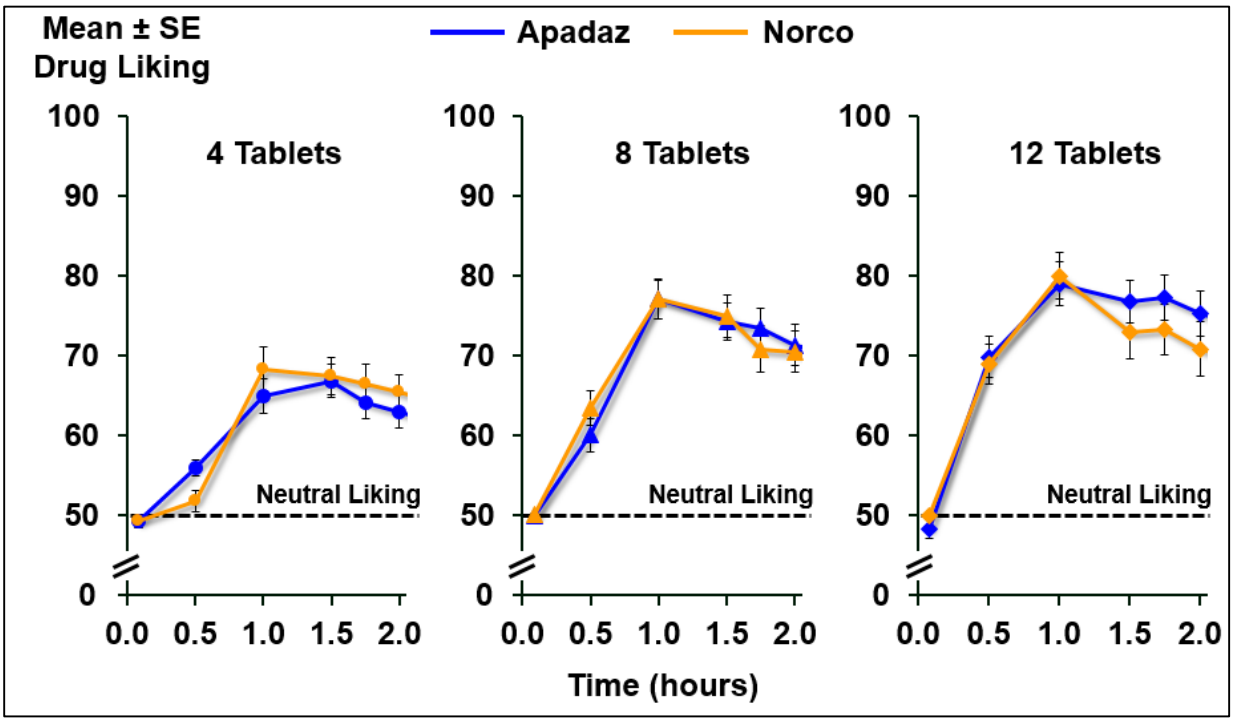
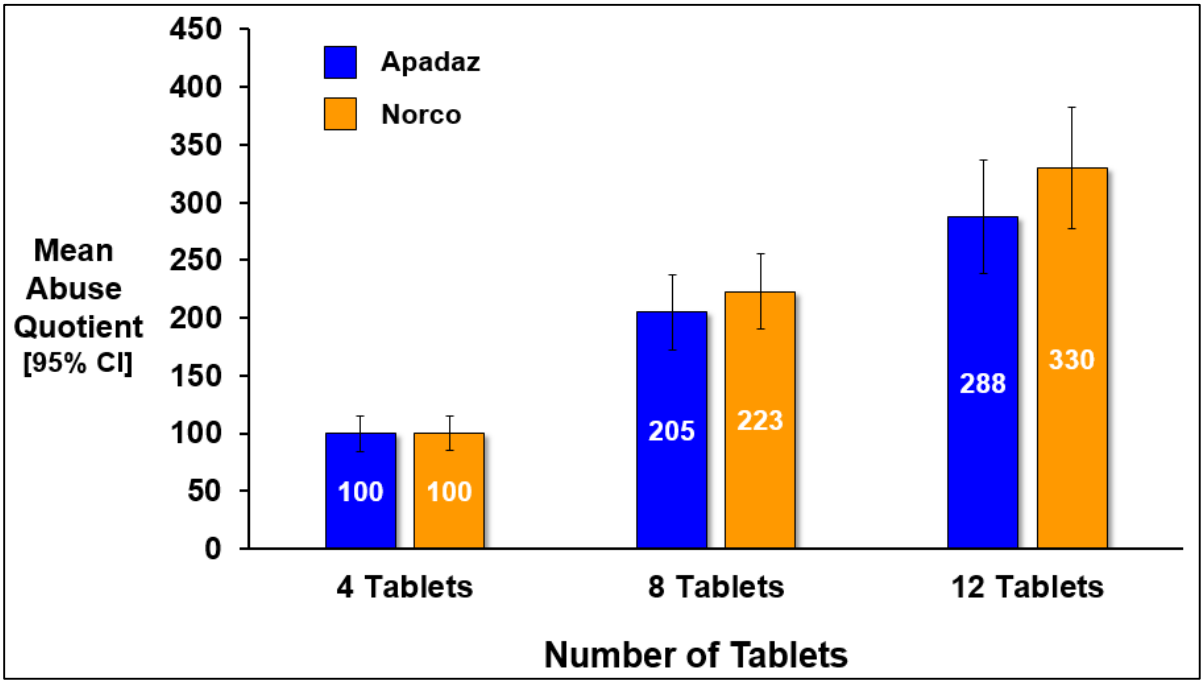


