CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	209777
Drug Name:	RoxyBond (Oxycodone ARIR)
Indication:	Human abuse liability
Study number:	O-ARIR-002
Applicant:	Inspirion Delivery Technologies, LLC
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Keywords: *Crossover design, Drug abuse potential study, Self-reported endpoint, Multiple endpoints*

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1. Executive Summary

Study O-ARIR-002 was a Randomized, Double-Blind, Double-Dummy, Active- and Placebo-Controlled, Four-Way Crossover Study to Assess the Relative Bioavailability and Abuse Potential of Intranasal Administration of Ground Oxycodone ARIR Tablets (Abuse Deterrent) versus an Equivalent Dose of Crushed Roxicodone in Nondependent Recreational Opioid Users.

The primary objective was to assess the relative abuse potential of ground Oxycodone ARIR to crushed Roxicodone when administered intranasally to nondependent, recreational opioid users with intranasal experience.

The primary PD endpoint for this study was Drug Liking measured using the Bipolar Visual Analog Scale (VAS). There were four treatments in the study, the primary comparison was crushed Roxicodone to ground Oxycodone ARIR 30 mg administered intranasally.

The primary objective was to assess the relative abuse potential of Ground Oxycodone ARIR to crushed Roxicodone when administered intranasally to nondependent, recreational opioid users with intranasal experience.

The reviewer analyzed the primary PD endpoint Drug Liking, and the secondary PD endpoints: Drug Liking AUE [0-1h] Emax, Drug Liking AUE [0-2h] Emax, High, Take Drug Again and Overall Drug Liking. The results from the statistical reviewer's analyses establish that:

- The Crushed Roxicodone resulted in statistically significantly greater ($p<0.0001$) VAS scores compared to Ground placebo for Drug Liking, Drug Liking AUE [0-1h] Emax, Drug Liking AUE [0-2h] Emax, High, Take Drug Again and Overall Drug Liking, thereby validating these pharmacodynamic measures.

- The Emax for Drug Liking VAS was significantly ($p<0.0001$) lower for ground Oxycodone ARIR than crushed Roxicodone. The LS mean Emax for Drug Liking VAS for ground Oxycodone ARIR was 70.74 compared with 82.67 for crushed Roxicodone. There was no significant difference between Crushed Roxicodone and Intact Oxycodone ARIR (P value=0.53). Drug Liking of AUE [0-1h] and AUE [0-2h] showed similar results in Emax with statistically significant less liking for ground Oxycodone ARIR than crushed Roxicodone ($p<0.0001$). These data support a possible deterrent effect of Ground Oxycodone ARIR to abuse.

- Ground Oxycodone ARIR and Crushed Roxicodone resulted in LS mean Emax values for High VAS of 38.65 and 66.41, respectively. This reduction in maximum High VAS following Ground Oxycodone ARIR was statistically significant lower comparing Crushed Roxicodone ($p<0.0001$) and supports a deterrent effect of Ground Oxycodone ARIR to abuse.

- For Take Drug Again VAS, the median difference between Crushed Roxicodone and Ground Oxycodone ARIR was 21 ($p<0.0001$). This reduction suggests that if given the opportunity again, subjects would have a greater willingness to Crushed Roxicodone, as opposed to Ground Oxycodone ARIR. This supports a deterrent effect of Ground Oxycodone ARIR to abuse.

- For Overall Drug Liking VAS, the median difference between Crushed Roxicodone and Ground Oxycodone ARIR was 16 (p=0.0004). This provides additional support for a deterrent effect of Ground Oxycodone ARIR to abuse.

- There was no significant difference in TEmax between Crushed Roxicodone and Ground Oxycodone ARIR for Drug Liking VAS (P=0.06) and High VAS (P=0.3119).

- There was no significant difference between Crushed Roxicodone and Intact Oxycodone ARIR for Drug Liking VAS, High VAS, Take Drug Again VAS and Overall Drug Liking VAS (P-values>0.05).

- 25 out of the 29 subjects who completed the study (~86%) had some reduction in Drug Liking VAS with Ground Oxycodone ARIR compare to Crushed Roxicodone, while 14% subjects had no reduction or negative reduction. 19 subjects (~66%) had at least 30% reduction and 7 subjects (~24%) had at least 50% reduction in Drug Liking VAS with Ground Oxycodone ARIR compare to Crushed Roxicodone.

By following the 2015 new guidance:

- Emax of Crushed Roxicodone is significantly greater than Ground placebo (P<0.0001) for Drug Liking VAS, High VAS, Take Drug Again VAS and Overall Drug Liking VAS, thereby confirming study validity.
- For the primary comparison between Crushed Roxicodone vs. Ground Oxycodone ARIR, Ground Oxycodone ARIR had statistically significant 20% reduction in Emax of Drug Liking VAS, 25% reduction in Emax of High VAS, 35% reduction in Emax of Take Drug Again VAS and 30% reduction in Emax of Overall Drug Liking VAS comparing with Crushed Roxicodone.

Additional comments:

- In this study, for the statistical analyses of the PD parameters, sponsor used the rank transformations analysis while the normality assumption was not met for.
  Reviewer's comments:
  The results from Rank transformation should be interpreted carefully. The mixed model uses the rankings of VAS scores instead of their values as outcome, so it is the result of testing the differences of mean rankings from two treatment arms, not the mean or median of paired differences (in VAS score values) from two treatments.

