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STATISTICAL REVIEW(S)
Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number: 208653/0000

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Indication:

Study number: KP201.A01, KP201.A02, KP201.A03

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<td>12</td>
<td>Summary statistics of other endpoints for Drug Liking VAS (N=42)</td>
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<td>Heat map display for Drug Liking Emax by treatment for Cohort 2 (N=25)</td>
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<tr>
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1. Executive Summary

The applicant, KemPharm Inc., submitted the results from two clinical abuse potential studies KP201.A01 (oral), KP201.A02 (intranasal), and a pharmacokinetic (PK) Study KP201.A03 (API, intranasal) in support of the claim for abuse-deterrent formulation of KP201/APAP.

Study KP201.A01 was a randomized, double-blind, placebo-controlled, single-dose, seven-way crossover study to determine the relative bioavailability, abuse potential and safety of equivalent oral doses of KP201/APAP compared with hydrocodone bitartrate/APAP (HB/APAP) in opioid-experienced nondependent subjects. The primary objective was to determine the abuse potential of KP201/APAP relative to HB/APAP when administered orally to nondependent, recreational opioid users. Treatments in the study were KP201/APAP (26.68/1,300 mg), KP201/APAP (56.36/2,600 mg), KP201/APAP (80.04/3,900 mg), HB/APAP (30/1,300 mg), HB/APAP (60/2,600 mg), HB/APAP (90/3,900 mg), and placebo. Seventy one subjects were randomized to the treatment phase. Of these, 62 subjects completed the study.

Study KP201.A02 was a randomized, double-blind, placebo-controlled, single-dose, two-part, five-way crossover study to determine the relative bioavailability, abuse potential, and safety of equivalent doses of crushed and intact KP201/APAP compared with HB/APAP and placebo in opioid-experienced, non-dependent subjects following intranasal administration. The primary objective of the Main Study (Part B) was to determine the abuse potential of crushed KP201/APAP relative to crushed HB/APAP at the dose determined in the Dose Selection Phase (Part A) when administered intranasally to non-dependent, recreational opioid users. The treatments in the study were HB/APAP (15/650 mg) crushed, KP201/APAP (13.4/650 mg), HB/APAP (15/650 mg) intact, KP201/APAP (13.34/650 mg) intact. Forty six subjects were randomized to the Treatment Phase. Of these, 42 subjects completed the study.

Both Studies KP201.A01 and KP201.A02 failed to demonstrate that KP201/APAP reduced mean of maximum liking compared to HB/APAP with p-values 0.4658, 0.3631, and 0.5315 for low dose, medium dose and high dose respectively in Study KP201.A01, and with p-value 0.1654 and 0.3851 for intranasal route and oral route, respectively in Study KP201.A02. Results from other measures for example, High VAS and Take Drug Again VAS also supported the findings from Drug Liking VAS. The statistically significant mean difference in maximum liking between HB/APAP and placebo in both studies validated the study.

In conclusion, Studies KP201.A01, and KP201.A02 for pharmacodynamics (PD) assessment did not demonstrate that KP201/APAP had abuse-deterrent effects compared to HB/APAP.

Per Pharmacologist Dr. James Tolliver’s request, the reviewer also reviewed Study KP201.A03 for PD assessment. Study KP201.A03 was a randomized, double-blinded, single dose two-way crossover study to determine the relative bioavailability of equivalent doses of KP201 API compared with HB API in opioid experienced, non-dependent subjects, following intranasal administration. The primary objective was to compare the rate and extent of absorption of hydrocodone and hydromorphone from KP201 API relative to HB API when administered intranasally to non-dependent, recreational opioid users. The treatments in the study were 13.4 mg...
KP201 API and 15 mg HB API. A total of 66 subjects (33 subjects in Cohort 1 and 33 subjects in Cohort 2) were enrolled into the study, with 54 subjects randomized in the Treatment Phase. Of these, Fifty one subjects (26 in Cohort 1 and 25 in Cohort 2) completed PD assessment.

The study was not designed for the evaluation of PD abuse-deterrent effects for KP201/APAP due to the following reasons:

1. Study involved insufflation of KP201 API and HB API, and not the products KP201/APAP and HB/APAP.
2. There was no Drug Discrimination (Qualification) Phase intended to select subjects having an appropriate placebo and active comparator response using the Drug Liking VAS.
3. There was no placebo treatment in the Treatment Phase of the study.
4. There were no additional subjective reinforcing measures (i.e., High VAS or Take Drug Again VAS) conducted which could be used to support observed effects on the Drug Liking VAS.

Due to blood sample handling problem, the PK data from Cohort 1 was excluded from the sponsor’s PK analysis. However, the sponsor reported statistical analysis results on Drug Liking Emax using data from subjects of both cohorts in the proposed label. Based on the sponsor’s definition of the Completers Population in the protocol, without any PK data none of the subjects in Cohort 1 should be considered as a completer. Therefore, this reviewer provided some descriptive statistics for Cohort 2 (See 4.3.1. Descriptive statistics). According to the protocol, these results are for information only.

The reviewer also examined difficulty for insufflation of KP201 API and HB API. The summary statistics for Ease of Insufflation VAS indicate that KP201 API was more difficult to be insufflated compared to HB API. However, there is a clear difference in the magnitude of the mean difference in Ease of Insufflation scores between KP201 API and HB API by sequence due to sequence effect. The percent of dose insufflated (% mg) using the weights was not recorded before and after each dose was insufflated in this study.

In conclusion, Study KP201.A03 had significant deficiencies, and then cannot be used to assess abuse potential or abuse deterrent effects of KP201/APAP relative to HB/APAP via intranasal route of administration.
2. Review report on Study KP201-A01

2.1. Overview

Study KP201-A01 is a randomized, double-blind, placebo-controlled, single-dose, seven-way crossover study to determine the relative bioavailability, abuse potential, and safety of equivalent oral doses of KP201/Acetaminophen (APAP) compared with Hydrocodone/APAP in opioid-experienced nondependent subjects.

2.1.1. Objectives of the study

Primary Objective:

- To determine the abuse potential of KP201/APAP relative to hydrocodone bitartrate/APAP (HB)/APAP when administered orally to nondependent, recreational opioid users.

Secondary Objectives:

- To determine the abuse potential of KP201/APAP relative to placebo.
- To determine the relative bioavailability of KP201, hydrocodone, hydromorphone, and APAP in plasma from KP201/APAP compared with HB/APAP.
- To determine the safety of KP201/APAP compared with HB/APAP and placebo.

2.1.2. Study design

This was a single-center, randomized, double-blind, active- and placebo-controlled, 7-period crossover study assessing the abuse potential of KP201/APAP tablets in nondependent recreational opioid users. The study consisted of a Screening Period, in-clinic Qualification and Treatment Phases, and a Follow-up Period.

Qualification Phase

Subjects who successfully completed the Screening Period returned to the research clinic as inpatients to complete the Qualification Phase. This period comprised a Naloxone Challenge Test to confirm that subjects were not physically dependent on opioids and a Drug Discrimination Test to ensure that subjects could differentiate between the effects of a single dose of HB/APAP 45 mg/1, 950 mg and placebo.

Treatment Phase

Subjects who successfully completed the Qualification Phase entered the Treatment Phase. Subjects who were discharged after the Qualification Phase checked into the clinic the day before the Treatment Phase. Subjects remained in the unit throughout the Treatment Phase during which they received all 7 treatments with each treatment separated by a minimum 72-hour washout period. Subjects were randomized to 1 of 14 treatment sequences using a computer-generated randomization scheme based on a Williams pair design.
Subjects received each of the following 7 treatments according to their randomized treatment sequence during Treatment Phase:

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

Subjects received study drug following a minimum 8-hour fast. Study capsules were swallowed with approximately 240 mL of water. Additional water was provided in 50 mL increments, if necessary, and the amount of any additional water was documented. Each dose of study drug was taken within 3 minutes. Subjects were discharged from the clinical unit on the following day after the final treatment was administered, following completion of all study procedures.

Follow-up Period

After completing the last dose in the Treatment Phase, subjects returned in 7 ± 2 days for the Follow-up Visit.

2.1.3. Study Subjects

A sample size of 56 completed subjects was planned. A total of 151 subjects were enrolled, with 125 subjects undergoing the Naloxone Challenge Test and 119 subjects being dosed in the Drug Discrimination Test (safety population). Of these 119 subjects, 48 discontinued the study and 1 discontinued and re-entered the study. Consequently, 71 subjects entered the Treatment Phase (randomized population). Of these, 62 completed the study and constituted the primary analysis population (completer population). A total of 59 subjects completed the study without any major protocol deviations (per-protocol population). The sponsor’s Figure 10-1 summarizes subject disposition for all subjects.
Qualified subjects entering Treatment Phase must not only satisfy 9 inclusion criteria and 20 exclusion criteria but also 4 additional exclusion criteria to be evaluated after clinical admission to be eligible to participate the Treatment Phase. These additional Exclusion Criteria are listed below:

1. Physical dependence on opioids, as determined by the Naloxone Challenge Test (ie, subject had a COWS score of \( \geq 5 \)) precluded entry into the Drug Discrimination Test.

2. Inability to discriminate between opioid and placebo during the Drug Discrimination Test. Ability to discriminate was defined for Drug Liking as follows (inclusive):
   a. A minimum peak effect (Emax) of 65 points for Drug Liking in response to active treatment during the first 2 hours postdose;
   b. A \( \geq 15 \)-point Emax difference between active and placebo treatments at 1 or more time points during the first 2 hours following drug administration; and
   c. A placebo response \( \geq 40 \) and \( \leq 60 \) points for Drug Liking during the first 2 hours following drug administration.

3. Intolerant to study treatments in the Drug Discrimination Test (eg, emesis within the first 2 hours after dosing precluded entry into the Treatment Phase).
4. Unacceptable response to other study assessments or inability to successfully complete the study as judged by the Investigator.

2.1.4. Abuse potential measures

**Primary measure**

- Drug Liking (DL) (prior to each PK sample collection time point from 0.5 hours up to 24 hours postdose) on a bipolar 0- to 100-point Visual Analog Scale (VAS).

**Secondary measures**

- Drug Effects Questionnaire (DEQ) including Any Drug Effects, Good Drug Effects, Bad Drug Effects, High, Sick, Nausea, Sleep, and Dizzy were collected prior to each PK sample collection time point from 0.5 hours up to 24 hours postdose on a 0-100 point VAS. DEQ-VAS for High, Sick, Nausea, Sleep, and Dizzy were also collected within 1 hour predose.
- Addiction Research Center Inventory—Morphine Benzedrine Group (ARCI–MBG) subscale measurements were collected within 1 hour pre-dose and at 2 and 4 hours postdose.
- Take Drug Again Assessment (TDAA) at 12 and 24 hours postdose on a bipolar 0-100-point VAS.
- Global Assessment of Overall Drug Liking (ODL) at 12 and 24 hours postdose on a bipolar 0-100 point VAS.
- Psychomotor Assessment: Reaction Time Test at predose and 30 minutes and 1, 2, 4, and 8 hours postdose.
- Pupil Constriction (mm dilation) at predose and prior to PK sample collection time points from 0.5 hours up to 24 hours postdose.

2.1.5. Statistical methodologies used in the Sponsor’s analyses

The primary analysis of abuse potential was conducted on the pharmacodynamics (PD) primary endpoint (ie, Emax of the DL-VAS), using a mixed-effects model of analysis of variance (ANOVA) for the completer population. The statistical model included treatment (7 levels) and period (7 levels) as well as sequence (14 levels) as fixed effects, and subject nested-in-sequence as a random effect. The method of variance components was used to define the covariance structure of the model.

Based on the analysis of the ANOVA model, pairwise comparisons of least-square means between individual treatments were further conducted at the significance level of 0.05 (2-sided) for consistency with the 95% confidence interval (CI), using a model-based t-test. The differences of pairwise least-square means along with the 95% CI were reported for each comparison. Based on equivalent dose, the primary null hypotheses of no difference in abuse potential between the reference drug and test drug were tested for the following comparisons:

a) HB/APAP high dose vs KP201/APAP high dose
b) HB/APAP medium dose vs KP201/APAP medium dose
c) HB/APAP low dose vs KP201/APAP low dose

The comparisons between the reference drug and placebo were tested at the significance level of
0.05 (2-sided) to check the interval validity of the study design. These comparisons included the following:

d) HB/APAP high dose vs placebo
e) HB/APAP medium dose vs placebo
f) HB/APAP low dose vs placebo

2.1.6. Sponsor’s Summary and Conclusions

The LS mean difference in the Emax of the DL-VAS for each of the primary comparisons between HB/APAP and KP201/APAP were not statistically significant, and the lower 95% CI of the difference was not > 0; hence the primary analysis did not establish a lower oral abuse potential for KP201/APAP relative to HB/APAP. In general, secondary measures of the DL-VAS (TEmax and AUE) and the secondary endpoints (DEQ-VAS, TDAA, and ODL-VAS) also revealed no significant difference in oral abuse potential between HB/APAP and KP201/APAP at any of the dose-level comparisons evaluated.

The DL-VAS Emax LS mean differences between each dose of KP201/APAP and placebo were statistically significant, with KP201/APAP doses demonstrating a higher oral abuse potential than placebo based on this endpoint. Secondary measures of DL-VAS and secondary endpoints of abuse potential also generally showed a higher oral abuse potential for KP201/APAP vs placebo, more consistently for high- and mid-dose KP201/APAP than low-dose KP201/APAP. The oral KP201/APAP abuse potential relative to placebo was generally dose-dependent based on these measures.

2.2. Data Location

The datasets used in the reviewer’s analysis are located at

`\CDSESUB1\evsprod\NDA208653\0006\m5\datasets\kp201-a01\analysis\legacy\datasets`

2.3. Reviewer’s Assessment

In this report, the reviewer used the following notations for treatments in Study KP201.A01.
KP201/APAP L: 4 Tablets – KP201/APAP (26.8/1,300 mg);
KP201/APAP M: 8 Tablets – KP201/APAP (56.36/2,600 mg);
KP201/APAP H: 12 Tablets – KP201/APAP (80.4/3,900 mg);
HB/APAP L: 4 Tablets – HB/APAP (30/1,300 mg);
HB/APAP M: 8 Tablets – HB/APAP (60/2,600 mg);
HB/APAP H: 12 Tablets – HB/APAP (90/3,900 mg);
P: Placebo.

2.3.1. Primary Analysis

2.3.1.1. Descriptive statistics

Table 1 summarizes the mean, standard deviation (SD), minimum (Min), the first quartile (Q1), median (Med), the third quartile (Q3), and maximum (Max) for the 6 treatments in the study for the primary endpoints Emax of Drug Liking VAS.

<table>
<thead>
<tr>
<th>TRT</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Q1</th>
<th>Med</th>
<th>Q3</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>HB/APAP L</td>
<td>72.5</td>
<td>16.46</td>
<td>50</td>
<td>60</td>
<td>68.5</td>
<td>82.5</td>
<td>100</td>
</tr>
<tr>
<td>HB/APAP M</td>
<td>83.4</td>
<td>16.41</td>
<td>50</td>
<td>71.75</td>
<td>86</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>HB/APAP H</td>
<td>87.4</td>
<td>15.63</td>
<td>50</td>
<td>78.75</td>
<td>93</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>KP201/APAP L</td>
<td>72.6</td>
<td>17.17</td>
<td>50</td>
<td>56.75</td>
<td>71.5</td>
<td>84</td>
<td>100</td>
</tr>
<tr>
<td>KP201/APAP M</td>
<td>82.4</td>
<td>16.42</td>
<td>50</td>
<td>69.25</td>
<td>83</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>KP201/APAP H</td>
<td>87.8</td>
<td>14.78</td>
<td>50</td>
<td>77.75</td>
<td>94</td>
<td>100</td>
<td>100</td>
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<td>50</td>
<td>50</td>
<td>51</td>
<td>51</td>
<td>69</td>
</tr>
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</table>

Table 1 shows that there is not much difference in means between each dose of KP201/APAP and corresponding dose of HB/APAP. Approximately 25% of subjects responded 100 for maximum liking, and median response is above 90 for both high dose of KP201/APAP and high dose of HB/APAP.

Figure 2 is the mean time course profiles by treatment for Drug Liking VAS. Note that the medium and high doses of both KP201/APAP and HB/APAP reach peak mean liking at hour 1.
Figure 1: The mean time course profiles in 12 hours on Drug Liking VAS by treatment (N=62)

The heat map display for Drug Liking Emax by treatment is in Figure 2. One may see how each subject responded to each treatment. The orange line separates females from males. In the graph, HBL, HBM, and HBL denote HB/APAP L, HB/APAP M and HB/APAP H, respectively, and KP201L, KP201M and KP201H denote KP201/APAP L, KP201/APAP M, and KP201/APAP H, respectively.
2.3.1.2. Statistical Testing

For examining the abuse-deterrent properties of K201/APAP, the reviewer studied the following comparisons.