Figure 24: Abuse Quotients for Treatments in Oral HAP Study A01



4.3.2.2 Intranasal Human Abuse Potential Study of Apadaz – Study A02

Administration of two tablets of Apadaz intranasally (crushed), or oral dosing (intact), resulted in statistically similar results for Drug Liking E_{max} relative to the same conditions for Norco. Mean peak Drug Liking (E_{max}) were similar for Apadaz, both IN (75.9) and oral (76.9), compared to that of Norco (79.0, IN; 77.9, oral), which is likely due to the large volume of material that may have been swallowed, or simply the inherent nature of IR combination products. Subjective and objective PD measures related to abuse potential, including positive effects, willingness to take again, and pupillometry were generally similar between Apadaz and Norco.

Importantly, within the first 2 hours of dosing through peak effect, the area under the curve for drug liking was significantly lower for crushed and snorted Apadaz than crushed and snorted Norco ($p \leq 0.0079$ at each time point through 2 hours). The mean Drug Liking curves for oral and IN administration is show in Figure 25.

Nasal Effect scores were significantly less severe after snorting crushed Norco than snorting crushed Apadaz. Maximum scores for Nasal Burning, Facial Pain or Pressure, the Need to Blow Nose, Nasal Irritation, Nasal Congestion, and Nasal Discharge scores were all significantly higher for Apadaz. Additionally, all subjects were able to insufflate both tablets of Norco, though several subjects could not insufflate both tablets of Apadaz.

When translating PK into AQ, there was little difference in the abuse quotient for oral administration of Apadaz and Norco, as expected. However, the more rapid increase in hydrocodone concentration at early time points with Norco administered intranasally translated into to nearly double the AQ of Apadaz (Figure 26).

Figure 25: Mean Drug Liking in First Two Hours of Study A02

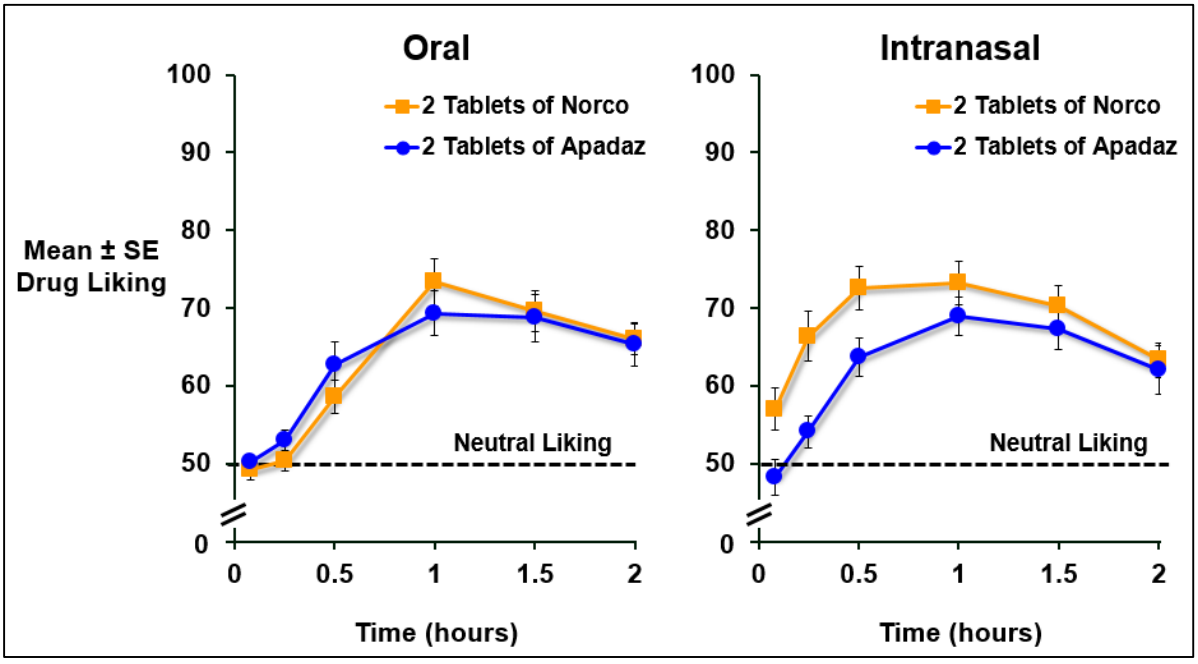
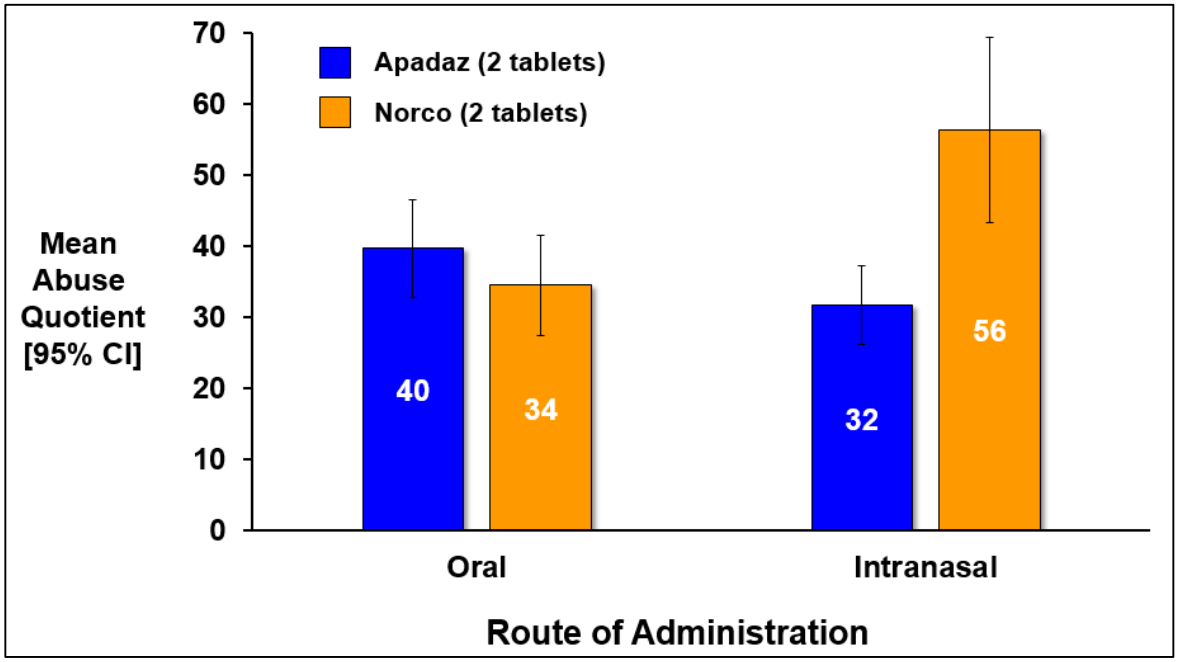