1. KP201/APAP L versus HB/APAP L
2. KP201/APAP M versus HB/APAP M
3. KP201H/APAP H versus HB/APAP H
4. HB/APAP L versus P
5. HB/APAP M versus P
6. HB/APAP H versus P

The comparisons #4, #5 and #6 are for the study validation.
The statistical model used in the reviewer’s primary analysis was a mixed-effects model which included sequence, period and treatment as fixed effects, and subject as a random effect. With heteroscedasticity adjustment, the Shapiro-Wilk W-test on the residual was not significant for Drug Liking VAS (p=0.6494). Table 2 shows the least square mean, standard error and confidence interval for Drug Liking Emax for each treatment.

**Table 2: The least square mean estimates for Drug Liking Emax (N=62)**

<table>
<thead>
<tr>
<th>Treatments</th>
<th>LSMean</th>
<th>StdErr</th>
<th>95% CI LCL</th>
<th>UCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>KP201/APAP L</td>
<td>72.3</td>
<td>1.96</td>
<td>68.6</td>
<td>76.5</td>
</tr>
<tr>
<td>KP201/APAP M</td>
<td>82.3</td>
<td>1.94</td>
<td>79.1</td>
<td>87.0</td>
</tr>
<tr>
<td>KP201/APAP H</td>
<td>87.5</td>
<td>1.81</td>
<td>84.0</td>
<td>91.3</td>
</tr>
<tr>
<td>HB/APAP L</td>
<td>72.5</td>
<td>2.00</td>
<td>68.6</td>
<td>76.5</td>
</tr>
<tr>
<td>HB/APAP M</td>
<td>83.1</td>
<td>1.98</td>
<td>79.1</td>
<td>87.0</td>
</tr>
<tr>
<td>HB/APAP H</td>
<td>87.5</td>
<td>1.83</td>
<td>83.8</td>
<td>91.1</td>
</tr>
<tr>
<td>P</td>
<td>51.5</td>
<td>1.74</td>
<td>48.0</td>
<td>55.0</td>
</tr>
</tbody>
</table>

The following test was performed.

1. \( H_0 : \mu_{HB/APAP} - \mu_{KP201/APAP} \leq 0 \) vs. \( H_a : \mu_{HB/APAP} - \mu_{KP201/APAP} > 0 \),

where \( \mu_{HB/APAP} \) and \( \mu_{KP201/APAP} \) denote means of HB/APAP and KP201/APAP, respectively.

For study validation, test

2. \( H_0 : \mu_{HB/APAP} - \mu_P \leq 15 \) vs. \( H_a : \mu_{HB/APAP} - \mu_P > 15 \),

where \( \mu_P \) denotes placebo mean.

Table 3 shows the results from the primary analysis on Drug liking Emax. The primary analysis failed to demonstrate the mean of KP201/APAP was statistically significantly smaller than that of HB/APAP for all doses (p-values are 0.4658, 0.3631 and 0.5315 for low, medium, and high dose comparisons, respectively). The statistically significant results from the validation tests validated the study.

Reference ID: 3933492
Table 3: Primary analysis results on Drug Liking Emax (N=62)

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>LSmear Diff</th>
<th>StdErr</th>
<th>t value</th>
<th>P-value (Pr&gt;t)</th>
<th>95% CI LCL</th>
<th>95% CI UCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>HB/APAP L – KP201/APAP L</td>
<td>0.2</td>
<td>2.20</td>
<td>0.09</td>
<td>0.4658</td>
<td>-4.2</td>
<td>4.6</td>
</tr>
<tr>
<td>HB/APAP M – KP201/APAP M</td>
<td>0.8</td>
<td>2.17</td>
<td>0.35</td>
<td>0.3631</td>
<td>-3.5</td>
<td>5.1</td>
</tr>
<tr>
<td>HB/APAP H – KP201/APAP H</td>
<td>-0.2</td>
<td>1.91</td>
<td>-0.08</td>
<td>0.5315</td>
<td>-4.0</td>
<td>3.7</td>
</tr>
<tr>
<td>HB/APAP L – P</td>
<td>21.0</td>
<td>2.01</td>
<td>3.00</td>
<td>0.0035</td>
<td>17.0</td>
<td>25.0</td>
</tr>
<tr>
<td>HB/APAP M – P</td>
<td>31.6</td>
<td>1.99</td>
<td>8.33</td>
<td>&lt;.0001</td>
<td>27.6</td>
<td>35.6</td>
</tr>
<tr>
<td>HB/APAP H – P</td>
<td>36.0</td>
<td>1.85</td>
<td>11.38</td>
<td>&lt;.0001</td>
<td>32.3</td>
<td>39.7</td>
</tr>
</tbody>
</table>

Note: Since test #1 failed to reject the null for all doses with the abuse-deterrent margin 0, this implies test #1 would be failed to reject null when the abuse-deterrent margin is greater than 0.

2.3.2. Other Descriptive Statistics

Per Pharmacologist Dr. James Tolliver’s request, this reviewer provided Table 4 for descriptive statistics on High Emax and Take Drug Again Emax, and Table 5 for endpoints TEmax, AUE0.05, AUE0.1, and AUE0.2 for Drug Liking VAS.

Table 4: Summary statistics for High Emax and Take Drug Again Emax (N=62)

<table>
<thead>
<tr>
<th>Measures</th>
<th>TRT</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Q1</th>
<th>Med</th>
<th>Q3</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Effects</td>
<td>HB/APAP L</td>
<td>48.2</td>
<td>30.79</td>
<td>0</td>
<td>21.5</td>
<td>49</td>
<td>72.25</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>HB/APAP M</td>
<td>76.6</td>
<td>25.84</td>
<td>4</td>
<td>62</td>
<td>83.5</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>HB/APAP H</td>
<td>85.1</td>
<td>21.68</td>
<td>0</td>
<td>76</td>
<td>97</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>KP201/APAP L</td>
<td>49.6</td>
<td>32.98</td>
<td>0</td>
<td>16.5</td>
<td>56.5</td>
<td>72.25</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>KP201/APAP M</td>
<td>72.6</td>
<td>25.06</td>
<td>4</td>
<td>57.25</td>
<td>77</td>
<td>96</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>KP201/APAP H</td>
<td>85.5</td>
<td>19.32</td>
<td>9</td>
<td>76.5</td>
<td>95</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>2.6</td>
<td>9.79</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>67</td>
</tr>
<tr>
<td>Take Drug Again</td>
<td>HB/APAP L</td>
<td>66.3</td>
<td>20.65</td>
<td>37</td>
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<td>52</td>
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<td>100</td>
</tr>
<tr>
<td></td>
<td>HB/APAP M</td>
<td>66.0</td>
<td>28.30</td>
<td>0</td>
<td>49</td>
<td>66.5</td>
<td>94</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>HB/APAP H</td>
<td>66.5</td>
<td>25.51</td>
<td>0</td>
<td>49</td>
<td>63</td>
<td>94.5</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>KP201/APAP L</td>
<td>69.3</td>
<td>22.48</td>
<td>11</td>
<td>49</td>
<td>65</td>
<td>91.5</td>
<td>100</td>
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<tr>
<td></td>
<td>KP201/APAP M</td>
<td>71.5</td>
<td>23.28</td>
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<td>93</td>
<td>100</td>
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<td></td>
<td>KP201/APAP H</td>
<td>72.4</td>
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<td>49</td>
<td>50</td>
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</tbody>
</table>

Table 4 shows that there is no much difference in means between HB/APAP and KP201/APAP on High Emax as well as Take Drug Again Emax.

Table 5 shows summary statistics for endpoints TEmax, AUE0.05, AUE0.10 and AUE0.20 for Drug Liking VAS.
Table 5: Summary statistics of other endpoints for Drug Liking VAS (N=62)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>TRT</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Q1</th>
<th>Med</th>
<th>Q3</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HB/APAP H</td>
<td>1.9</td>
<td>3.39</td>
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<td>24</td>
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<tr>
<td></td>
<td>KP201H/APAP H</td>
<td>1.6</td>
<td>1.88</td>
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<td>0.5</td>
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<td>1.8</td>
<td>12</td>
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<tr>
<td></td>
<td>HB/APAP L</td>
<td>1.3</td>
<td>0.85</td>
<td>0.1</td>
<td>1</td>
<td>1.5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>KP201/APAP L</td>
<td>1.6</td>
<td>2.05</td>
<td>0.1</td>
<td>1</td>
<td>1.6</td>
<td>12</td>
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</tr>
<tr>
<td></td>
<td>HB/APAP M</td>
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<td>1.57</td>
<td>0.1</td>
<td>1</td>
<td>1.5</td>
<td>6</td>
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<tr>
<td></td>
<td>KP201/APAP M</td>
<td>2.1</td>
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<td>1.8</td>
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<td>P</td>
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<td>0.1</td>
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<tr>
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<td>HB/APAP H</td>
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<td>61</td>
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<tr>
<td></td>
<td>HB/APAP L</td>
<td>25.2</td>
<td>2.34</td>
<td>13</td>
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<td>25</td>
<td>25.3</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>KP201/APAP L</td>
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<td>25</td>
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<td>55.4</td>
<td>6.13</td>
<td>35</td>
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<td>54</td>
<td>61.0</td>
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<tr>
<td></td>
<td>KP201/APAP L</td>
<td>56.4</td>
<td>8.65</td>
<td>38</td>
<td>50</td>
<td>55</td>
<td>62.3</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>HB/APAP M</td>
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<td>10.26</td>
<td>45</td>
<td>56</td>
<td>62</td>
<td>69.3</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>KP201/APAP M</td>
<td>61.4</td>
<td>10.18</td>
<td>41</td>
<td>54</td>
<td>59</td>
<td>66.3</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>49.9</td>
<td>2.78</td>
<td>38</td>
<td>50</td>
<td>50</td>
<td>50.0</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>HB/APAP H</td>
<td>140.9</td>
<td>31.90</td>
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<td>125.5</td>
<td>144.5</td>
<td>163.0</td>
<td>187</td>
</tr>
<tr>
<td></td>
<td>KP201H/APAP H</td>
<td>143.3</td>
<td>29.59</td>
<td>43</td>
<td>125</td>
<td>146.5</td>
<td>164.5</td>
<td>186</td>
</tr>
<tr>
<td></td>
<td>HB/APAP L</td>
<td>122.5</td>
<td>19.76</td>
<td>96</td>
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<td>119</td>
<td>137.5</td>
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</tr>
<tr>
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<td>KP201/APAP L</td>
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<td>185</td>
</tr>
<tr>
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<td>HB/APAP M</td>
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<tr>
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<td>25.78</td>
<td>58</td>
<td>114.8</td>
<td>138.5</td>
<td>153.8</td>
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<tr>
<td></td>
<td>P</td>
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<td>5.80</td>
<td>74</td>
<td>100</td>
<td>100</td>
<td>100.0</td>
<td>120</td>
</tr>
</tbody>
</table>

All treatments had median TEmax at hour 1 post-dose except placebo.

2.4. Conclusion

The oral study KP201.A01 failed to demonstrate abuse-deterrent effects for KP201/APAP compared to HB/APAP.
3. Review report on Study KP201.A02

3.1. Overview

Study KP201.A02 was a randomized, double-blind, double-dummy, placebo-controlled, single-dose, two-Part, five-way crossover study to determine the relative bioavailability, abuse potential, and safety of equivalent doses of crushed and intact KP201/APAP compared with hydrocodone bitartrate/APAP (HB/APAP) and placebo in opioid-experienced, non-dependent subjects following Intranasal Administration.

3.1.1. Objectives of the study

Primary Objectives
- The primary objective of the Main Study (Part B) was to determine the abuse potential of crushed KP201/acetaminophen (KP201/APAP) relative to crushed hydrocodone bitartrate/APAP (HB/APAP) at the dose determined in the Dose Selection Phase (Part A) when administered intranasally to non-dependent, recreational opioid users.

Secondary Objectives
- The secondary objectives of the Main Study (Part B) were to determine the:
  - Abuse potential of crushed intranasal and intact oral KP201/APAP relative to placebo.
  - Relative bioavailability of KP201, hydrocodone, hydromorphone, and APAP in plasma from crushed intranasal and intact oral KP201/APAP compared with crushed intranasal and intact oral HB/APAP.
  - Safety of crushed intranasal and intact oral KP201/APAP compared with crushed intranasal and intact oral HB/APAP and placebo.

Exploratory Objective
- The exploratory objectives of the Dose Selection Phase (Part A) were to:
  - Evaluate the safety and pharmacodynamic (PD) effects of various doses of crushed KP201/APAP and crushed HB/APAP tablets administered intranasally to non-dependent, recreational opioid users and to determine the maximum tolerated dose (MTD) of crushed KP201/APAP and crushed HB/APAP.
  - Determine the relative bioavailability of KP201, hydrocodone, hydromorphone, and APAP in plasma from crushed tablets of KP201/APAP compared with crushed tablets of HB/APAP administered intranasally.
  - Determine the abuse potential of crushed intranasal KP201/APAP relative to placebo.

3.1.2. Study design

This was a single-center, randomized, double-blind, double-dummy, two-part study to assess the abuse potential of crushed KP201/APAP 6.67/325 mg tablets administered intranasally in opioid experienced, non-dependent users.
Since the relative bioavailability and PD effects of KP201/APAP and bioavailability and PD effects of HB/APAP when administered intranasally were not well known, the first part of this study (Part A) was designed to evaluate various doses of each drug. Part A included a Dose Selection Phase to identify the MTD of both the investigational drug KP201/APAP and the active comparator HB/APAP (HB/APAP®). The lowest IN dose of either KP201/APAP or HB/APAP that met the protocol specified criteria for insufflation, PD, and safety was to be selected in order to minimize subject exposure to APAP. The data collected in Part A were used to select a dose that was considered well tolerated and produced robust responses on PD measures for inclusion into the Main Study (Part B).

Overall, the study was conducted as follows:
- Dose Selection (Part A)
- Screening (Visit 1)
- Qualification Phase (Visit 2), including a Naloxone Challenge (Day -1) and Drug Discrimination Test (Days 1 to 3)
- Dose Selection Phase (Visit 3)

Main Study (Part B)
- Screening (Visit 1)
- Qualification Phase (Visit 2), including a Naloxone Challenge Test (Day -1) and Drug Discrimination Test (Days 1 to 3)
- Treatment Phase (Visits 3 to 7)
- Follow-up (Visit 8)

Study Treatments

Qualification Phase (Part A and Part B)
- Naloxone Challenge Test: An initial dose of 0.2 mg naloxone was administered by IV bolus. If no evidence of withdrawal occurred within 30 seconds, an additional 0.6 mg naloxone was administered by IV bolus.
- Drug Discrimination Test (Part A): Single IN doses of 40 mg HB API powder and weight-matched microcrystalline cellulose (placebo) powder.
- Drug Discrimination Test (Part B): Single IN doses of crushed HB/APAP (15/650 mg) tablets and weight-matched microcrystalline cellulose (placebo) powder.

Dose Selection Phase (Part A)
Subjects received a single dose of one of the following two treatments on one occasion:
- Single IN doses of crushed KP201/APAP tablets (6.67/325 mg up to 26.68/1300 mg) and weight-matched microcrystalline cellulose (placebo) powder (Treatment W).
- Single IN doses of crushed HB/APAP tablets (7.5/325 mg up to 30/1300 mg) and weight-matched microcrystalline cellulose (placebo) powder (Treatment X).

Main Study Treatment Phase (Part B):
Treatments A to E were administered to subjects in a randomized, crossover, double-blind, double-dummy manner.
- Treatment A - Placebo
Single IN dose of microcrystalline cellulose (placebo) powder and single oral dose of two lactose tablets, over-encapsulated

- **Treatment B - Oral intact KP201/APAP**
  Single IN dose of microcrystalline cellulose (placebo) powder and single oral dose of two tablets KP201/APAP (13.34/650mg), over-encapsulated

- **Treatment C - IN crushed KP201/APAP**
  Single IN dose of two crushed tablets KP201/APAP (13.34/650 mg) and single oral dose of two lactose tablets, over-encapsulated

- **Treatment D - In crushed HB/APAP**
  Single IN dose of two crushed tablets HB/APAP (15/650 mg) and single oral dose of two lactose tablets, over-encapsulated

- **Treatment E - Oral intact HB/APAP**
  Single IN dose of microcrystalline cellulose (placebo) powder and single oral dose of two tablets HB/APAP (15/650mg), over-encapsulated

### 3.1.3. Study subjects

For Part A, Dose Selection Phase, approximately 48 subjects (24 subjects per treatment arm) were planned. Fifty-one subjects received at least one dose of study drug, with 27 subjects in one treatment arm (subjects were to receive both KP201/APAP and placebo) and 24 subjects in the other treatment arm (subjects were to receive both HB/APAP and placebo).

For Part B, Treatment Phase, approximately 50 subjects were to be randomized to treatment to ensure 40 completers. Forty-six subjects were randomized in the Treatment Phase and 42 subjects completed all five treatment periods.

The following are sponsor’s flowcharts of subject disposition for Part A and B, respectively.
Sponsor’s Figure 3: Flowchart of Subject Disposition for Part A

AE=adverse event; CS=clinically significant; ICF=informed consent form; LTF=lost to follow-up; UDS=urine drug screen
Sponsor’s Figure 4. Flowchart of Subject Disposition for Part B

COWS=Clinical Opiate Withdrawal Scale; CS=clinically significant; ECG=electrocardiogram; LTF=lost to follow-up

a Four subjects (9037, 9146, 9147, and 9190) who had participated in Part A and entered the Qualification Phase for Part B did not have to repeat the naloxone challenge for participation in the Drug Discrimination Test for Part B in accordance with the protocol. Results for the naloxone challenge for these subjects are listed in Sponsor’s Data 2.5A (Appendix 16.4.1 data tabulation listings).

b Subject 9211 was withdrawn due to an adverse event (mild tachycardia). This subject also had a COWS score=8 (fail) and would not have been eligible to participate in the Drug Discrimination Test because the score exceeded 5 and indicated that the subject was dependent on opioids.

Source: The sponsor’s Figure 4.
3.1.4. Endpoints

**Primary endpoint**
Drug Liking maximum peak (Emax) effect measured on a visual analog scale (VAS) assessed during the Main Study Treatment Phase in Part B.

**Secondary endpoints**
- Drug Liking area under the effect curve (AUE) to 0.5 hours (AUE0-0.5), 1 hour (AUE0-1), 2 hours (AUE0-2), 4 hours (AUE0-4), 8 hours (AUE0-8), and 24 hours (AUE0-24) post-dose
- Drug Effects Questionnaire (DEQ) (i.e., Any Effects, Good Effects, Bad Effects, High, Sick, Nausea, Sleepy, Dizzy) Emax and AUE0-0.5, AUE0-1, AUE0-2, AUE0-4, AUE0-8, and AUE0-24
- Ease of Snorting VAS at 5 minutes after completion of IN drug administration

The time of Emax (TEmax) and Emin (TEmin) were also calculated as appropriate. Overall Drug Liking (ODL) and Take Drug Again (TDA) VAS were assessed by time point. The percent (%) reduction in the primary endpoint, Drug Liking Emax, relative to the corresponding reference dose and adjusted for placebo was calculated.

Other secondary PD endpoints included:
- Addiction Research Center Inventory-Morphine-Benzodrine Group Subscale (ARCI-MBG): Emax and TEmax
- Pupillometry Emax (maximum pupil constriction), TEmax, AUE0-0.5, AUE0-1, AUE0-2, AUE0-4, AUE0-8, and AUE0-24
- Percent of dose insufflated (mg %) was calculated using the weight of the dose recorded before and after the dose was insufflated

3.1.5. Statistical methodologies used in the Sponsor’s analyses

Statistical analysis of the primary endpoint Drug Liking Emax was performed using a mixed-effects model of analysis of variance (ANOVA) for the Completer Population. The model utilized SAS PROC MIXED to perform the analysis and included treatment (five levels), period (five levels), and sequence (10 levels) as fixed effects, and subject-nested-in-sequence as random effect. The method of variance components was used to define the covariance structure of the model, and the SAS Type III estimation was reported.

Based on the analysis of the ANOVA model, pairwise comparisons of least-squares means (LSMs) between individual treatments were conducted at the significance level of 0.05 (two-sided) for consistency with the 95% confidence interval (CI), using a model-based t-test. The differences of pairwise LSMs along with 95% CI were reported for each comparison. Based on equivalent dose, the primary null hypotheses of no difference in Drug Liking Emax between the reference drug and test drug were tested for the following comparisons:

- IN crushed HB/APAP versus IN crushed KP201/APAP
- Oral intact HB/APAP versus oral intact KP201/APAP

Given that a comparison reaches the significance level and the lower bound (i.e., one-sided at 0.025 level) of the 95% CI for the difference between the LSMs is greater than zero for the corresponding reference-to-test comparison, the proposed null hypothesis that Drug Liking Emax of
HB/APAP was equal to or less than KP201/APAP (H0: \( \mu_R - \mu_T \leq 0 \)) would therefore be rejected for the corresponding route of drug administration, and the alternative hypothesis that Drug Liking Emax of HB/APAP was greater than KP201/APAP (Ha: \( \mu_R - \mu_T > 0 \)) would be established for that route of drug administration.

- The following treatment comparisons were also evaluated for Drug Liking Emax:
  - IN crushed HB/APAP versus placebo
  - Oral intact HB/APAP versus placebo
  - IN crushed HB/APAP versus oral intact KP201/APAP
  - Oral intact HB/APAP versus IN crushed KP201/APAP
  - IN crushed KP201/APAP versus oral intact KP201/APAP
  - Oral intact KP201/APAP versus IN crushed HB/APAP
  - IN crushed KP201/APAP versus placebo
  - Oral intact KP201/APAP versus placebo

The comparison of the active control (HB/APAP) versus placebo determined the validity of the study design.

For the secondary PD endpoints, the same mixed-effects model and analytical approach described above for the primary endpoint, Drug Liking Emax, were used to evaluate, respectively, the secondary endpoints (Emax, AUE) for Drug Liking, DEQ, pupillometry, ARCI-MBG (Emax only), as well as VAS scores for ODL, TDA, and Ease of Snorting.

The percent (%) reduction of Drug Liking Emax for IN crushed or oral intact KP201/APAP relative to the corresponding IN crushed HB/APAP or oral intact HB/APAP treatment, was calculated using FDA recommended formula, and was grouped by an increment of 10%, ranging from \(<0\%\), \(0\%\), \(1-9\%\), \(10-19\%\), \(20-29\%\), \(30-39\%\), \(40-49\%\), \(50-59\%\), \(60-69\%\), \(70-79\%\), \(80-89\%\), \(90-99\%\), and \(\geq100\%\). Profile plots of % subjects over each category of % reduction of Drug Liking Emax were provided for each comparison. For the exploratory PD endpoints from Part A, descriptive statistics and select graphical displays for the mean scores at each time point were generated, as well as descriptive statistics of derived endpoints.

### 3.1.6. Sponsor’s Summary and Conclusions

**Pharmacodynamics summary for Part B, Main Study**

Study validity was confirmed by statistically significant (P<0.0001) differentiation of the positive control, HB/APAP, relative to placebo for the primary endpoint Drug Liking Emax. Differentiation was statistically significant for HB/APAP relative to placebo via both the oral and IN routes of administration.

Administration of IN crushed or oral intact KP201/APAP (13.34/650 mg) resulted in comparable results for Drug Liking Emax (primary endpoint) relative to IN crushed or oral intact HB/APAP (15/650 mg), a finding that was supported by subjective and objective measures related to abuse potential (i.e., Any Effects, Good Effects, High, TDA, ODL, pupillometry). The median observed time of Drug Liking Emax was longer for IN crushed KP201/APAP (1.1 hours) versus IN crushed HB/APAP (0.6 hours). Approximately 30% of subjects had at least a 30% reduction in Drug Liking
Emax for the comparisons of IN crushed KP201/APAP versus IN crushed HB/APAP and oral intact KP201/APAP versus oral intact HB/APAP. Differences in Drug Liking Emax were not statistically significant for any treatment comparisons evaluated for HB/APAP versus KP201/APAP, therefore, the primary endpoint of the study was not met.

Subjects indicated that insufflating crushed KP201/APAP was more difficult compared to crushed HB/APAP and the LSM difference in Ease of Snorting VAS scores were statistically significant (P=0.0100).

Conclusion
Administration of IN crushed or oral intact KP201/APAP (13.34/650 mg) resulted in similar subjective positive effects and physiological effects relative to IN crushed or oral intact HB/APAP (15/650 mg), indicating that KP201/APAP had a similar abuse potential profile compared to HB/APAP in recreational non-dependent opioid users. Hydrocodone, hydromorphone, and APAP exposures were similar for IN crushed KP201/APAP compared with IN crushed HB/APAP and for oral intact KP201/APAP compared with oral intact HB/APAP, though lower early exposure was observed for IN crushed KP201/APAP compared to IN crushed HB/APAP. The safety profile of KP201/APAP was comparable and characterized by higher adverse nasal effects following IN administration when compared to that of HB/APAP in recreational non-dependent opioid users.

3.2. Data Location
The data used in the reviewer’s analysis is:
\CDSESUB1\evsprod\NDA208653\0006\m5\datasets\kp201-a02\analysis\legacy\datasets.

3.3. Reviewer’s assessment
The following notations for the treatments were used in the reviewer’s analyses:

P: Placebo
KPi: KP201/APAP (13.34/650 mg) intact (oral treatment)
KPcIN: KP201/APAP (13.34/650 mg) crushed intranasal treatment
HBi: HB/APAP (15/650 mg) intact (oral treatment)
HBcIN: HB/APAP (15/650 mg) crushed intranasal treatment

3.3.1. Insufflation
Because this was an intranasal study, this reviewer examined the dose insufflation first. During the Treatment Phase, all 43 subjects were able to insufflate the crushed 2-tablet dose of HB/APAP (15/650 mg), while 38 of 44 subjects (86.4%) were able to insufflate the crushed 2-tablet
dose of KP201/APAP (13.34/650 mg). The following Sponsor’s Table 21 summarized the compliance of insufflation during Part B of the Treatment Phase.

Table 21. Treatment Compliance for the Treatment Phase in Part B

<table>
<thead>
<tr>
<th>Percent (%) of Dose Not Insufflated</th>
<th>IN placebo powder</th>
<th>Oral intact KP201/APAP (13.34/650 mg)</th>
<th>IN crushed KP201/APAP (13.34/650 mg)</th>
<th>IN crushed HB/APAP (15/650 mg)</th>
<th>Oral intact HB/APAP (15/650 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed insufflation, n (%)</td>
<td>37 (88.1)</td>
<td>41 (97.6)</td>
<td>38 (86.4)</td>
<td>43 (100.0)</td>
<td>42 (95.5)</td>
</tr>
<tr>
<td>Percent (%) dose not insufflated (range)</td>
<td>0.6 – 39.9</td>
<td>22.2 ± 2</td>
<td>0.4 – 9.2</td>
<td>NA</td>
<td>4.2 – 5.2</td>
</tr>
</tbody>
</table>

APAP=acetaminophen; HB=hydrocodone bitartrate; IN=intanasal; NA=not applicable

* data value for one subject

For oral intact treatments, data correspond to intranasal administration of placebo.

Source: Table 14.1.8.2

Table 6 summarizes the mean, standard deviation (SD), minimum, the first quartile (Q1), median (Med), the third quartile (Q3), and maximum for the 5 treatments in the study for Ease of Insufflation scores.

Table 6: Summary Statistics for Ease of Insufflation VAS

<table>
<thead>
<tr>
<th>TRT</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Q1</th>
<th>Med</th>
<th>Q3</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPcIN</td>
<td>44</td>
<td>58.6</td>
<td>35.7</td>
<td>0</td>
<td>31.25</td>
<td>72</td>
<td>84.75</td>
<td>100</td>
</tr>
<tr>
<td>HBcIN</td>
<td>43</td>
<td>42.3</td>
<td>32.8</td>
<td>0</td>
<td>13</td>
<td>41</td>
<td>68</td>
<td>100</td>
</tr>
<tr>
<td>KPcI</td>
<td>42</td>
<td>52.2</td>
<td>35.1</td>
<td>0</td>
<td>17.5</td>
<td>63</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>HPcI</td>
<td>44</td>
<td>43.5</td>
<td>34.7</td>
<td>0</td>
<td>6.75</td>
<td>44</td>
<td>72.75</td>
<td>100</td>
</tr>
<tr>
<td>P</td>
<td>42</td>
<td>50.5</td>
<td>34.5</td>
<td>0</td>
<td>16</td>
<td>53</td>
<td>86</td>
<td>100</td>
</tr>
</tbody>
</table>

Ease of Insufflation VAS is a bipolar measure. Subjects responded to the statement “Insufflation the drug was:” at 5 minutes after the snorting the drug. The question was scored using a 0-100 point, unipolar VAS anchored on the left with “very easy” (score of 0) and anchored on the right with “very difficult” (score of 100). It appears crushed KP201/APAP was relatively difficult insufflated compared to crushed HB/APAP.

3.3.2. Primary Analysis

3.3.2.1. Descriptive Statistics

Table 6 summarizes the mean, standard deviation (SD), minimum (Min), the first quartile (Q1), median (Med), the third quartile (Q3), and maximum (Max) for the 4 treatments in the study for the primary endpoint Emax of Drug Liking VAS.
Table 7: Summary statistics for Drug Liking Emax (N=42)

<table>
<thead>
<tr>
<th>TRT</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Q1</th>
<th>Med</th>
<th>Q3</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeIN</td>
<td>79.0</td>
<td>17.59</td>
<td>50</td>
<td>64.75</td>
<td>80</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>HBi</td>
<td>77.9</td>
<td>16.71</td>
<td>50</td>
<td>64.75</td>
<td>74.5</td>
<td>99.25</td>
<td>100</td>
</tr>
<tr>
<td>KPcIN</td>
<td>75.9</td>
<td>15.08</td>
<td>50</td>
<td>64.5</td>
<td>74</td>
<td>88.25</td>
<td>100</td>
</tr>
<tr>
<td>KPi</td>
<td>76.9</td>
<td>17.28</td>
<td>50</td>
<td>63.5</td>
<td>76</td>
<td>93.25</td>
<td>100</td>
</tr>
<tr>
<td>P</td>
<td>53.0</td>
<td>7.68</td>
<td>50</td>
<td>50</td>
<td>51</td>
<td>51</td>
<td>85</td>
</tr>
</tbody>
</table>

Figure 3 is the mean time course profiles by treatment for Drug Liking VAS. The peak mean responses of HB/APAP intact, KP201/APAP intact and KP201/APAP crushed (IN) are reached at hour 1. HB/APAP crushed (IN) reaches peak at hour 0.5.

Figure 3: The mean time course profiles on Drug Liking VAS by treatment (N=42)

Figure 4 is the heat map display for Drug Liking Emax by treatment. Note that two subjects (ID 9009 and ID 9241) had high placebo responses on Drug Liking Emax.
3.3.2.2. Statistical testing

For examining the abuse-deterrent properties of KP201/APAP, the reviewer studied the following comparisons:

1. KPcIN versus BHcIN (Primary)
2. KPi versus BHi (Secondary)
3. BHcIN versus P (Study validation)
4. BHi versus P (validation for the secondary comparison)

Corresponding hypotheses for these comparisons on Drug Liking Emax are listed below:

1. $H_0: \mu_{BHcIN} - \mu_{KPcIN} \leq 0$ versus $H_a: \mu_{BHcIN} - \mu_{KPcIN} > 0$,
2. $H_0: \mu_{BHi} - \mu_{KPi} \leq 0$ versus $H_a: \mu_{BHi} - \mu_{KPi} > 0$.

Study validation
3. \( H_0: \mu_{\text{HBclN}} - \mu_p \leq 15 \) versus \( H_a: \mu_{\text{HBclN}} - \mu_p > 15 \).
4. \( H_0: \mu_{\text{Hbi}} - \mu_p \leq 15 \) versus \( H_a: \mu_{\text{Hbi}} - \mu_p > 15 \).

The same statistical model and analysis method as Study KP201.A01 were used in this study.

Tables 7 and 8 provide the results from the statistical analysis.

**Table 8: The least square mean estimates for Drug Liking Emax (N=42)**

<table>
<thead>
<tr>
<th>TRT</th>
<th>LSmear</th>
<th>StdErr</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>LCL</td>
</tr>
<tr>
<td>HBclN</td>
<td>79.0</td>
<td>2.54</td>
<td>73.9</td>
</tr>
<tr>
<td>HBi</td>
<td>77.8</td>
<td>2.49</td>
<td>72.8</td>
</tr>
<tr>
<td>KPcIN</td>
<td>75.9</td>
<td>2.30</td>
<td>71.3</td>
</tr>
<tr>
<td>KPi</td>
<td>76.9</td>
<td>2.60</td>
<td>71.6</td>
</tr>
<tr>
<td>P</td>
<td>53.0</td>
<td>1.61</td>
<td>49.4</td>
</tr>
</tbody>
</table>

**Table 9: Results from the statistical analysis on Drug Liking Emax (N=42)**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Test value</th>
<th>LSmear Diff</th>
<th>StdErr</th>
<th>t-value</th>
<th>Pr &gt; t</th>
<th>Two-sided 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LCL</td>
</tr>
<tr>
<td>HBclN - KPcIN</td>
<td>0.00</td>
<td>3.1</td>
<td>3.16</td>
<td>0.98</td>
<td>0.1654</td>
<td>-3.3</td>
</tr>
<tr>
<td>HBi - KPi</td>
<td>0.00</td>
<td>1.0</td>
<td>3.35</td>
<td>0.29</td>
<td>0.3851</td>
<td>-5.7</td>
</tr>
<tr>
<td>HBclN - P</td>
<td>15</td>
<td>26.0</td>
<td>2.70</td>
<td>4.09</td>
<td>0.0001</td>
<td>20.6</td>
</tr>
<tr>
<td>HBi - P</td>
<td>15</td>
<td>24.9</td>
<td>2.65</td>
<td>3.73</td>
<td>0.0003</td>
<td>19.6</td>
</tr>
</tbody>
</table>

Table 9 shows that crushed KP201/APAP does not have statistically significant lower mean response compared to crushed HB/APAP though intranasal route (\( p=0.1654 \)). This table also shows that KP201/APAP intact does not have statistically significant lower mean response compared to HB/APAP intact (\( p=0.3851 \)), which supports the results from Study KP201.A01. The statistically significant mean differences between crushed HB/APAP and Placebo, and between HB/APAP intact and placebo with margin 15 (\( p=0.0001 \) and 0.0003, respectively) on Drug Liking Emax validated study.