Figure 26: Abuse Quotients for Treatments in Intranasal HAP Study A02



4.3.2.3 Intranasal Bioavailability Study of Benzhydrocodone with Abuse Potential Assessments – Study A03

The intranasal study of the APIs (i.e., benzhydrocodone for Apadaz, and hydrocodone bitartrate for Norco) without APAP found significantly lower Drug Liking E_{max} scores for benzhydrocodone than hydrocodone bitartrate (p=0.0039). Additionally, the median time to maximum drug liking of half an hour with hydrocodone bitartrate was more than double for benzhydrocodone (1.1 hours vs. 0.5 hours). The mean Drug Liking curves for IN administration of the APIs is shown in Figure 27. These findings are particularly notable because this trial did not include a drug discrimination test, which would enrich the population for subjects who could discriminate between active drug and placebo and would have likely led to greater differences in Drug Liking.

Similar to Study A02, benzhydrocodone was more difficult to insufflate compared with hydrocodone bitartrate, as demonstrated by a significant difference in Ease of Insufflation scores (p=0.0004).

The considerably lower exposure at early time points and the associated delay in time to maximum concentration produced an AQ that was 5 times lower for benzhydrocodone than the hydrocodone bitartrate (Figure 28).

Taken together, the results of the intranasal human abuse studies – with and without APAP – suggest that benzhydrocodone has a lower intranasal abuse potential than existing hydrocodone IR combination products.

Figure 27: Mean Drug Liking in First Two Hours of Study A03

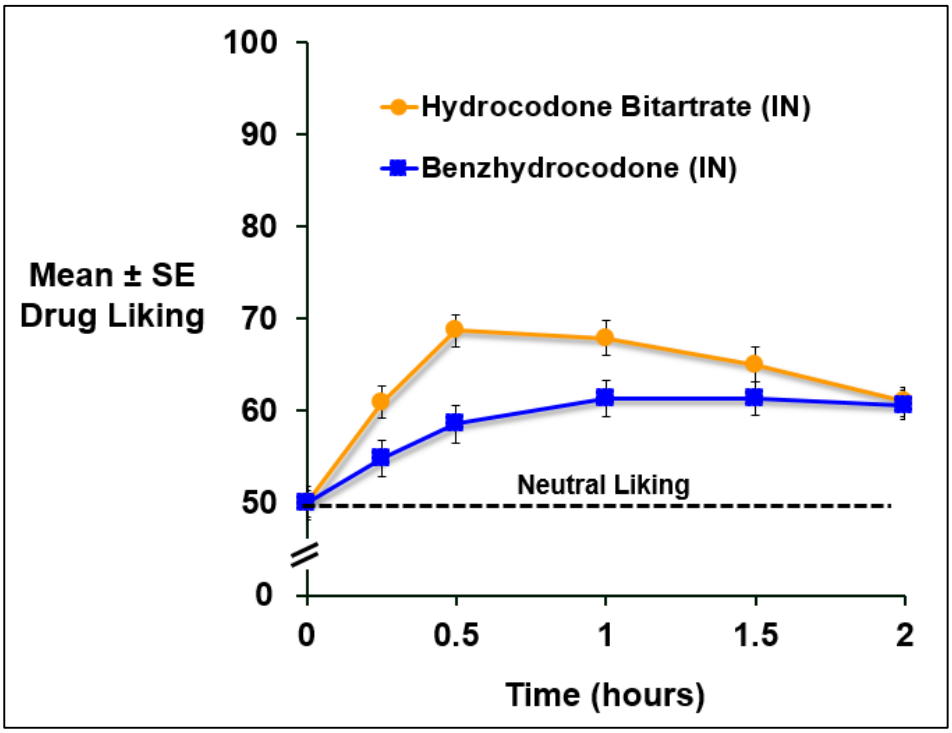
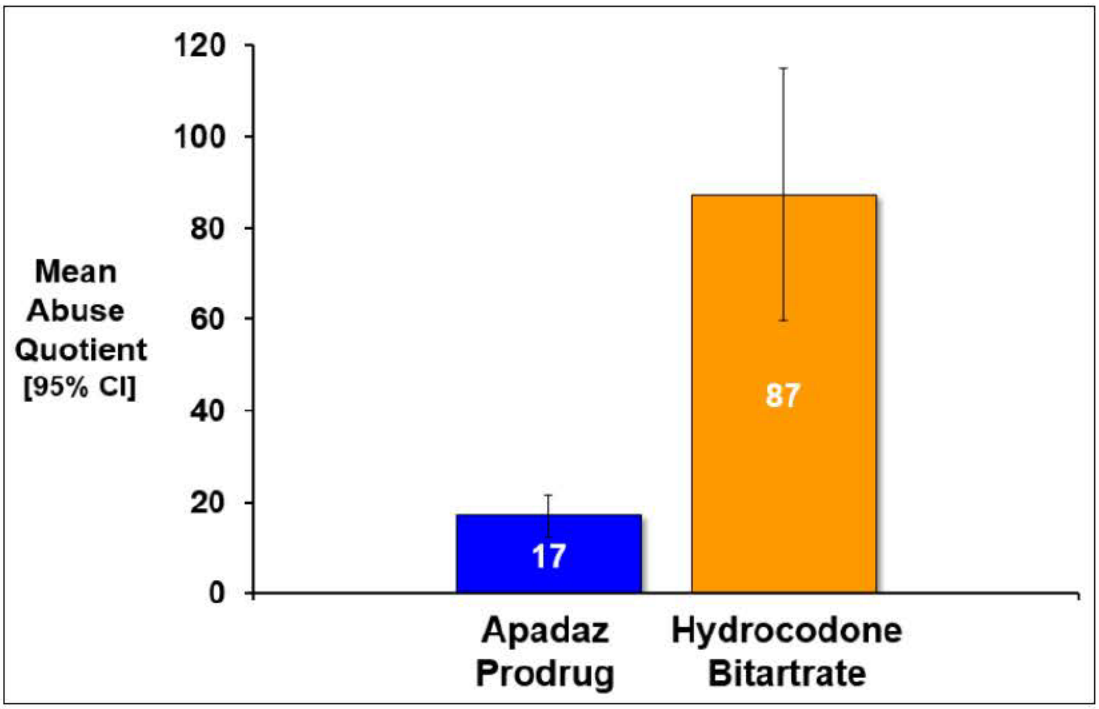