**3.3.3. Other descriptive statistics and supportive analysis**

Per Pharmacologist Dr. James Tolliver's request, this reviewer provided descriptive statistics for High Emax and Take Drug Again Emax in Table 9, and for endpoints TEmax, AUE\(_{0.05}\), AUE\(_{0.1}\), and AUE\(_{0.2}\) for Drug Liking VAS in Table 10.
Table 10: Summary statistics for High Emax and Take Drug Again Emax (N=42)

<table>
<thead>
<tr>
<th>Measure</th>
<th>TRT</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Q1</th>
<th>Med</th>
<th>Q3</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>HBCn</td>
<td>59.1</td>
<td>32.74</td>
<td>0</td>
<td>28.75</td>
<td>67.5</td>
<td>85.25</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>HBI</td>
<td>60.3</td>
<td>31.54</td>
<td>0</td>
<td>37.75</td>
<td>69</td>
<td>84.5</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>KPCI</td>
<td>61.8</td>
<td>30.13</td>
<td>0</td>
<td>39</td>
<td>68.5</td>
<td>84</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>KPI</td>
<td>61.2</td>
<td>33.24</td>
<td>0</td>
<td>32.75</td>
<td>70</td>
<td>88</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>8.8</td>
<td>24.56</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>Take Drug</td>
<td>HBCn</td>
<td>74.5</td>
<td>25.54</td>
<td>0</td>
<td>55</td>
<td>81.5</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Again</td>
<td>HBI</td>
<td>75.6</td>
<td>23.59</td>
<td>0</td>
<td>61.75</td>
<td>75</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>KPCI</td>
<td>69.5</td>
<td>25.11</td>
<td>0</td>
<td>52.5</td>
<td>68</td>
<td>97</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>KPI</td>
<td>73.3</td>
<td>26.46</td>
<td>0</td>
<td>51</td>
<td>78.5</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>48.2</td>
<td>14.55</td>
<td>0</td>
<td>50</td>
<td>50</td>
<td>51</td>
<td>100</td>
</tr>
</tbody>
</table>

Since the study failed for the primary analysis, usually the secondary analysis would not be conducted. For the AC meeting, this reviewer provided the analysis results for secondary endpoints High Emax and Take Drug Again Emax in Table 11, and descriptive statistics for TEmax, AUE0.05, AUE0.10, and AUE0.20 in Table 12.

Table 11: Analysis Results for High Emax and Take Drug Again Emax (N=42)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Comparison</th>
<th>Mean Diff</th>
<th>StdErr</th>
<th>t-value</th>
<th>Pr &gt; t</th>
<th>Two-sided 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LCL</td>
</tr>
<tr>
<td>High</td>
<td>HBCn - KPCI</td>
<td>-2.6</td>
<td>4.23</td>
<td>-0.62</td>
<td>0.7304</td>
<td>-11.2</td>
</tr>
<tr>
<td></td>
<td>HBI - KPI</td>
<td>-0.8</td>
<td>4.96</td>
<td>-0.17</td>
<td>0.8674</td>
<td>-10.8</td>
</tr>
<tr>
<td>Take Drug</td>
<td>HBCn - KPCI</td>
<td>5.0</td>
<td>3.43</td>
<td>1.44</td>
<td>0.1569</td>
<td>-2.0</td>
</tr>
<tr>
<td>Again</td>
<td>HBI - KPI</td>
<td>2.4</td>
<td>4.16</td>
<td>0.57</td>
<td>0.2872</td>
<td>-6.1</td>
</tr>
</tbody>
</table>
Table 12: Summary statistics of other endpoints for Drug Liking VAS (N=42)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>TRT</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Q1</th>
<th>Med</th>
<th>Q3</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>T_Emax</td>
<td>HbCN</td>
<td>1.0</td>
<td>1.09</td>
<td>0.1</td>
<td>0.3</td>
<td>0.6</td>
<td>1.1</td>
<td>6.1</td>
</tr>
<tr>
<td></td>
<td>Hbi</td>
<td>2.0</td>
<td>3.58</td>
<td>0.1</td>
<td>1.1</td>
<td>1.1</td>
<td>1.7</td>
<td>24.1</td>
</tr>
<tr>
<td></td>
<td>KpCN</td>
<td>1.8</td>
<td>3.66</td>
<td>0.1</td>
<td>0.5</td>
<td>1.1</td>
<td>2.1</td>
<td>24.1</td>
</tr>
<tr>
<td></td>
<td>Kpi</td>
<td>2.0</td>
<td>3.70</td>
<td>0.1</td>
<td>0.6</td>
<td>1.3</td>
<td>1.7</td>
<td>24.1</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.8</td>
<td>1.42</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>1.1</td>
<td>8</td>
</tr>
<tr>
<td>AUE_{0.5}</td>
<td>HbCN</td>
<td>36.1</td>
<td>8.90</td>
<td>22</td>
<td>29</td>
<td>33</td>
<td>12</td>
<td>56</td>
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<tr>
<td></td>
<td>Hbi</td>
<td>29.2</td>
<td>4.59</td>
<td>5</td>
<td>28.75</td>
<td>29</td>
<td>2.5</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>KpCN</td>
<td>30.2</td>
<td>6.31</td>
<td>10</td>
<td>28</td>
<td>29.5</td>
<td>4</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>Kpi</td>
<td>30.8</td>
<td>3.88</td>
<td>23</td>
<td>29</td>
<td>29</td>
<td>3.25</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>27.6</td>
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<td>6</td>
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<tr>
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<td>16.39</td>
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<td>71</td>
<td>88.5</td>
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</tr>
<tr>
<td></td>
<td>Hbi</td>
<td>62.3</td>
<td>11.57</td>
<td>12</td>
<td>55</td>
<td>63</td>
<td>69.25</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>KpCN</td>
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<td>55.75</td>
<td>63</td>
<td>68.25</td>
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<td></td>
<td>Kpi</td>
<td>63.7</td>
<td>11.72</td>
<td>32</td>
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<td>71</td>
<td>93</td>
</tr>
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<td>P</td>
<td>52.9</td>
<td>6.07</td>
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<td>54</td>
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</tr>
<tr>
<td>AUE_{2.0}</td>
<td>HbCN</td>
<td>141.8</td>
<td>30.30</td>
<td>101</td>
<td>117.25</td>
<td>136.5</td>
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<td>205</td>
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<tr>
<td></td>
<td>Hbi</td>
<td>131.9</td>
<td>25.05</td>
<td>46</td>
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<td>130</td>
<td>149</td>
<td>173</td>
</tr>
<tr>
<td></td>
<td>KpCN</td>
<td>129.8</td>
<td>26.63</td>
<td>62</td>
<td>113.75</td>
<td>124.5</td>
<td>144</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>Kpi</td>
<td>131.7</td>
<td>26.32</td>
<td>60</td>
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<td>130.5</td>
<td>150</td>
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<td></td>
<td>P</td>
<td>102.4</td>
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<td>43</td>
<td>102.75</td>
<td>104</td>
<td>105</td>
<td>143</td>
</tr>
</tbody>
</table>

The median T_Emax_were 0.5 and 1.1 for crushed HB/APAP IN and crushed KP201/APAP IN respectively.

3.4. Conclusion

Study KP201.A02 did not demonstrate abuse-deterrent effects for KP201/APAP compared to HB/APAP through intranasal route. The results from the comparison between KP201/APAP intact and HB/APAP intact also supported the conclusion from Study KP201.A01, that is, KP201/APAP does not have abuse deterrent effects compared to HB/APAP through oral route.

4. Review report on Study KP201.A03

4.1. Overview

KP201-A03 is a randomized double-blind, single-dose, two-way crossover study to determine the relative bioavailability of equivalent doses of KP201 API compared with hydrocodone bitartrate API in opioid experienced, non-dependent subjects, following intranasal administration.
4.1.1. Objectives of the study

Primary Objective was:

- To compare the rate and extent of absorption of hydrocodone and hydromorphone from KP201 active pharmaceutical ingredient (API), 13.34 mg relative to hydrocodone bitartrate (HB) API, 15.00 mg when administered intranasally to non-dependent, recreational opioid users.

Secondary Objectives were:

- To determine the abuse potential of KP201 API relative to HB API when administered intranasally to non-dependent, recreational opioid users; and
- To determine the safety of KP201 API compared with HB API following intranasal administration in non-dependent, recreational opioid user.

4.1.2. Study design

This was a randomized, double-blind, single-dose, two-way crossover, single-center study in recreational non-dependent opioid users. Subjects participated in a Screening Phase (Visit 1), Naloxone Challenge Test (Visit 2, Check-in), Treatment Phase (Visit 2, inpatient) and Follow-up Phase (Visit 3).

Study participation was approximately 41 days for individual subjects (depending on the actual days of Screening and Follow-up Visits). A sufficient number of male and female subjects between the ages of 18-55 years were to be screened in order to enroll approximately 30 subjects into the Treatment Phase to ensure 24 completers. Within 28 days of the Screening Visit (Visit 1), subjects returned to the study center and underwent a Naloxone Challenge Test (Visit 2) to confirm that they were not physically dependent on opioids. A minimum washout interval of 12 hours was required between the Naloxone Challenge Test and first study drug administration in the Treatment Phase. Following the Naloxone Challenge Test, eligible subjects were randomized to the inpatient Treatment Phase. Study drug administration occurred on Day 1 and Day 4 of the Treatment Phase (i.e., washout intervals of approximately 72 hours). Subjects received each of the following treatments in a randomized, double-blind, crossover manner following an overnight fast of at least 8 hours:

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

Subjects were randomized in a 1:1 ratio to 1 of 2 treatment sequences according to a Williams Square design. On each day of dosing, subjects received the drug at approximately 8:00 a.m. (±3 hours). Serial PK samples were obtained pre-dose and up to 24 hours after each study drug administration. Drug liking assessments were collected up to 8 hours after each study drug administration. Pupillometry and nasal effects measures were
collected pre-dose (pupillometry only) and up to 24 hours after each study drug administration. Safety monitoring included recording of adverse events (AEs), vital signs measurements, 12-lead electrocardiogram (ECG) findings, and clinical laboratory assessments.

Subjects remained in the study clinic for at least 24 hours following the last dose of study medication. A Follow-up Phase (Visit 3) was conducted approximately 4 to 8 days (Day 11±2) following discharge from the Treatment Phase or after Early Termination (ET) from the study. Any subject who withdrew prior to completion of the study completed an ET assessment.

4.1.3. Abuse potential measures and endpoints of interest

Pharmacodynamic (PD) Assessments:
- Drug Liking (collected at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours post-dose) on a bipolar 0--100 point visual analog scale (VAS).
- Pupillometry (mm dilation) at pre-dose (within 1 hour prior to dosing) and at 0.083, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours post-dose.
- Ease of Insufflation VAS (collected within 5 minutes of completion of drug administration) on a unipolar 0-100 point VAS.

The following PD parameters were calculated for applicable PD measures (Drug Liking VAS and pupillometry):
- Emax: The peak effect.
- TEmax: The time of peak effect.
- AUE0-xh: The area under the effect curve to x hours, where x is 0.5, 1, 2, 4, 8 and 24 (pupillometry only) hours.

4.1.4. Study subjects

A total of 66 subjects (33 subjects in Cohort 1; 33 subjects in Cohort 2) were enrolled into the study. An additional group of subjects (Cohort 2) was enrolled as the integrity of the PK samples collected in Cohort 1 (original planned sample size of approximately 30 subjects) was compromised due to incorrect blood sample processing. Fifty-four subjects (27 subjects per sequence) were subsequently randomized to the Treatment Phase and received at least 1 dose of study drug. Cohort 1 consisted of 28 randomized subjects, and Cohort 2 consisted of 26 randomized subjects. Fifty-one (94.4%) subjects completed both treatment periods.
4.1.5. Statistical methodologies used for summarizing PD data

All PD parameters of interest and endpoints were be summarized by treatment using descriptive statistics (e.g., n, arithmetic means, standard deviations [SD], medians, minima, maxima, first and third quartile limits, and coefficients of variation [CVs]) for subjects who complete both periods. In addition, the percent dose insufflated was calculated and presented by treatment using descriptive statistics.

No statistical analysis was performed with the collected PD data

4.1.6. Pharmacodynamic Results

The Sponsor reported that Intranasal KP201 API had a lower mean and median Drug Liking VAS Emax compared to the positive control, intranasal HB API. Furthermore, TEmax was longer for KP201 API compared with HB API (1.1 hours vs. 0.5 hour). AUE values were generally smaller for KP201 API compared with HB API.

- Most subjects showed some reduction in Drug Liking VAS scores following intranasal administration of KP201 API relative to HB API; however, 16 (31.4%) subjects did not show any reduction in Drug Liking following intranasal administration of KP201 API. Approximately 45% of subjects showed at least a 30% reduction in Drug Liking VAS Emax following intranasal administration of KP201 API compared to HB API, and ~29% showed at least a 50% reduction.
- Intranasal administration of KP201 API resulted in smaller Emax (defined as a reduction from pre-dose) for pupillometry compared to HB API, and TEmax was longer for KP201 API compared with HB API (2.0 hours vs. 1.0 hour). AUE values were generally smaller for HB API (i.e., greater constriction) compared with KP201 API.
- Mean (SD) Ease of Insufflation VAS score was higher following intranasal administration of KP201 API (78.7 [20.0]) relative to HB API (65.6 [26.3]), indicating that KP201 API was more difficult to insufflate compared with HB API powder.
- There was no clear relationship between hydrocodone/hydromorphone exposure and response on Drug Liking VAS; however, there was an inverse relationship between plasma hydrocodone/hydromorphone concentration and pupil diameter.

4.2. Data Location

The data used in the reviewer’s analysis is located at

\CDSESUB1\evsprod\NDA208653\0006\m5\datasets\kp201-a03\analysis\legacy\datasets.
4.3. Reviewer’s assessment

The study was not designed for the evaluation of PD abuse-deterrent effects for KP201/APAP due to the following reasons:

- Study involved insufflation of KP201 API and HB API, and not the products KP201/APAP and HB/APAP.
- There was no Drug Discrimination (Qualification) Phase intended to select subjects having an appropriate placebo and active comparator response using the Drug Liking VAS.
- There was no placebo treatment in the Treatment Phase of the study.
- There were no additional subjective reinforcing measures (i.e., High VAS or Take Drug Again VAS) conducted which could be used to support observed effects on the Drug Liking VAS.

Thus, no inferential statistics was performed with the PD data from this study by the reviewer.

The sponsor defined the Completers Population as the primary population for the PD evaluation as follows:

Completers population: included all randomized subjects who completed both periods of the Treatment Phase and contributed at least one post-dose PK time point from each period. Subjects who experienced sneezing up to 1 hour after insufflation of study drug were not included for that period. This population was analyzed as the primary population for PD analysis.

Because the data handling problem with blood sample, the PK study did not include Cohort 1. Based on the definition of the Completers Population, the PD evaluation should also exclude Cohort 1.

In the following sections, the reviewer provided descriptive statistics for Cohort 2.

4.3.1. Descriptive statistics

Table 13 summarizes the mean, standard deviation (SD), minimum, the first quartile (Q1), median (Med), the third quartile (Q3), and maximum of Drug Liking Emax, TEmax, AUE_{0:0.5}, AUE_{0:1.0} and AUE_{0:2.0} for Cohort 2.
Table 13: Summary statistics for Drug Liking Emax for Cohort 2 (N=25)

<table>
<thead>
<tr>
<th>Measure</th>
<th>TRT</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Q1</th>
<th>Med</th>
<th>Q3</th>
<th>Max</th>
</tr>
</thead>
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<td>82.5</td>
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<td>13.42</td>
<td>50</td>
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<td>67</td>
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<td>TEmax</td>
<td>HBAPI</td>
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<td>0.83</td>
<td>0.3</td>
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<td>4</td>
</tr>
<tr>
<td></td>
<td>KP201API</td>
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<td>1.14</td>
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<td>0.3</td>
<td>1</td>
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<td>78</td>
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</table>

Figure 5 is the mean time course profiles by treatment for Drug Liking Emax for Cohort 2.

![Graph showing mean response over time for HBAPI and KP201API treatments.](image)

Figure 5: Mean time course profiles by treatment for Drug Liking VAS (Cohort 2, N=25)

Figure 5 shows that mean course profile of HB API for Drug Liking VAS of Cohort 2 rose to a peak of ~69 at 0.5 hour post-dose, whereas the mean scores of KP201-API rose to ~64 at 1.0 hour and kept ~64 to 1.5 hour post-dose (63.64 and 64.16, respectively), with a peak score of ~64.
Figure 6 is the heat map display for Drug Liking Emax by treatment for Cohort 2. Above the orange line are female responses.

**Figure 6: Heat map display for Drug Liking Emax by treatment for Cohort 2 (N=25)**

### 4.3.2. Evaluation of Ease for Insufflation

Percent of dose insufflated (% mg) using the weights recorded before and after each dose was insufflated was not recorded in this study. Data were collected for Ease of Insufflation VAS (a bipolar scale). This scale assesses the difficulty of insufflation of the study drugs. Subjects responded to the statement “Insufflation the drug was:” at 5 minutes after the snorting the drug. The question was scored using a 0-100 point, unipolar VAS anchored on the left with “very easy” (score of 0) and anchored on the right with “very difficult” (score of 100).