Figure 28: Abuse Quotients in Intranasal Bioavailability Study A03



5 RISK MANAGEMENT AND POST-MARKET STUDIES

On May 3-4, 2016, a joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee will be held in order to discuss, in part, whether the ER/LA Opioid Analgesics Risk Evaluation and Mitigation Strategies (REMS) ought to be expanded to include IR opioids. If approved, Apadaz would be the first IR hydrocodone product with abuse-deterrent properties approved for marketing in the United States. As such, there is currently no precedent for the conduct of a formal risk management program of an abuse-deterrent IR opioid. KemPharm is committed to the safe and appropriate usage of Apadaz, and looks forward to incorporating the advice and recommendations of the joint Advisory Committee as well as a continued dialogue with the FDA on the scope and content of the risk management strategy for Apadaz.

In addition to the risk management program, which will be determined following the joint Advisory Committee meeting and in discussion with the FDA, KemPharm proposes an epidemiologic approach to post-market surveillance and formal epidemiologic studies intended to evaluate its abuse profile.

The 4 overall objectives of the program are:

1) To evaluate abuse and route of administration patterns for Apadaz among populations considered at high-risk for abuse of opioid analgesics;
2) To evaluate the potential impact of the market introduction of Apadaz in relation to the abuse prevalence of other hydrocodone IR combination products currently on the market;
3) To assess the extent to which the physicochemical properties of Apadaz may present a deterrence for abuse of the product when compared to other hydrocodone IR combination products, and other relevant opioids within the marketplace;
4) And finally, to evaluate the recreational desirability of the product relative to other hydrocodone IR combination products and other relevant opioids within the market.

KemPharm, in collaboration with Inflexxion, proposes to conduct a series of examinations of Apadaz using data from the NAVIPPRO system. These will include data from adults assessed for substance abuse treatment in the ASI-MV network, as well as data collected from individuals who frequent and participate in online drug-related discussion forums with the WIS Internet Monitoring tool.

These two data sources will allow for timely capture of product-specific data on abuse, routes of abuse, and methods of tampering over time. Both of these data sources have several years of historical data from which to assess baseline levels of abuse for many prescription opioid products, including hydrocodone IR combination products.

5.1 Phase 1: Surveillance Monitoring for Abuse of Apadaz

During the initial period of market introduction, it is expected that abuse of Apadaz may be low and sporadic as the drug gains market share and its availability increases.

Therefore, regular surveillance monitoring and review of observations of abuse on a frequent basis via the WIS: Internet Monitoring and ASI-MV data streams will provide an appropriate, early assessment of Apadaz in terms of its abuse potential, as well as descriptive analyses of initial prevalence rates of abuse, and the frequency of abuse for Apadaz via various routes of administration.

KemPharm will begin the formal post-market epidemiology studies after Apadaz has gained sufficient level of prescription volume and a sufficient length of time on the market has elapsed in order to provide a basis for the analysis of rates of abuse.

5.2 Phase 2: Formal Post-Market Epidemiology Study

KemPharm will also conduct formal epidemiologic studies to determine whether the product's abuse-deterrent properties result in meaningful reductions in abuse in the post-approval setting.

KemPharm proposes to conduct two studies to assess abuse-deterrence of Apadaz. The first is a primary formal post-market epidemiology study among a high-risk population of adults entering or assessed for substance abuse treatment. The second is a supportive study of drug-related discussion among recreational drug abusers on Internet websites and forums.

5.2.1 ASI-MV Network Data Analysis

The primary study will utilize data from the ASI-MV network to answer several research questions, including:

- Does Apadaz demonstrate lower levels of relative abuse prevalence and route-specific abuse compared to comparator prescription opioids?
- Does Apadaz demonstrate lower frequency of abuse compared to comparator prescription opioids?
- Does Apadaz demonstrate a change in overall abuse pattern of hydrocodone IR combination products?
- How does abuse of Apadaz compare to all other ADFs on the market?

5.2.2 Tracking Internet Discussions to Support ASI-MV Data

Tracking of drug-related Internet discussion will serve as a supportive study to assess several other key metrics. These will answer several additional questions, including:

- Does Apadaz demonstrate tampering that only results in the extraction of the inactive prodrug, benzhydrocodone, for purposes of abuse?
- Does Apadaz demonstrate a lower number of successful tampering recipes that lead to the hydrolysis of hydrocodone for purposes of abuse compared to other comparator prescription opioids?
- Does the Apadaz combination demonstrate a lower incidence of alternative routes of administration?
- Does Apadaz demonstrate a lower level of endorsement of the product for abuse among recreational drug users compared to other comparator prescription opioids?

6 BENEFIT-RISK ASSESSMENT

Drug abuse may have an impact on public health with respect to the safety of the drug and potential for 'addiction/dependence' that may require treatment. In addition, recreational drug abusers may engage in high risk behaviors that can result in harm to themselves or others such as taking supratherapeutic doses (toxicity and overdose), tampering with and altering routes of administration (toxicity and overdose), self-harm (suicide), concomitant substance use (interactions), and engaging in activities while impaired that may lead to accidents.

Currently, there are no IR formulations of hydrocodone combination products with abuse-deterrent properties and most of the common abuse-deterrent approaches applied to other opioid products have been focused on changing the physiochemical properties of ER tablet formulations. By changing the inherent pharmacology and PK profile of the opioid by chemically creating a prodrug, KemPharm is attempting to provide a more robust barrier to abuse that does not just focus on tampering, manipulation, or one route of abuse. Instead, the prodrug 'protects' hydrocodone at the molecular level and thus, reduces the abuse potential for non-oral routes of administration and makes success of manipulation extremely difficult. While there are no perfect barriers and no opioid product is "abuse-proof", the prodrug, benzhydrocodone, represents a significant step forward in abuse-deterrent technologies while still providing the same therapeutic benefits to patients that are expected from an opioid like hydrocodone.

Based on the totality of evidence collected during development, the abuse potential of Apadaz was determined to be reduced compared to currently marketed hydrocodone IR combination products because hydrocodone exposure is consistently lower when Apadaz is administered via non-oral routes (e.g., when crushed and snorted), and because its abuse-deterrent features are maintained even when the tablet formulation is manipulated or the prodrug is isolated from the tablet.

Based on results from in vitro tampering studies, Apadaz has far more resistance to attempts of isolating the hydrocodone component when compared to Norco. No simple method to hydrolyze and isolate active hydrocodone from benzhydrocodone could be identified. Additionally, successful isolation of the inactive benzhydrocodone prodrug from its tablet formulation notably increases the inherent abuse-resistant effects and safety of benzhydrocodone upon insufflation when compared to hydrocodone, as supported by clinical PK and PD data.