Table 13 summarizes the scores for EASE of Insufflation based on all subjects who had a score to this measure.
Table 14: Summary Statistics for Ease of Insufflation VAS

<table>
<thead>
<tr>
<th>TRT</th>
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<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Q1</th>
<th>Med</th>
<th>Q3</th>
<th>Max</th>
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</thead>
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<td>HBAPI (B)</td>
<td>54</td>
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<td>26.4</td>
<td>18</td>
<td>40</td>
<td>75</td>
<td>91.25</td>
<td>100</td>
</tr>
<tr>
<td>KP201API (A)</td>
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<td>79.0</td>
<td>19.83</td>
<td>33</td>
<td>66</td>
<td>87.5</td>
<td>92.75</td>
<td>100</td>
</tr>
<tr>
<td>A-B (AB)</td>
<td>27</td>
<td>20.3</td>
<td>29.06</td>
<td>-43</td>
<td>0</td>
<td>14</td>
<td>45</td>
<td>82</td>
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<tr>
<td>A-B (BA)</td>
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<td>6.9</td>
<td>18.33</td>
<td>-17</td>
<td>-3</td>
<td>1</td>
<td>14</td>
<td>51</td>
</tr>
</tbody>
</table>

Figure 7 shows the heat map for Ease of Insufflation scores by treatment sequences AB or BA. The grey indicates missing. From the graph, there is sequence effect on responses to Ease of Insufflation VAS.

Note: Grey indicates missing.

Figure 7: Heat map for Ease of Insufflation VAS by treatment sequences.
From Table 13 and Figure 7, one may see the mean difference in ease of insufflation scores between KP201 API and HB API. However, the magnitude of the mean difference was different between two sequences, which may be due to period and treatment interaction.

4.4. Conclusion

Because the study was not designed for PD statistical analysis, no conclusion can be made from this study on PD measures.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LING CHEN
05/18/2016

QIANYU DANG
05/18/2016
STATISTICAL REVIEW AND EVALUATION

OBSERVATIONAL STUDIES

NDA Number: 208653

Drug Name: benzhydrocodone-hydrochloride/acetaminophen (KP201/APAP)

Indications: short-term (no more than 14 days) management of acute pain

Applicant: KemPharm

Date(s): NDA submitted on December 09, 2015
Review completed on May 16, 2016

Review Priority: Priority

Biometrics Division: Division of Biometrics VII

Statistical Reviewer: Kunthel By, PhD
Concurring Reviewers: Stephine Keeton, PhD; Mark Levenson, PhD

Epidemiological Division: Office of Surveillance and Epidemiology

Epidemiological Team: Cynthia Kornegay, PhD; Jana McAninch, MD

Project Manager: Davis Mathew
Executive Summary

The sponsor submitted NDA 208653 seeking approval for benzhydrocodone hydrochloride and acetaminophen combination, an abuse-deterrent formulation for hydrocodone/APAP combination. Based on the results from three abuse potential clinical studies, the sponsor is seeking abuse-deterrent labeling language for both oral and intra-nasal routes of administration.

It was important for FDA to understand why intra-nasal abuse of IR hydrocodone combination products is a relevant route of administration. The sponsor conducted observational epidemiological studies using data collected by surveillance systems. Based on the results of these studies, the sponsor maintained that intra-nasal abuse is a relevant route of abuse for IR hydrocodone combination products.

We approach the question of relevance of intra-nasal abuse of IR hydrocodone combination products using two criteria:

- **Scope**: is this ROA pervasive in the population? How many individuals in the population are abusing IR hydrocodone combination products intra-nasally?

- **Severity**: how severe are the AEs associated with this ROA? What are the health consequences of intra-nasal abuse of IR hydrocodone combination products and how serious are they?

In principle, if intra-nasal abuse of IR hydrocodone combination products satisfies the scope and severity criteria, then it could be considered a relevant route of administration. Unfortunately, what the data enable us to conclude about scope and severity is limited. This limitation stems, in part, from the fact that:

- the underlying sampling mechanism that determines how individuals from the underlying populations are captured by the surveillance systems cannot be quantified. Therefore, it is very difficult to determine whether estimated prevalence of intra-nasal abuse of IR hydrocodone combination products observed in the sample are valid for prevalence of intra-nasal abuse of IR hydrocodone combination products in the underlying population.

- the size and specific characteristics of the underlying population is unknown. Therefore, even if the estimated prevalence generalizes to the underlying population, it is still not possible to know how extensive (scope) is the problem of intra-nasal abuse of IR hydrocodone combination products.

The underlying population from which the ASI-MV data arose can be characterized as consisting of adults who are at high-risk of substance abuse. Within this population, we are interested in assessing the scope of the problem of intra-nasal abuse of IR hydrocodone combination products. What we are able to understand from the sample however is that a lower bound for the number of intra-nasal abuse of IR hydrocodone combination products within this population is approximately 2122 for the period from 2014Q1 to 2015Q2. Using auxiliary data from a 2013 TEDS report published by the Substance Abuse and Mental Health Services Administration, we obtained a more informative lower bound for the number of intra-nasal abuse of IR hydrocodone combination products within this underlying population: 34,830 cases.
We can also obtain a lower bound for the underlying adolescent population from which the CHAT data arose. This underlying population can be characterized as consisting of adolescents who are at high-risk of substance abuse. Within the TEDS 2013 admissions, there were 101665 individuals between the ages of 12 and 18, not including 18. After applying the estimates from the CHAT study, a lower bound for the number of intra-nasal abuse of IR hydrocodone combination products within the underlying high-risk adolescent population is approximately 1579.

Whether these lower bound information on intra-nasal abuse of IR hydrocodone combination products are sufficient to make a determination of scope is beyond the capabilities of the statistical analyses.

Even if intra-nasal abuse of IR hydrocodone combination products satisfies the scope criterion, the other important criterion is severity. The ASI-MV study compares counts of intra-nasal abuse of IR hydrocodone combination products to other opioid categories such as ERLAs. Such a comparison could be meaningful if the health consequences of snorting IR hydrocodone combination products are similar to the health consequences of snorting other opioids. However, there is little information captured by the surveillance systems that could provide a basis for making statements about severity of intra-nasal abuse of IR hydrocodone combination products.
1 Introduction

On December 09, 2015 KemPharm submitted NDA 208653 seeking approval for benzhydrocodone hydrochloride (HCl) and acetaminophen (APAP) combination (KP201/APAP). KP201/APAP is a fixed-dose (6.67mg/325mg) abuse-deterrent formulation of immediate-release (IR) hydrocodone/APAP (KemPharm, 2015c) with a proposed indication for the short-term (no more than 14 days) management of acute pain. KP201/APAP is an abuse-deterrent formulation because benzhydrocodone is an inactive prodrug; activation from benzhydrocodone to the opioid analgesic hydrocodone requires interaction with enzymes in the intestinal tract (KemPharm, 2015d, Section 9.2, p. 9). If approved, KP201/APAP will be the first abuse-deterrent IR hydrocodone combination product.

The sponsor conducted three abuse potential clinical studies:

- KP201/APAP Oral Human Abuse Liability Study
- KP201/APAP Intranasal Human Abuse Liability Study
- KP201/APAP Benzhydrocodone Intranasal Pharmacokinetic Study

Based on the results of these studies, the sponsor claimed (KemPharm, 2015d, Section 9.2, p. 14) that KP201/APAP’s abuse-deterrent properties

... reduce exposure to active hydrocodone when more than the recommended oral dose is consumed at one time or when benzhydrocodone HCl is administered intra-nasally with or without APAP.

Furthermore,

... KP201/APAP and benzhydrocodone HCl are more difficult to snort than hydrocodone/APAP and hydrocodone bitartrate ...

The sponsor also claimed that non-clinical studies show that KP201/APAP is resistant to physical and chemical tampering (KemPharm, 2015c).

Based on the totality of these results, the sponsor is seeking abuse-deterrent labeling language in accordance with the FDA’s abuse-deterrent and labeling guidance (US Food and Drug Administration, 2015).

In the evaluation of this NDA submission, one issue that is important for FDA to consider is whether intra-nasal abuse is a relevant route of administration (ROA) for hydrocodone/APAP combination products and whether the sponsor should obtain labeling for it (Section 9.2 KemPharm, 2015d, page 15)

... the clinical data indicate that KP201/APAP has pharmacological properties which reduce exposure to active hydrocodone when more than the recommended oral dose is consumed at one time or when benzhydrocodone HCl is administered intra-nasally with or without APAP. Ease of insufflation scores from both Study 2 and Study 3 indicate that KP201/APAP and benzhydrocodone HCl are more difficult to snort than hydrocodone/APAP and hydrocodone bitartrate, respectively. However, abuse of KP201/APAP by these routes is still possible ...

Reference ID: 3932096
The sponsor commissioned three observational studies to characterize the patterns of abuse and routes of administration among various currently-marketed prescription opioid classes, including IR hydrocodone combination products. Based on the results of these studies, the sponsor maintained that intra-nasal abuse of IR hydrocodone combination products is highly prevalent in both absolute and relative terms (Section 2.5.1.1 KemPharm, 2015b, page 4).

To be clear, this statistical review does not address the efficacy question of whether the drug works or the question of whether the abuse-deterrent technology actually leads to reduction of abuse. The primary purpose of this document is to provide a statistical assessment of the sponsor’s observational studies with a view towards establishing a principled approach for determining whether intra-nasal abuse of IR hydrocodone combination products is a relevant route of administration and whether the sponsor’s studies are capable of demonstrating relevance based on this principled approach.

2 Data Sources

Table 1 lists the documents associated with NDA 208653 that were reviewed. Note that the documents drug-abuse-20151102.pdf and drug-abuse-surv-20150410.pdf pertain to essentially the same study with the following differences:


- the number of individuals captured by the surveillance systems for 2012 and 2013 are greater in document drug-abuse-20151102.pdf than in document drug-abuse-surv-20150410.pdf. The reason for this difference has to do with the fact that after the conclusion of the September 2014 study, new sites joined the NAVIPPRO network. For actual numbers, see page 104 in drug-abuse-20151102.pdf and page 21 in drug-abuse-surv-20150410.pdf.

3 Epidemiological Studies

3.1 Overview

The sponsor commissioned observational epidemiological studies to examine prevalence and patterns of abuse of IR hydrocodone combination products and other opioid classes. Each of the studies are based on separate data sources captured by the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO®) surveillance systems:

- NAVIPPRO Addiction Severity Index - Multimedia Version (ASI-MV®)
- NAVIPPRO Comprehensive Health Assessment for Teens (CHAT®)
- NAVIPPRO Internet Survey Report: Use and Abuse of Hydrocodone Combination Products Internet Survey 2014
- NAVIPPRO Internet Survey Report: Progression of Hydrocodone Combination Products Use Internet Survey 2015
Table 1: *Documents relevant to NDA 208653 that were reviewed.*

<table>
<thead>
<tr>
<th>Document Name</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>8-factor-report.pdf</td>
<td>Study report supporting the sponsor’s request for</td>
</tr>
<tr>
<td>drug-abuse-20151102.pdf</td>
<td>Study report that characterizes the magnitude and routes of abuse of currently-marketed immediate-release hydrocodone combination products in comparison to other opioids from January 01, 2012 to June 30, 2015 based on a sample of individuals assessed for substance abuse.</td>
</tr>
<tr>
<td>drug-abuse-surv-20150410.pdf</td>
<td>Study report that characterizes the magnitude and routes of abuse of currently-marketed immediate-release hydrocodone combination products in comparison to other opioids from January 01, 2012 to September 30, 2014 based on a sample of individuals assessed for substance abuse.</td>
</tr>
<tr>
<td>cor-pm-com.pdf</td>
<td>Proposal for post-market studies of abuse of KP201/APAP in the community after it is approved.</td>
</tr>
</tbody>
</table>
Note, while the ASI-MV and CHAT studies span 2012Q1 to 2015Q2, the focus of this document will only cover 2014Q1 to 2015Q2. This does not imply that results based on data within this interval are incompatible with results based on data from 2012Q1 to 2015Q2. Our reason for focusing on the 2014Q1 to 2015Q2 interval is because we felt that relevance should be evaluated with the most recent data.

3.2 ASI-MV

The NAVIPPRO ASI-MV surveillance system obtains information on abuse, ROA, and the prescription opioids being abused when individuals are assessed for substance abuse. Individuals are said to be assessed for substance abuse if they take the ASI-MV computerized self-administered questionnaire. The settings under which these assessments are performed include the following treatment modalities:

- Residential/Inpatient
- Outpatient/Non-Methadone
- Methadone/LAAM
- Corrections
- Other

To illustrate, suppose 10 individuals visited substance abuse treatment centers that are part of the NAVIPPRO network. They are asked to take the ASI-MV questionnaire. Suppose

- 8 individuals took the questionnaire: 2 indicated that they did not abuse prescription opioids
- 4 individuals reported abusing IR hydrocodone combination products: 3 indicated abuse via oral ROA, 1 indicated abuse via intra-nasal ROA.
- 2 individuals reported abusing extended release long-acting opioids (ERLAs): both indicated abuse via intra-nasal ROA

Based on the information,

- the number of assessments is 8
- the number of individuals who indicate abuse of IR hydrocodone combination products is 4
- the number of individuals who indicate abuse of ERLAs is 2

Note, in this example, the 3 individuals who indicated oral ROA are distinct from the individual who indicated intra-nasal ROA. Note, however, that in the ASI-MV sample, an individual who indicated oral ROA may also indicate intra-nasal ROA. For example, it is possible that among the 4 individuals who indicated abuse of IR hydrocodone combination products, 1 contributes to only the total oral count while 3 contribute to both the total oral count and intra-nasal count. Similarly, it is also possible that an individual who indicated abuse of IR hydrocodone combination products also indicated abuse of ERLAs and in this case the individual contributes to both the total IR hydrocodone combination products count and ERLAs count. It is important to keep these distinctions in mind when examining results in Sections 3.4 and 3.5.
3.2.1 Capturing Abuse, ROA, and Opioid Information

When individuals are assessed for substance abuse (i.e., takes the self-administered computerized ASI-MV questionnaire), a question asks whether they have used prescription opioids non-medically in the past 30 days prior to being assessed. For the purpose of the ASI-MV observational study, abuse is defined as non-medical use of a product in ways that are not consistent with how the product was prescribed to the individuals. If they indicated abuse of prescription opioids, they are presented with a screen where they are asked to select pictures of the drugs that they used. In addition, they are asked to identify all the relevant ROA.

We would like to elaborate on what it means to use the drug non-medically and on how abuse is defined based on non-medical use. According to a submitted report (Section 3.3 KemPharm, 2015a, page 22), a series of questions is used to establish whether

- the individual has a current chronic pain problem and has taken prescribed opioid medication for pain in the past 30 days
- he/she has obtained his/her medications only from his/her own physician
- he/she have not used the drug via an alternate ROA

The individual is also asked if he/she has used prescription opioids in the past 30 days “not in a way prescribed by your doctor, that is, for the way it makes you feel and not for pain relief.” A proprietary algorithm\(^1\) is applied to answers of these questions resulting in

- the individual being classified as having engaged in non-medical use and are assumed to be abusing the medication or
- the individual being classified as not abusing the medication

3.3 CHAT

The NAVIPPRO CHAT surveillance system obtains information on abuse, ROA, and prescriptions opioids being abused when adolescents (≤ 18 years of age) are assessed for substance abuse. Individuals are said to be assessed for substance abuse if they take the CHAT self-administered computerized questionnaire. The settings in which the assessments are performed include

- substance abuse treatment centers (drug or alcohol) that are part of the NAVIPPRO network
- alternative schools
- mental health programs
- others

\(^1\)We neither have access to this algorithm nor do we have data to evaluate the performance of this algorithm with respect to its ability to correctly identify abuse.
3.3.1 Capturing Abuse, ROA, and Opioid Information

When individuals are assessed for substance abuse (i.e., take the self-administered computerized CHAT questionnaire), they are asked whether they have used any prescription opioids in the past 30 days prior to assessment and if so, whether they have done so in ways not prescribed by a doctor. Those who indicated that they have used prescription opioid products in such a way are classified as having abused prescription opioids. Like ASI-MV, CHAT also asks individuals to identify all prescription opioids they have used in the past 30 days and ROAs in which they have used the products.

3.4 Results From ASI-MV

3.4.1 Some Characterization of the Assessed

Before presenting abuse prevalence for various opioid classes, it may be useful to consider some characteristics of the people that were assessed by ASI-MV. The following descriptive statistics were calculated from the submitted data.

Non-medical Use of Prescription Opioids  From 2014Q1 to 2015Q2, a total of 96357 individuals were assessed by ASI-MV. Among these individuals,

- 74.16% did not indicate non-medical use of prescription opioids
- 3.63% indicated medical use (as prescribed) of prescription opioids
- 22.21% indicated non-medical use of prescription opioids

Referral By Criminal Justice Systems  Among the 96357 individuals assessed by ASI-MV, 60.86% indicated that they were required or encouraged by the criminal justice system\(^2\) to obtain substance abuse treatment. Note however that among those who indicated non-medical use of prescription opioids, 35.74% indicated that they were required or encouraged by the criminal justice system to obtain substance abuse treatment.

Concurrent Use of IR HCPs and Other Substances  Among the 9064 individuals who indicated non-medical use of HCPs within the past 30-days, 5260 (or 58.03%) indicated that they have used\(^3\) IR HCPs along with other prescription opioids. Table 2 provides information on concurrent use of IR HCPs with other substances. The Count column provides the number of individuals who indicated abuse of check-marked substances. The Denominator column provides the count from which the prevalence is computed and also provides the interpretation of the prevalence. For example, in row 1, IR HCP is checked. We observe 9064 individuals who indicated abuse of IR HCPs. The denominator is 96357 – the number of individuals that were assessed. Thus, the prevalence of 9.41% is interpreted as the proportion of individuals assessed who indicated non-medical use of HCPs within the past 30-days. Based on Table 2 the following statements can be made about the 9064 individuals who indicated abuse of IR HCPs:

\(^2\)Judge, probation or parole officer, or other criminal justice official

\(^3\)Note, the term used, instead of abuse is intentional. In the data dictionary that was provided to FDA, the sponsor’s contractor made use of used.
• 7887 or 87.01% indicated abuse of illicit drugs.
• 4026 or 44.42% indicated abuse of IR oxycodone combination products (OCPs). Among these, 3689 or 91.63% indicated abuse of illicit drugs.
• 1790 or 19.75% indicated abuse of IR oxycodone single-entity products (OSEs). Among these, 1644 or 91.84% indicated abuse of illicit drugs.
• 3098 or 34.18% indicated abuse of extended-release long-acting products (ERLAs). Among these, 2857 or 92.22% indicated abuse of illicit drugs.
• 2193 or 24.19% indicated abuse of OCPs, OSEs, and ERLAs. Among these, 2028 or 92.48% indicated abuse of illicit drugs.

Table 3 compares individuals who indicated exclusively abusing IR hydrocodone combination products to those who did not indicate exclusively abusing IR hydrocodone combination products among those who indicated abuse IR hydrocodone combination products. With respect to ROAs,

• the prevalence of intra-nasal ROA among non-exclusive abusers is roughly 3 times higher than exclusive abusers (33.08% versus 10.04%)
• the prevalence of oral ROA among non-exclusive abusers is roughly the same as exclusive abusers (87.28% versus 94.45%)

With respect to severity of drug problem, the prevalence of those being classified as having an extreme drug problem among non-exclusive abusers is roughly more than 2 times higher than exclusive abusers (48.90% versus 19.43%).
Table 2: Concurrent use of IR HCPs and other substances among individuals assessed by ASI-MV from 2014Q1 to 2015Q2. Within this time-frame, 96357 individuals were assessed by ASI-MV. Rates are expressed as number of individuals who indicated abuse per 100 individuals assessed for substance abuse.

<table>
<thead>
<tr>
<th>IR HCP</th>
<th>IR OCP</th>
<th>IR OSE</th>
<th>ERLAs</th>
<th>Illicit Drugs</th>
<th>Count</th>
<th>Denominator</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9064</td>
<td>96357</td>
<td>9.41%</td>
</tr>
<tr>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>7887</td>
<td>9064</td>
<td>87.01%</td>
</tr>
<tr>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>4026</td>
<td>9064</td>
<td>44.42%</td>
</tr>
<tr>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>3689</td>
<td>4026</td>
<td>91.63%</td>
</tr>
<tr>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>1790</td>
<td>9064</td>
<td>19.75%</td>
</tr>
<tr>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>1644</td>
<td>1790</td>
<td>91.84%</td>
</tr>
<tr>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>3098</td>
<td>9064</td>
<td>34.18%</td>
</tr>
<tr>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>2857</td>
<td>3098</td>
<td>92.22%</td>
</tr>
<tr>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>2193</td>
<td>9064</td>
<td>24.19%</td>
</tr>
<tr>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>2028</td>
<td>2193</td>
<td>92.48%</td>
</tr>
</tbody>
</table>

**HCP**: hydrocodone combination prescription opioids  
**OCP**: oxycodone combination prescription opioids  
**OSE**: oxycodone single-entity prescription opioids  
**ERLA**: extended-release long-acting prescription opioids  
**Illicit Drugs**: heroin, methadone, barbiturates, sedatives, cocaine/crack, amphetamines, marijuana, hallucinogens, inhalants, and/or past 30-day abuse of alcohol

**Source**: Produced by statistical reviewer from sponsor’s ASI-MV data
Table 3: *Comparison of characteristics between individuals who indicated exclusively abusing IR HCPs to those who did not indicate exclusively abusing IR HCPs among those who indicate abuse of IR HCPs.*

<table>
<thead>
<tr>
<th>Age</th>
<th>No (N = 5260)</th>
<th>Yes (N = 3804)</th>
<th>Frequency</th>
<th>Prevalence (%)</th>
<th>Frequency</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 21</td>
<td>320</td>
<td>175</td>
<td>6.08</td>
<td>4.60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21 - 34</td>
<td>3262</td>
<td>2019</td>
<td>62.02</td>
<td>53.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35 - 54</td>
<td>1537</td>
<td>1401</td>
<td>29.22</td>
<td>36.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 54</td>
<td>141</td>
<td>209</td>
<td>2.68</td>
<td>5.49</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Severity**

<table>
<thead>
<tr>
<th>Severity</th>
<th>No (N = 5260)</th>
<th>Yes (N = 3804)</th>
<th>Frequency</th>
<th>Prevalence (%)</th>
<th>Frequency</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing</td>
<td>227</td>
<td>145</td>
<td>4.32</td>
<td>3.81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No real problem</td>
<td>155</td>
<td>837</td>
<td>2.95</td>
<td>22.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slight problem</td>
<td>130</td>
<td>329</td>
<td>2.47</td>
<td>8.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate problem</td>
<td>395</td>
<td>548</td>
<td>7.51</td>
<td>14.41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Considerable problem</td>
<td>1781</td>
<td>1206</td>
<td>33.86</td>
<td>31.70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extreme problem</td>
<td>2572</td>
<td>739</td>
<td>48.9</td>
<td>19.43</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Treatment Modality**

<table>
<thead>
<tr>
<th>Treatment Modality</th>
<th>No (N = 5260)</th>
<th>Yes (N = 3804)</th>
<th>Frequency</th>
<th>Prevalence (%)</th>
<th>Frequency</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing</td>
<td>71</td>
<td>32</td>
<td>1.35</td>
<td>0.84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resident/Inpatient</td>
<td>3096</td>
<td>1268</td>
<td>58.86</td>
<td>33.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient/non-methadone</td>
<td>1207</td>
<td>1114</td>
<td>22.95</td>
<td>29.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone/LAAM</td>
<td>145</td>
<td>78</td>
<td>2.76</td>
<td>2.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug Court</td>
<td>43</td>
<td>60</td>
<td>0.82</td>
<td>1.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probation/Parole</td>
<td>227</td>
<td>331</td>
<td>4.32</td>
<td>8.70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DUI/DWI</td>
<td>40</td>
<td>190</td>
<td>0.76</td>
<td>4.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>431</td>
<td>731</td>
<td>8.19</td>
<td>19.22</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Oral ROA**

<table>
<thead>
<tr>
<th>Oral ROA</th>
<th>No (N = 5260)</th>
<th>Yes (N = 3804)</th>
<th>Frequency</th>
<th>Prevalence (%)</th>
<th>Frequency</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>669</td>
<td>211</td>
<td>12.72</td>
<td>5.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4591</td>
<td>3593</td>
<td>87.28</td>
<td>94.45</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Snort ROA**

<table>
<thead>
<tr>
<th>Snort ROA</th>
<th>No (N = 5260)</th>
<th>Yes (N = 3804)</th>
<th>Frequency</th>
<th>Prevalence (%)</th>
<th>Frequency</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>3520</td>
<td>3422</td>
<td>66.92</td>
<td>89.96</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Continued on next page*
3.4.2 Prevalence of Abuse

Measures of abuse of prescription opioids were defined based on three denominators:

- patients assessed by ASI-MV
- number of prescriptions written.
- number of morphine equivalent units

Results presented hereafter are based only on the first denominator.

Table 4 displays the counts and prevalence of abuse for certain opioid classes. Consider row 1. From 2014Q1 to 2015Q2, 96357 individuals were assessed by NAVIPPRO’s ASI-MV. Out of these 96357 individuals, 9064 individuals or 9.41% (= 9064/96357) indicated that they abused IR hydrocodone combination products within the past 30 days prior to being assessed.

Table 5 displays route-specific abuse for various opioid classes. Consider for example IR hydrocodone combination products. Among the 9064 individuals who indicated abusing IR hydrocodone combination products within the past 30 days prior to being assessed, 8184 or 90.3% (= 8184/9064) indicated oral ROA. Similarly, among the 9064 individuals who indicated abusing IR hydrocodone combination products within the past 30 days prior to being assessed, 2122 or 23.4% (= 2122/9064) indicated intra-nasal ROA. The sponsor made the observation that 23.4% intra-nasal abuse among those who indicated abusing IR hydrocodone combination products is small relative to
- oral abuse among those who indicated abusing IR hydrocodone combination products
- intra-nasal abuse among those who indicated abusing prescription opioids from other classes

The sponsor also examined intra-nasal abuse counts across various opioid classes. They noted for example that among 7250 individuals who indicated abuse of IR oxycodone combination products, 2861 indicated intra-nasal ROA; and among 6234 individuals who indicated abuse of ERLAs, 2457 indicated intra-nasal abuse (see Table 5). Thus, although intra-nasal abuse prevalence of IR hydrocodone combination products appear to be smaller compared to other opioid classes, intra-nasal abuse counts of IR hydrocodone combination products are similar in magnitude to some of the other opioid classes. This line of reasoning is the basis for the sponsor maintaining that intra-nasal abuse of IR hydrocodone combination products is a relevant ROA.

Table 4: Abuse of various prescription opioid classes among individuals assessed by ASI-MV from 2014Q1 to 2015Q2. Within this time-frame, 96357 individuals were assessed by ASI-MV.

<table>
<thead>
<tr>
<th>Opioid Classes</th>
<th>Counts</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR HCP</td>
<td>9,064</td>
<td>9.41</td>
</tr>
<tr>
<td>IR OCP</td>
<td>7,250</td>
<td>7.52</td>
</tr>
<tr>
<td>IR OSE</td>
<td>3,314</td>
<td>3.44</td>
</tr>
<tr>
<td>All Other IR</td>
<td>2,732</td>
<td>2.84</td>
</tr>
<tr>
<td>All ERLAs</td>
<td>6,234</td>
<td>6.47</td>
</tr>
<tr>
<td>All ADF ERLAs</td>
<td>3,493</td>
<td>3.63</td>
</tr>
<tr>
<td>All Non-ADF ERLAs</td>
<td>4,602</td>
<td>4.78</td>
</tr>
</tbody>
</table>

HCP: hydrocodone combination products  
OCP: oxycodone combination products  
OSE: oxycodone single-entity products  
ADF: abuse-deterrent formulation  
ERLAs: extended-release long-acting products

**Source:** Reproduced by statistical reviewer from sponsor’s report (Table 8 KemPharm, 2015a, page 39)
Table 5: ROAs across various prescription opioid classes among individuals assessed by ASI-MV from 2014Q1 to 2015Q2. The prevalence of each ROA for each opioid class is obtained by dividing the frequency for the route by the number of individuals who indicated abuse of that opioid class. For specific denominators used in the calculation of prevalence, see Table 4.

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Frequency</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IR HCP</td>
<td>8184</td>
<td>90.3</td>
</tr>
<tr>
<td>IR OCP</td>
<td>5455</td>
<td>75.2</td>
</tr>
<tr>
<td>IR OSE</td>
<td>1387</td>
<td>41.9</td>
</tr>
<tr>
<td>Other IR</td>
<td>727</td>
<td>26.6</td>
</tr>
<tr>
<td>ERLA</td>
<td>3632</td>
<td>58.3</td>
</tr>
<tr>
<td>ADF ERLA</td>
<td>2080</td>
<td>59.5</td>
</tr>
<tr>
<td>Non-ADF ERLA</td>
<td>2216</td>
<td>48.2</td>
</tr>
<tr>
<td><strong>Snort</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IR HCP</td>
<td>2122</td>
<td>23.4</td>
</tr>
<tr>
<td>IR OCP</td>
<td>2861</td>
<td>39.5</td>
</tr>
<tr>
<td>IR OSE</td>
<td>1856</td>
<td>56.0</td>
</tr>
<tr>
<td>Other IR</td>
<td>620</td>
<td>22.7</td>
</tr>
<tr>
<td>ERLA</td>
<td>2457</td>
<td>39.4</td>
</tr>
<tr>
<td>ADF ERLA</td>
<td>987</td>
<td>28.3</td>
</tr>
<tr>
<td>Non-ADF ERLA</td>
<td>2004</td>
<td>43.5</td>
</tr>
<tr>
<td><strong>Inject</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IR HCP</td>
<td>139</td>
<td>1.5</td>
</tr>
<tr>
<td>IR OCP</td>
<td>913</td>
<td>12.6</td>
</tr>
<tr>
<td>IR OSE</td>
<td>1206</td>
<td>36.4</td>
</tr>
<tr>
<td>Other IR</td>
<td>1766</td>
<td>64.6</td>
</tr>
<tr>
<td>ERLA</td>
<td>2164</td>
<td>34.7</td>
</tr>
<tr>
<td>ADF ERLA</td>
<td>1206</td>
<td>34.5</td>
</tr>
<tr>
<td>Non-ADF ERLA</td>
<td>1742</td>
<td>37.9</td>
</tr>
<tr>
<td><strong>Smoke</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IR HCP</td>
<td>99</td>
<td>1.1</td>
</tr>
<tr>
<td>IR OCP</td>
<td>261</td>
<td>3.6</td>
</tr>
<tr>
<td>IR OSE</td>
<td>218</td>
<td>6.6</td>
</tr>
<tr>
<td>Other IR</td>
<td>44</td>
<td>1.6</td>
</tr>
</tbody>
</table>

*Continued on next page*
3.5 Results From CHAT

Table 6 displays abuse prevalence for various opioid classes among adolescents assessed by CHAT. Consider row 1. There were a total of 4965 individuals that were assessed by NAVIPPRO’s CHAT from 2014Q1 to 2015Q2. Out of these 4965 individuals, 181 individuals (or 3.65%) indicated abuse of IR hydrocodone combination products within the past 30 days prior to being assessed.

Table 7 displays route-specific abuses. Consider for example IR hydrocodone combination products. Among the 181 individuals who indicated abusing IR hydrocodone combination products within the past 30 days prior to assessment, 147 or 81.22% indicated oral abuse. Similarly, among the 181 individuals who indicated abusing IR hydrocodone combination products within the past 30 days prior to assessment, 77 or 42.54% indicated intra-nasal abuse.
Table 6: Abuse of various prescription opioid classes among individuals assessed by CHAT from 2014Q1 to 2015Q2. Within this time-frame, 4965 adolescents were assessed by CHAT.

<table>
<thead>
<tr>
<th>Opioid Classes</th>
<th>Frequency</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR HCP</td>
<td>181</td>
<td>3.65</td>
</tr>
<tr>
<td>IR OCP</td>
<td>149</td>
<td>3.00</td>
</tr>
<tr>
<td>IR OSE</td>
<td>38</td>
<td>0.77</td>
</tr>
<tr>
<td>All Other IR</td>
<td>38</td>
<td>0.77</td>
</tr>
<tr>
<td>All ERLAs</td>
<td>98</td>
<td>1.97</td>
</tr>
<tr>
<td>All ADF ERLAs</td>
<td>52</td>
<td>1.05</td>
</tr>
<tr>
<td>All Non-ADF ERLAs</td>
<td>72</td>
<td>1.45</td>
</tr>
</tbody>
</table>

HCP: hydrocodone combination products  
OCP: oxycodone combination products  
OSE: oxycodone single-entity products  
ADF: abuse-deterrent formulation  
ERLA: extended-release long-acting products

Source: Reproduced by statistical reviewer from sponsor’s report (Table 23 KemPharm, 2015a, page 77)

Table 7: ROAs across various prescription opioid classes among adolescents assessed by CHAT. The prevalence of each ROA for each opioid class is obtained by dividing the frequency of the ROA by the number of adolescents who indicated abuse of that opioid class. For specific denominators used in the calculation of prevalence, see Table 6.