Both hydrocodone IR combination products and Apadaz can be abused by oral and IN routes. However, the abuse potential of an opioid should be determined by focusing on the comparison of clinical effects between test product and reference product in head-to-head studies. Apadaz differentiates itself from the reference product, Norco, by changing its absorption and PK pattern as methods of administration escalate in severity (i.e., switching from swallowing to snorting, isolating benzhydrocodone from its tablet formulation, high resistance to manipulation and inability to be smoked).

Epidemiological data suggest that hydrocodone IR combination products are abused at high rates and may be considered a "gateway" to other opioids, illicit drugs and/or routes of abuse. The most common routes of abuse for hydrocodone IR combination products are via the oral and intranasal routes. Given that Apadaz does not provide any additional euphoric reward by snorting

the product (as demonstrated by both PK, lower Drug Liking, and more adverse nasal effects), it is at least plausible to hypothesize that novice abusers may be discouraged to manipulate Apadaz, which may ultimately limit escalation to riskier behavior.

While there are currently no available data that conclusively demonstrate a positive correlation between reduction in Drug Liking of an abuse-deterrent product, and reduction in abuse frequency and abuse severity, any significant decrease in exposure after misuse or abuse of an opioid and potentially lowering its reinforcing effects due to repeated dosing suggests at least some safety benefit to an abuser. Apadaz provides this benefit by reducing hydrocodone exposure when snorted, especially if benzhydrocodone has been isolated for insufflation. Ultimately, by reducing exposure to hydrocodone and its metabolite hydromorphone, products like benzhydrocodone and Apadaz may "teach" abusers, particularly novice adolescent abusers, away from riskier drug abuse behaviors such as snorting and tampering.

In a direct comparison to Norco, Apadaz demonstrated similarity with respect to the following attributes:

- Risk of injection: Apadaz and Norco have a similar risk of introducing solid particles into the blood stream when prepared for injection
- Bioequivalent PK at oral therapeutic doses

In a direct comparison to Norco, Apadaz demonstrated superiority with respect to the following properties:

- Highly tamper resistant: hydrocodone is difficult to obtain from benzhydrocodone and from Apadaz tablets while hydrocodone can easily be extracted from Norco
- Resistance to injection and smoking: benzhydrocodone may be converted to hydrocodone slowly if injected and also cannot be smoked
- Reduction in exposure to hydrocodone and Drug Liking at early time points when administered as crushed Apadaz intranasally
- Reduction in exposure to hydrocodone and Drug Liking overall and at early time points when administered as benzhydrocodone without APAP

Based on bioequivalence to a currently marketed hydrocodone IR combination product, Apadaz will provide the same effective analgesia expected from an IR opioid product with a comparable safety profile when taken as intended. Apadaz has shown a significantly improved abuse potential via non-oral routes of administration compared to current hydrocodone IR combination products. Furthermore, in no studied situation was it found to be inferior to Norco.

If approved, Apadaz would be the first IR formulation of hydrocodone with abuse-deterrent properties. In light of the fact that Apadaz poses no additional risks beyond existing hydrocodone IR combination products, and offers several robust abuse-deterrent features in a class where there are currently none, Apadaz has a positive benefit-to-risk profile.

7 REFERENCE LIST

Butler SF, Black RA, Serrano JM, Wood ME, Budman SH. Characteristics of prescription opioid abusers in treatment: prescription opioid use history, age, use patterns, and functional severity. *J Opioid Manag* 2010; 6(4):239-241, 246-252.

Cone EJ, Giordano J, Weingarten B. An iterative model for in vitro laboratory assessment of tamper deterrent formulations. *Drug Alcohol Depend* 2013;131(1-2):100-5.

DOJ. US Department of Justice. Schedules of controlled substances: Rescheduling of hydrocodone combination products from schedule III to schedule II. Federal Register, 2014; 79(163), 49661–49682. Accessed at: http://www.deadiversion.usdoj.gov/fed_regs/rules/2014/fr0822.htm

Food and Drug Administration, Center for Drug Evaluation and Research, US Department of Health and Human Services, Draft Guidance for Industry: Assessment of Abuse Potential of Drugs. Jan 2010.