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Frequency</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IR HCP</td>
<td>147</td>
<td>81.22</td>
</tr>
<tr>
<td>IR OCP</td>
<td>110</td>
<td>73.83</td>
</tr>
<tr>
<td>IR OSE</td>
<td>24</td>
<td>63.16</td>
</tr>
<tr>
<td>Other IR</td>
<td>23</td>
<td>60.53</td>
</tr>
<tr>
<td>ERLA</td>
<td>74</td>
<td>75.51</td>
</tr>
<tr>
<td>ADF ERLA</td>
<td>37</td>
<td>71.15</td>
</tr>
<tr>
<td>Non-ADF ERLA</td>
<td>52</td>
<td>72.22</td>
</tr>
</tbody>
</table>

Snort

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Frequency</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR HCP</td>
<td>77</td>
<td>42.54</td>
</tr>
<tr>
<td>IR OCP</td>
<td>73</td>
<td>48.99</td>
</tr>
<tr>
<td>IR OSE</td>
<td>18</td>
<td>47.37</td>
</tr>
</tbody>
</table>

Continued on next page
<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Frequency</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other IR</td>
<td>17</td>
<td>44.74</td>
</tr>
<tr>
<td>ERLA</td>
<td>52</td>
<td>53.06</td>
</tr>
<tr>
<td>ADF ERLA</td>
<td>25</td>
<td>48.08</td>
</tr>
<tr>
<td>Non-ADF ERLA</td>
<td>39</td>
<td>54.17</td>
</tr>
</tbody>
</table>

**Inject**

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Frequency</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR HCP</td>
<td>9</td>
<td>4.97</td>
</tr>
<tr>
<td>IR OCP</td>
<td>7</td>
<td>4.70</td>
</tr>
<tr>
<td>IR OSE</td>
<td>2</td>
<td>5.26</td>
</tr>
<tr>
<td>Other IR</td>
<td>1</td>
<td>2.63</td>
</tr>
<tr>
<td>ERLA</td>
<td>5</td>
<td>5.10</td>
</tr>
<tr>
<td>ADF ERLA</td>
<td>4</td>
<td>7.69</td>
</tr>
<tr>
<td>Non-ADF ERLA</td>
<td>3</td>
<td>4.17</td>
</tr>
</tbody>
</table>

**Smoke**

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Frequency</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR HCP</td>
<td>2</td>
<td>1.10</td>
</tr>
<tr>
<td>IR OCP</td>
<td>7</td>
<td>4.70</td>
</tr>
<tr>
<td>IR OSE</td>
<td>4</td>
<td>10.53</td>
</tr>
<tr>
<td>Other IR</td>
<td>5</td>
<td>13.16</td>
</tr>
<tr>
<td>ERLA</td>
<td>8</td>
<td>8.16</td>
</tr>
<tr>
<td>ADF ERLA</td>
<td>5</td>
<td>9.62</td>
</tr>
<tr>
<td>Non-ADF ERLA</td>
<td>6</td>
<td>8.33</td>
</tr>
</tbody>
</table>

**Other**

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Frequency</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR HCP</td>
<td>2</td>
<td>1.10</td>
</tr>
<tr>
<td>IR OCP</td>
<td>3</td>
<td>2.01</td>
</tr>
<tr>
<td>IR OSE</td>
<td>1</td>
<td>2.63</td>
</tr>
<tr>
<td>Other IR</td>
<td>2</td>
<td>5.26</td>
</tr>
<tr>
<td>ERLA</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>ADF ERLA</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>Non-ADF ERLA</td>
<td>0</td>
<td>0.00</td>
</tr>
</tbody>
</table>

**Source:** Reproduced by statistical reviewer from sponsor’s report (Table 26 KemPharm, 2015a, page 87)
3.6 Sponsor Conclusions

Based on the results of the epidemiological studies (see Table 5), the sponsor concluded that (KemPharm, 2015a, page 97)

*These data suggest that snorting of hydrocodone IR combination products may be a route of abuse used by a significant number of abusers of these products.*

In stating this conclusion, the sponsor maintains that intra-nasal abuse of IR hydrocodone combination products is a relevant route of abuse.

4 Statistical Considerations

4.1 Overview

In discussing the relevance of intra-nasal abuse of IR hydrocodone combination products, the sponsor estimated the prevalence of intra-nasal abuse among those who indicated abuse of IR hydrocodone combination products within the sample of individuals assessed by NAVIPPRO’s ASI-MV surveillance system. Among the 9064 individuals who indicated abuse of IR hydrocodone combination products, 2122 or 23.4% indicated intra-nasal abuse. The magnitude of this prevalence estimate, although smaller than intra-nasal abuse prevalence estimates of other prescription opioid classes, is arguably not that small (see Table 5).

The sponsor noted similar patterns among adolescents assessed by NAVIPPRO’s CHAT surveillance system. Among 181 adolescents who indicated abuse of IR hydrocodone combination products, 77 or 42.54% indicated intra-nasal abuse. From Table 7, we see that this prevalence estimate is similar in magnitude to other opioid categories.

Based on the magnitude of the observed prevalence estimates of intra-nasal ROA and from the fact that the observed frequency of intra-nasal abuse of IR hydrocodone combination products are comparable to the observed frequencies of intra-nasal abuse of other opioid classes, the sponsor concluded relevance of intra-nasal abuse of IR hydrocodone combination products (see Section 3.6).

Although this line of reasoning appears reasonable, it is not based on any principled approach to assessing relevance. In the following sections, we

- clarify the distinction between population and sample
- discuss the selection process that brought about the data
- develop a criteria to determine relevance
- discuss the impact of the selection process on our ability determine relevance based on our criteria

4.2 Population and Sample

The selection process that we will discuss has bearings on whether we can estimate the population quantities necessary to make a determination of relevance of intra-nasal abuse of IR hydrocodone...
combination products. For the simple reason that we are using data to estimate population quantities, we refer to issues that arise from the selection process as estimability issues. Note that the use of estimability in this statistical discussion is not universal; it is well-known elsewhere as the identification problem (Manski, 1999, 2003).

To understand why selection and estimability are important, we need to first make the distinction between population and sample. For convenience, we focus only on the NAVIPPRO ASI-MV study. However, the principles raised in the discussion are also applicable to the CHAT and Internet Survey studies. The data gathered by the NAVIPPRO ASI-MV surveillance system constitute a sample from an underlying population. The term population can refer to the entire US or some subset thereof. In this discussion, we adopt the view that the underlying population from which the data arose is some subset of the US population. This view immediately raises the issue of how do we characterize this population. One way of thinking about this population is to consider the kinds of people that are assessed by ASI-MV for substance abuse. These are individuals

- who are likely to make contact with substance abuse treatment centers
- who are likely to make contact with the correctional system (probation/parole, drug court, DUIs, etc...)

It is then not unreasonable to characterize the underlying population as some subset of the US population that consist of individuals who are at high-risk of substance abuse and that the ASI-MV data constitute a sample from this population.

Note, in the determination of relevance, it may be argued that the underlying population should be the general US population. This is a valid point but not an important one in our discussion because the estimability issue that we will discuss still holds even if we adopt the broader population as the underlying population from which the data arose.

### 4.3 Population Quantities

The sponsor estimated prevalence of

- abuse of IR hydrocodone combination products and other opioid classes as a proportion of those assessed
- oral, intra-nasal, and other ROAs among those who indicated abuse of IR hydrocodone combination products and among those who indicated abuse of other opioid classes

With these sample quantities, we can begin to think about the population quantities of interest. Let $Y$ denote the opioid that was abused and $R$ denote ROA. The population analogue of the above quantities are

- $\Pr(Y = y)$ - the proportion of the population who indicated abuse of substance $y$. We will use the shorter notation $[Y = y]$ for the remainder of the document. For concreteness, let the possible values of $y$ be
  - 0: no substance was abused
- 1: IR hydrocodone combination products
- 2: IR oxycodone combination products
- 3: ERLAs

\[ \Pr(R = r \mid Y = y) \] - the proportion who indicated abuse via route \( r \) among those in the population who indicated abuse of substance \( y \). We will use the shorter notation \([R = r \mid Y = y]\) for the remainder of the document. For concreteness, let the possible values of \( r \) be
- 0: oral
- 1: intra-nasal
- 2: inject
- 3: smoke

### 4.4 Selection and Estimability

First, what do we mean by selection? In the context of ASI-MV, selection is the process that drives individuals from the underlying population to be assessed by ASI-MV. The end-result of this process are the data which are then used to make statements about the underlying population.

The estimability issue has to do with whether the data can be used to make statements about the underlying population, after taking the selection process into account. For example, based on the ASI-MV data, we estimate prevalence of intra-nasal ROA among those who indicated abuse of IR hydrocodone combination products to be 23.4%. Does this value represent a valid estimate of the corresponding quantity in the underlying population? Similarly, does the relative magnitude of intra-nasal abuse counts between IR hydrocodone combination products and ERLAs (2122 versus 2457, respectively) represent a valid estimate of the relative magnitude in the underlying population?

Let \( S \) denote the selection indicator; that is, \( S = 1 \) means that an individual from the underlying population is assessed for substance abuse by ASI-MV and \( S = 0 \) means that an individual from the underlying population is not assessed for substance abuse by ASI-MV. With respect to the above population quantities, we can frame the estimability issues as follows:

- \([Y = y \mid S = 1] \approx [Y = y]\). In words, is the prevalence of abuse of substance \( y \) in the ASI-MV sample equal the prevalence of abuse of substance \( y \) in the underlying population?

- \([R = r \mid Y = y, S = 1] \approx [R = r \mid Y = y]\). In words, is abuse prevalence via route \( r \) among those who abuse substance \( y \) in the ASI-MV sample equal the abuse prevalence via route \( r \) among those who abuse substance \( y \) in the population?

For each of these quantities, the left-hand-side is the prevalence model based on the sample of individuals assessed by ASI-MV. We will refer to this as the sample model. The right-hand-side is the prevalence model for the underlying population. We will refer to this as the population model. In Section 4.4, we asked the question
... Does this value represent a valid estimate of the corresponding quantity in the underlying population?

This question can be rephrased as: does the sample model equal the population model?

### 4.4.1 Abuse Prevalence For Specific Substances

We first consider making inferences about \( Y = y \). Ideally, the sample model should equal the population model; that is,

\[ [Y = y \mid S = 1] = [Y = y] . \]

However, it can be shown that the sample model is related to the population model through the following relationship:

\[
[Y = y \mid S = 1] = \left\{ \frac{[S = 1 \mid Y = y]}{[S = 1]} \right\} [Y = y] \tag{1}
\]

From equation (1), we see that selection induces a sample model for prevalence of abuse of substance \( y \) that is not equal to the population model for prevalence of abuse of substance \( y \). From the right-hand-side, we see that the sample model is a confounding of the population model \([Y = y]\) and the selection ratio \([S = 1 \mid Y = y]/[S = 1]\). This confounding goes away when

\[ [S = 1 \mid Y = y]/[S = 1] = 1 . \]

This occurs when the likelihood of getting assessed by ASI-MV for substance abuse in no way depends on the substance \( y \).

To better understand what the selection ratio means, let us suppose that the underlying population has size \( N \) within the study period 2014Q1 to 2015Q2. Suppose further that within the study period, \( n \) individuals were assessed by ASI-MV for substance abuse. The selection quantity \([S = 1]\) can be viewed as the proportion of people in the population that were assessed; that is

\[ [S = 1] = \frac{n}{N} . \]

Now suppose that among the \( n \) assessed

- \( n_0 \) is the number individuals who indicated abuse of no substance
- \( n_1 \) is the number individuals who indicated abuse of IR hydrocodone combination products
- \( n_2 \) is the number individuals who indicated abuse of IR oxycodone combination products
- \( n_3 \) is the number individuals who indicated abuse of ERLAs

where \( n = \sum_j n_j, j = 0, \ldots, 3 \). Similarly denote the number of individuals in the population who abuse substance \( y \) by \( N_y \); that is,

- \( N_0 \) is the number individuals who indicated abuse of no substance
- \( N_1 \) is the number individuals who indicated abuse of IR hydrocodone combination products
• $N_2$ is the number individuals who indicated abuse of IR oxycodone combination products

• $N_3$ is the number individuals who indicated abuse of ERLAs

That is, $N = \sum_j N_j$, $j = 0, \ldots, 3$. The selection quantity $[S = 1 \mid Y = y]$ can be viewed as the probability of getting assessed for substance abuse among those in the population who abuse substance $y$; that is,

$$[S = 1 \mid Y = y] = \frac{n_y}{N_y}$$

This means that if the sample model $[Y = y \mid S = 1]$ is to be valid for the population model, the probability of getting assessed must be constant across all substances:

$$\frac{n_0}{N_0} = \cdots = \frac{n_3}{N_3} = \frac{n}{N}$$

This means that if individuals with $Y = 0$ have a low probability of getting assessed by ASI-MV relative to those with $Y = 1$, the estimate of prevalence of abuse of IR hydrocodone combination products could severely over-estimate the prevalence of IR hydrocodone combination products in the population.

In summary, if it is plausible that individuals who abuse certain substances have a higher (or lower) probability of getting assessed for substance abuse, then the prevalence or rate of abuse in the population for specific substances cannot be estimated from the data.

### 4.4.2 ROA Prevalence

We now consider making inferences about $[R = r \mid Y = y]$ – the prevalence of ROA $r$ among those who abuse substance $y$. It can be shown that

$$[R = r \mid Y = y, S = 1] = \left\{ \frac{[S = 1 \mid R = r, Y = y]}{[S = 1 \mid Y = y]} \right\} [R = r \mid Y = y]$$

From equation (2), we see that selection induces a sample model for prevalence of route $r$ among those who abuse substance $y$ that is not equal to the population model. From the right-hand-side, we see that the sample model is a confounding of the population model $[R = r \mid Y = y]$ and the selection ratio $[S = 1 \mid R = r, Y = y]/[S = 1 \mid Y = y]$. This confounding goes away when

$$[S = 1 \mid R = r, Y = y]/[S = 1 \mid Y = y] = 1 .$$

This occurs when the probability of getting assessed by ASI-MV for substance abuse in no way depends on the route of administration.

Again, we can get a better understanding of this selection ratio from a finite population ratio framework. Let $N_1$ denote the number of individuals in the population who abuse IR hydrocodone combination products. And suppose that among these $N_1$ individuals, $n_1$ were assessed by ASI-MV substance abuse.

The selection quantity $[S = 1 \mid Y = 1]$ can be viewed as the proportion of people in the population who abuse IR hydrocodone combination products who were assessed by ASI-MV; that is

$$[S = 1 \mid Y = 1] = \frac{n_1}{N_1} .$$

Now suppose that among the $n_1$ individuals in the ASI-MV sample who indicated abuse of IR hydrocodone combination products,
- $n_{10}$ is the number individuals who indicated oral ROA
- $n_{11}$ is the number individuals who indicated intra-nasal ROA
- $n_{12}$ is the number individuals who indicated inject ROA
- $n_{13}$ is the number individuals who indicated smoke ROA

where $n_1 = \sum_j n_{1j}, j = 0, \ldots, 3$. Similarly denote the number of individuals in the population who abuse IR hydrocodone combination products via route $r$ by $N_{1r}$; that is,

- $N_{10}$ is the number individuals who indicated oral ROA
- $N_{11}$ is the number individuals who indicated intra-nasal ROA
- $N_{12}$ is the number individuals who indicated inject ROA
- $N_{13}$ is the number individuals who indicated smoke ROA

That is, $N_1 = \sum_j N_{1j}, j = 0, \ldots, 3$. The selection quantity $[S = 1 \mid R = r, Y = 1]$ can be viewed as the probability of getting assessed for substance abuse among those in the population who abuse IR hydrocodone combination products via route $r$; that is,

$$[S = 1 \mid R = r, Y = 1] = \frac{n_{1r}}{N_1}$$

This means that if the sample model $[R = r \mid Y = 1, S = 1]$ is to be valid for the population model $[R = r \mid Y = 1]$, the probability of getting assessed must be constant across all routes:

$$\frac{n_{10}}{N_{10}} = \cdots = \frac{n_{13}}{N_{13}} = \frac{n_1}{N_1}$$

This means that if individuals who abuse IR hydrocodone combination products via snorting ($R = 1$) have a higher probability of getting assessed by ASI-MV relative to those who abuse orally, the prevalence of intra-nasal abuse of IR hydrocodone combination products observed in the sample could severely over-estimate the prevalence of intra-nasal abuse of IR hydrocodone combination products in the population. The implication is that if we are interested in making statements about prevalence of different ROAs among those who abuse a specific opioid class such as IR hydrocodone combination products, it is not possible to do so if getting assessed depends in an important way on the ROA. By extension, if the ROA-dependent selection mechanism is different from opioid class to opioid class, it makes even less sense to compare prevalence of intra-nasal ROA between IR hydrocodone combination products with another opioid class like ERLAs using data from ASI-MV.

In summary, if individuals who abuse a specific product via a certain route is more likely to get assessed relative to other routes, then the ROA distribution for that product cannot be estimated from the data.
4.5 Criteria for Assessing Relevance

Whether intra-nasal abuse of IR hydrocodone combination products is a relevant route of administration is a difficult question to answer. For the ASI-MV study, the sponsor noted that among those who indicated abuse of IR hydrocodone combination products, 23.4% indicated intra-nasal ROA. For the CHAT study, the sponsor noted that among adolescents assessed by CHAT and who indicated abuse of IR hydrocodone combination products, 42.5% indicated intra-nasal ROA. If we ignore the estimability issue for the moment, what these numbers suggest is that intra-nasal abuse rates of IR hydrocodone combination products can vary depending on the underlying population. It is not inconceivable that another surveillance system may capture data that could suggest an intra-nasal abuse rate for IR hydrocodone combination products that is even smaller, for example 5%. This would not be incompatible with the two numbers observed in the ASI-MV and CHAT studies because it may be describing a different underlying population.

From a public health perspective however, it seems incomplete to try to interpret relevance based on how large or how small these rates are. The reason is this: an outcome due to drug exposure can have a very small incident rate but if the drug is widely-prescribed or widely-used, a small rate can translate into a large number of events for the outcome. However, having a large number of events is neither sufficient nor necessary for determining relevance. It could be argued that some outcomes such as headaches and nausea are highly prevalent but may not be relevant from a public health perspective. On the other hand, it could be argued that other outcomes such as myocardial infarction (MI), although not as prevalent as headaches and nausea, are relevant from a public health perspective. These examples suggest that relevance has two components: scope and severity. Headaches and nausea could be considered as having scope but not severity. On the other hand, MI could be considered as having less scope but very severe.

Guided by these examples, we approach the question of relevance in a principled way using these two criteria:

- **scope** - how pervasive or how large is intra-nasal abuse of IR hydrocodone combination products in the population?
- **severity** - how serious are the consequences of intra-nasal abuse of IR hydrocodone combination products?

If intra-nasal abuse of IR hydrocodone combination products satisfies the criteria of scope and severity, this may provide a justification for making the determination that it is a relevant ROA. We acknowledge that this raises more questions:

- What is the threshold beyond which we say that the scope criterion is satisfied?
- What is the threshold beyond which we say that the severity criterion is satisfied?

These are very important public health questions but unfortunately, ones that cannot be answered statistically. As such, we leave them unanswered, relying on the readers’ expertise to make his or her own judgment. The statistical narrative is intended to provide a basis for thinking about these questions and to evaluate whether the studies provide any useful information that we can use to make statements about scope and severity of intra-nasal abuse of IR hydrocodone combination products.

We now discuss whether the data allows us to make statements about scope and severity of intra-nasal abuse of IR hydrocodone combination products.
4.6 Scope of Intra-nasal Abuse

4.6.1 Metrics For Assessing Scope

As was defined in the previous section, the scope of the intra-nasal abuse problem is how widespread the problem is in the population that is of interest to us. We can consider several metrics that we can use to assess scope:

- metric 1: the proportion of people in the underlying population that abuse IR hydrocodone combination products via the intra-nasal route
- metric 2: among those that abuse IR hydrocodone combination products in the underlying population, the proportion who abuse via the intra-nasal route
- metric 3: the number of people in the underlying population who abuse IR hydrocodone combination products via the intra-nasal route

Note that all three metrics have an important limitation: what is the threshold beyond which we can conclude that we have scope? We re-emphasize that this is something that we cannot answer statistically. What we can say statistically is whether the data enable us to estimate these population metrics so that if we have a threshold in mind, we can make a scope determination.

In Section 4.4, we discussed how the underlying selection process induces a sample model that is confounded between the population model and the probability of getting assessed by ASI-MV. Based on this discussion, none of the metrics listed above are estimable from the data.

Metric 1 If we want to estimate the proportion of individuals in the underlying population who abuse IR hydrocodone combination products via the intra-nasal route, we require that getting assessed does not depend on

- whether an individual is a substance abuser
- the substance being abused
- the route of administration

These conditions are not likely to hold given

- individuals who do not abuse substance are less likely to get assessed for substance abuse
- abusers who end up in treatment centers or referred by the correctional systems tend to be very serious abusers who likely
  - abuse more powerful substances or abuse multiple substances

Note that within the underlying population, not all individuals are substance abusers. This is important to keep in mind because abusing substance is not a requirement for getting assessed. Some individuals get assessed because they are entering substance abuse treatment centers to get treated. Based on conversations with the Dr. Jana McAninch from the Office of Surveillance and Epidemiology however, some get assessed because they were required or recommended to get assessed. For example, individuals on welfare may be required to get assessed for substance abuse.
– abuse via other routes such as injection and intra-nasal rather than the intended route

As such, the estimate of this metric from the ASI-MV surveillance data is likely to be much larger than the value of this metric in the underlying population of individuals at high risk of substance abuse.

Metric 2  For the same reasons discussed above, the estimate of this metric from the ASI-MV surveillance data is likely to be much larger than the corresponding value in the underlying population.

Metric 3  Because not all individuals in the population who abuse IR hydrocodone combination products intra-nasally are assessed for substance abuse, it is evident that this metric cannot be estimated from the data. In fact, the data only inform us that the number of individuals who intra-nasally abuse IR hydrocodone combination products in the underlying high-risk population is likely to be greater than 1415 per year. If this lower bound is sufficient for determining that intra-nasal abuse is pervasive, then we may consider the scope criterion satisfied. However, if this information is insufficient, then we need recourse to other studies or data sources to evaluate scope.

4.6.2 Scope of Intra-nasal Abuse of IR Hydrocodone Combination Products: A Lower Bound From External Data

At the end of Section 4.6.1, we stated that within the underlying population from which the ASI-MV sample arose, there’s roughly 1415 or more intra-nasal abuses of IR hydrocodone combination products per year. There are, however, auxiliary data that could be used with the ASI-MV data to estimate a more informative lower bound.

The Substance Abuse and Mental Health Services Administration (SAMHSA) publishes the Treatment Episode Data Set (TEDS) which contains demographic characteristics and substance abuse problems of admissions to primarily publicly-funded treatment facilities in the US (SAMHSA, 2016). In 2013, there were 1581786 admissions to treatment facilities captured by TEDS who are at least 18 years old (See Table 2.1b SAMHSA, 2013, page 53). Note that while it is reasonable to think of the 1581786 admissions as a sample from the underlying population of individuals who are at high risk of substance abuse, this sample cannot be viewed as a random sample from that population for the same reason that the ASI-MV sample cannot be viewed as a random sample from that population. However, if we can reasonably assume that individuals admitted to TEDS treatment centers are similar to individuals assessed by ASI-MV, then we can apply the prevalence estimates from the ASI-MV data to estimate a more informative lower bound for the number of intra-nasal abuse of IR hydrocodone combination products in the underlying high-risk population:

- From Table 4, 9.4% of those assessed by ASI-MV indicated abusing IR hydrocodone combination products.
- If the individuals captured by TEDS in 2013 are similar in characteristics to those assessed by ASI-MV, then we can expect roughly 148,846 cases of abuse of IR hydrocodone combination products in TEDS: \(0.094 \times 1581786\).

\(^5\)There were 2122 intra-nasal abuse of IR hydrocodone combination products per 6 quarters or 1415 per year.

Reference ID: 3932096
From Table 5, 23.4% of those who indicated abuse of IR hydrocodone combination products also indicated that they abuse IR hydrocodone combination products intra-nasally.

If the individuals captured by TEDS in 2013 are similar in characteristics to those assessed by ASI-MV, then we can expect roughly 34,830 cases of intra-nasal abuse in TEDS: $0.2340 \times 148846$.

Ignoring the sampling variability of the ASI-MV estimates, we can reasonably conclude, based on TEDS 2013 admissions data, that although we do not know the extent of intra-nasal abuse of IR hydrocodone combination products in the underlying high-risk population, it is roughly at least 34,830. How far this value is away from the true value cannot be determined with the available information.

This exercise can also be repeated for the CHAT study. Within the TEDS 2013 admissions, there were 101665 admissions that were between the ages of 12 and 18, not including 18. If we can reasonably assume that adolescents admitted to TEDS treatment centers are similar to adolescents assessed by CHAT then we can apply the estimates from the CHAT study to estimate a more informative lower bound for the number of intra-nasal abuse of IR hydrocodone combination products in the underlying high-risk adolescent population:

From Table 6, 3.65% of those assessed by CHAT indicated abusing IR hydrocodone combination products.

If the adolescents captured by TEDS in 2013 are similar in characteristics to those assessed by CHAT, then we can expect roughly 3711 cases of abuse of IR hydrocodone combination products in TEDS: $0.0365 \times 101665$.

From Table 7, 42.54% of those who indicated abuse of IR hydrocodone combination products also indicated that they abuse IR hydrocodone combination products intra-nasally.

If the adolescents captured by TEDS in 2013 are similar in characteristics to those assessed by CHAT, then we can expect roughly 1579 cases of intra-nasal abuse in TEDS: $0.4254 \times 3711$.

Ignoring the sampling variability of the CHAT estimates, we can reasonably conclude, based on TEDS 2013 admissions data, that although we do not know the extent of intra-nasal abuse of IR hydrocodone combination products in the underlying adolescent high-risk population, it is roughly at least 1579. How far this value is away from the true value cannot be determined with the available information.

4.6.3 A Note on the Differences Between TEDS and ASI-MV

The sponsor noted that there are some differences between individuals captured by TEDS and ASI-MV(KemPharm, 2015a, page 18):

- ASI-MV has a larger proportion of Hispanics than TEDS (19% vs 13%).
- ASI-MV has a smaller proportion of unemployed than TEDS (19.9% vs 39.7%).
To this, we also add that the TEDS sample consists primarily of admissions to publicly funded substance abuse treatment centers whereas the ASI-MV sample consists of assessments by privately and publicly funded substance abuse treatment centers and assessments captured in parole, drug court, DUI/DWI, and other settings. Whether these differences biased the 34830 lower bound estimate cannot be determined.

4.7 Severity

As discussed in Section 4.5, the assessment of relevance of a specific route of abuse should not only include scope but also severity. That is, we should also consider the health consequences of snorting IR hydrocodone combination products.

The sponsor noted that the number of intra-nasal abuse of IR hydrocodone combination products are comparable to other opioid classes such as ERLAs. Such comparisons would be reasonable if the consequences of snorting IR hydrocodone combination products are similar to the consequences of snorting ERLAs (or other opioid classes). In other words, there is an underlying assumption that consequent AEs such as overdose and death from snorting IR hydrocodone combination products is similar to snorting other opioids. Unfortunately the data do not provide any information on the distributions of AEs from snorting of IR hydrocodone combination products and other opioids. As such, assessment of severity based on consequent AEs is not possible.

Furthermore, the definition of abuse used in the studies is any non-medical use of prescription opioids within the past-30 days prior to assessment. There are two concerns with this definition:

- First, the accuracy of this definition with respect defining abuse is uncertain. In these surveillance studies, non-medical use can mean
  - using the drug for pain but the drug was not prescribed to you.
  - using the drug off-label such as for the way it makes you feel. The phrase “makes you feel” does not make the distinction between using to get high or using to address other health outcomes such as anxiety or depression.

  It is not clear that using prescription opioids for pain but was not prescribed to you or for treating other health outcomes constitute abuse. The sponsor recognized this issue when they say (see KemPharm, 2015a, page 22)

    Since prescription opioids are used legitimately with a prescription for pain, there is disagreement around what constitutes “abuse” and how that is different from “misuse” of a prescription ...

- Second, the definition does not make any dose-response distinction.
  - A person who snorts IR hydrocodone combination products once within the past 30 days is treated the same way as a person who snorts twice a week within the past 30 days.
  - A person who snorts IR hydrocodone combination products once within the past 30 days and no other time within the past year is treated the same way as a person who snorts IR hydrocodone combination products once within the past 30 days but 10 times within the past year.
If severity of snorting IR hydrocodone combination products depends on some sort of dose-response relationship between frequency of snorting and AEs, the data provide little information to elicit such a relationship.

5 Summary

The sponsor submitted NDA 208653 seeking approval for benzhydrocodone hydrochloride and acetaminophen combination, an abuse-deterrent formulation for hydrocodone/APAP combination. Based on the results from three abuse potential clinical studies, the sponsor is seeking abuse-deterrent labeling claims for both oral and intra-nasal routes of administration. FDA felt that it was important to understand why intra-nasal abuse of IR hydrocodone combination products is a relevant route of administration. The sponsor conducted observational epidemiological studies using data collected by surveillance systems. A study based on a convenience sample of adults assessed by NAVIPPRO’s ASI-MV surveillance system shows that

- the prevalence of intra-nasal abuse among those who indicated abuse of IR hydrocodone combination products is approximately 23.4%
- the frequency of intra-nasal abuse among those who indicated abuse of IR hydrocodone combination products is approximately 2122

The sponsor compared the prevalence and frequency of intra-nasal abuse of IR hydrocodone combination products with those of other opioid categories such as IR oxycodone combination products and extended-release long-acting opioids. They noted that while the prevalence of intra-nasal abuse of 23.4% for IR hydrocodone combination products is relatively small compared to other opioid classes, the frequency of the intra-nasal abuse of IR hydrocodone combination products is comparable to those of other opioid classes:

- IR oxycodone combination products: 2861 (39.5%)
- IR oxycodone single entity: 1856 (56.0%)
- All ERLAs: 2457 (39.4%)

Similar results were observed from a study based on a convenience sample of adolescents assessed by the NAVIPPRO’s CHAT surveillance system:

- the prevalence of intra-nasal abuse among adolescents who indicated abuse of IR hydrocodone combination products is approximately 42.54%
- the frequency of intra-nasal abuse among adolescents who indicated abuse of IR hydrocodone combination products is approximately 77

These values are relatively large compared to other opioid classes:

- IR oxycodone combination products: 73 (49.0%)
- IR oxycodone single entity: 18 (47.4%)
Based on these results, the sponsor maintained that intra-nasal abuse is a relevant form of abuse. We approach the question of relevance of intra-nasal abuse of IR hydrocodone combination products using two criteria:

- **Scope**: is this ROA pervasive in the population? How many individuals in the population are abusing IR hydrocodone combination products intra-nasally?

- **Severity**: how severe are the AEs associated with this ROA? What are the health consequences of intra-nasal abuse of IR hydrocodone combination products and how serious are they?

In principle, if intra-nasal abuse of IR hydrocodone combination products satisfies the scope and severity criteria, then it could be considered a relevant route of administration. Unfortunately, what the data enable us to conclude about scope and severity is limited. This limitation stems, in part, from the fact that

- the underlying sampling mechanism that determines how individuals from the underlying populations are captured by the surveillance systems cannot be quantified. Therefore, it is very difficult to determine whether estimated prevalence of intra-nasal abuse of IR hydrocodone combination products observed in the sample are valid for prevalence of intra-nasal abuse of IR hydrocodone combination products in the underlying population.

- the size and specific characteristics of the underlying population is unknown. Therefore, even if the estimated prevalence generalizes to the underlying population, it is still not possible to know how extensive (scope) is the problem of intra-nasal abuse of IR hydrocodone combination products.

The underlying population from which the ASI-MV data arose can be characterized as consisting of adults who are at high-risk of substance abuse. Within this population, we are interested in assessing the scope of the problem of intra-nasal abuse of IR hydrocodone combination products. What we are able to understand from the sample however is that a lower bound for the number of intra-nasal abuse of IR hydrocodone combination products within this population is approximately 2122 for the period from 2014Q1 to 2015Q2. Using auxiliary data from a 2013 TEDS report published by the Substance Abuse and Mental Health Services Administration, we obtained a more informative lower bound for the number of intra-nasal abuse of IR hydrocodone combination products within this underlying population: 34,830 cases. This estimate was based on the assumption that the characteristics of individuals captured by TEDS are similar to the characteristics of individuals captured by ASI-MV.

We can also obtain a lower bound for the underlying adolescent population from which the CHAT data arose. This underlying population can be characterized as consisting of adolescents who are at high-risk of substance abuse. Within this population, we are interested in assessing the scope of the problem of intra-nasal abuse of IR hydrocodone combination products. Within the TEDS 2013 admissions, there were 101665 individuals between the ages of 12 and 18, not including 18. After applying the estimates from the CHAT study, a lower bound for the number of intra-nasal abuse of IR hydrocodone combination products within the underlying high-risk adolescent population is approximately 1579.
Whether these lower bound information on intra-nasal abuse of IR hydrocodone combination products are sufficient to make a determination of scope is beyond the capabilities of the statistical analyses.

Even if intra-nasal abuse of IR hydrocodone combination products satisfies the scope criterion, the other important criterion is severity. The ASI-MV study compares counts of intra-nasal abuse of IR hydrocodone combination products to other opioid categories such as ERLAs. Such a comparison could be meaningful if the health consequences of snorting IR hydrocodone combination products are similar to the health consequences of snorting other opioids. However, there is little information captured by ASI-MV that could provide a basis for making statements about severity of intra-nasal abuse of IR hydrocodone combination products. Furthermore, the definition of abuse used by the sponsor may have some limitations:

• First, the accuracy of this definition with respect defining abuse is uncertain. In these surveillance studies, non-medical use can mean
  – using the drug for pain but the drug was not prescribed to you.
  – using the drug off-label such as for the way it makes you feel. The phrase “makes you feel” does not make the distinction between using to get high or using to address other health outcomes such as anxiety or depression.

  It is not clear that using prescription opioids for pain but was not prescribed to you or for treating other health outcomes constitute abuse.

• Second, the definition does not make any dose-response distinction.
  – A person who snorts IR hydrocodone combination products once within the past 30 days is treated the same way as a person who snorts twice a week within the past 30 days.
  – A person who snorts IR hydrocodone combination products once within the past 30 days and no other time within the past year is treated the same way as a person who snorts IR hydrocodone combination products once within the past 30 days but 10 times within the past year.
References


KemPharm. NDA 208653: Clinical Overview - Benzhydrocodone Hydrochloride/Acetaminophen Tablet (KP201/APAP), 2015b.

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