Food and Drug Administration, Center for Drug Evaluation and Research, US Department of Health and Human Services, Guidance for Industry: Abuse-Deterrent Opioids — Evaluation and Labeling. Apr 2015.

Goliber P A, Wright C. (2005). Benchtop testing of opioid formulations for tamper liability. Impact of Drug Formulation on Abuse Liability, Safety and Regulatory Decisions Conference (North Bethesda, MD).

IMS Health. National Prescription Audit. Jan 2015.

Katz NP, Adams EH, Chilcoat H, Colucci RD, Comer SD, Goliber P, Weiss R. Challenges in the development of prescription opioid abuse-deterrent formulations. *Clin J Pain*, 2007;23(8):648-60.

Katz EC, Brown BS, Schwartz RP, O'Grady KE, King SD, Gandhi D. Transitioning opioid-dependent patients from detoxification to long-term treatment: efficacy of intensive role induction. *Drug Alcohol Depend* 2011;117(1):24-30.

Katz N, Dart RC, Bailey E, Trudeau J, Osgood E, Paillard F. Tampering with prescription opioids: nature and extent of the problem, health consequences, and solutions. *Am J Drug Alcohol Abuse* 2011;37(4):205-217.

Katz NP, Adams EH, Chilcoat H, Colucci RD, Comer SD, Goliber P, Weiss R. Challenges in the development of prescription opioid abuse-deterrent formulations. *Clin J Pain* 2007;23(8):648-60.

Kirsh K, Peppin J, Coleman J. Characterization of prescription opioid abuse in the United States: focus on route of administration. *J Pain Palliat Care Pharmacother*. 2012;26(4):348-361.

Moorman-Li R, Motycta CA, Inge LD, Congdon JM, Hobson S, Pokropski B. A review of abuse-deterrent opioids for chronic nonmalignant pain. *P T* 2012;37(7):412-8.

Surratt H, Kurtz SP, Cicero TJ. Alternate routes of administration and risk for HIV among prescription opioid abusers. *J Addict Dis* 2011;30(4):334-341.

Webster LR. The question of opioid euphoria. *Drug Discovery and Development*. July 30, 2009. Accessed on 20 Nov 2015: http://www.dddmag.com/articles/2009/07/questions-opioid-euphoria

Webster LR, Bath B, Medve RA. Opioid formulations in development designed to curtail abuse: who is the target? *Expert Opin Investig Drugs* 2009;18(3):255-63.

8 APPENDIX – TABLES AND FIGURES

Table 17: Target and Comparator Products for ASI-MV and CHAT Analyses

Target and comparator products	ASI-MV and CHAT monitored product categories
Hydrocodone IR combination products (brand and generic formulations)	Lorcet Lortab Vicodin Vicoprofen Norco Other hydrocodone (includes specific images of generic hydrocodone IR combination products) Other hydrocodone not shown (includes any other short acting hydrocodone combination product not presented with an image of the medication)
Oxycodone IR combination products (brand and generic formulations)	Percocet Tylox Oercidab Cinbybix Roxicet Other Roxicet not shown Other short acting oxycodone (includes specific images of other generic oxycodone IR combination products) Other short acting oxycodone not shown (would include Oxceta and any other short acting oxycodone not presented with an image of the medication)
Oxycodone IR single-entity (SE)	OxyIR Roxicodone Other Roxicodone not shown

Target and comparator products	ASI-MV and CHAT monitored product categories
All other IR prescription opioids (both single-entity and combination excluding Schedule III products)	Actiq Fentora Onsolis Dilaudid Other IR hydromorphone (includes images of generic hydromorphone IR products) Other IR hydromorphone not shown MISR Other IR morphine not shown Opana Generic IR oxymorphone not shown Nucynta
All ADF ER/LA opioids	Reformulated OxyContin Xartemis XR Exalgo EMBEDA Reformulated Opana ER Nucynta ER
All non-ADF ER/LA opioids (excluding path and buprenorphine products)	Original OxyContin Other non-combination ER oxycodone not shown Other ER oxycodone w/ acetaminophen not shown MS Contin KADIAN AVINZA Oramorph SR Generic ER morphine products not shown Original Opana ER Generic ER oxymorphone (Actavis) Generic ER oxymorphone (Impax) Other generic ER oxymorphone not shown Zohydro ER