- The reviewer doesn't agree with sponsor's percent reduction analysis method: sponsor set the percent reduction the largest percentage observed in the study in the case of the control was equal to placebo. The reviewer's suggestion: If the control was equal to placebo, a negative value or zero should be set to the percent reduction.

- The new ADF guidance has published in April 2015, in the future, you should follow the new guidance regarding the hypothesis testing and pre-specifications as well as primary and secondary statistical analysis at:
  http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf

2. Review Report on Study O-ARIR-002

2.1 Overview

The misuse and abuse of opioid medications continues to increase precipitously. The intranasal route is a widely used route of administration for progressive opioid abusers due to its rapid delivery compared with oral administration.
Due to concerns about the diversion and abuse of pharmaceutical opioids, various formulations have been developed to deter the non-medical use of the medication. Inspirion Delivery Technologies, LLC (IDT) has developed a new formulation of immediate-release oxycodone using the ARIR (Abuse Resistant Immediate Release) technology designed to have tamper resistant features. Oxycodone ARIR is an immediate-release abuse deterrent formulation that avoids the potential risks of opioid antagonists or aversive agents. The technology is based on physical and chemical tamper resistance which significantly increases the hurdle for the abuser to effectively prepare the formulation to quickly release active substance after administration or to use for unintended routes of administration. This formulation reduces the euphoric potential of oxycodone if adulterated. When taken as directed by a physician and as part of a pain management program, Oxycodone ARIR is expected to provide pain relief for moderate to severe pain equivalent to Roxicodone, which represents a widely used immediate release oxycodone profile in the United States.
The purpose of this study was to determine the relative pharmacodynamic (PD) effects (ie, drug liking), pharmacokinetics (PK), and safety of Oxycodone ARIR when ground (tampered) and administered intranasally. It was anticipated that grinding and insufflating Oxycodone ARIR would decrease the release of oxycodone and, therefore, would result in a reduction of the euphoria-inducing effects of oxycodone compared to crushed Roxicodone or intact Oxycodone ARIR. Ground and intact Oxycodone ARIR were compared to the equivalent dose of crushed Roxicodone and to placebo. All tampered study drug was prepared for snorting per the pharmacy manual.

2.1.1 Objectives of the study

The primary objective of this study was to assess the relative abuse potential of ground Oxycodone ARIR to crushed Roxicodone when administered intranasally to nondependent, recreational opioid users with intranasal experience.

Secondary objectives are:

- To assess the abuse potential of intact Oxycodone ARIR administered orally relative to ground Oxycodone ARIR administered intranasally to nondependent, recreational opioid users.
- To assess the abuse potential of ground and intact Oxycodone ARIR relative to placebo when administered intranasally and orally respectively to non-dependent, recreational opioid users.
- To assess the relative bioavailability of oxycodone in plasma from ground and intact Oxycodone ARIR compared with one another and crushed Roxicodone when administered intranasally (ground Oxycodone ARIR and crushed Roxicodone) and orally (intact Oxycodone ARIR) to non-dependent, recreational opioid users.

- To assess the safety of ground and intact Oxycodone ARIR compared with crushed Roxicodone and placebo following intranasal and oral administration in nondependent, recreational opioid users.

2.1.2 Study design

This was a randomized, double-blind, double-dummy, active- and placebo-controlled, single-dose, four-way crossover, single-center study. The study consisted of a Screening Period, Qualification Period, Treatment Period and Follow-up Period. The Screening Period was completed as an outpatient visit. The Qualification Period consisted of a 4-night inpatient, double-blind qualifying session during which a Naloxone Challenge Test and Drug Discrimination Test were administered. Subjects who successfully passed the Naloxone Challenge Test and Drug Discrimination Test underwent a minimum 72-hour washout period and then entered the Treatment Period. Subjects could remain in the clinical unit between the Qualification Period and Treatment Period or to facilitate subject schedules and clinical availability, could be discharged following the Qualification Period and return for the Treatment Period within 40 days. The Treatment Period consisted of an 11-night inpatient treatment session with a minimum 72-hour washout period between treatments. A post-treatment Follow-up Period was performed 7-10 days after the last dose of the Treatment Period and consisted of safety assessments.

During the Treatment Period, subjects received 4 treatments in a randomized, 1:1:1:1 ratio, double-blind, double-dummy, 4-way crossover design. Each dose was separated by at least a 72-hour period. The 4 treatments were prepared and administered as indicated below:

Treatment	**Tampered Intranasal Dose (Weight ≈ mg)**	**Intact Oral Dose**
Treatment A - Placebo	Ground placebo Oxycodone ARIR tablet (high volume, 587 mg)	Placebo tablet matching Oxycodone ARIR
Treatment B – Crushed Roxicodone	Crushed 30 mg Roxicodone tablet (low volume, 100 mg)	Placebo tablet matching Oxycodone ARIR
Treatment C – Ground Oxycodone ARIR	Ground 30 mg Oxycodone ARIR tablet (high volume, 587 mg)	Placebo tablet matching Oxycodone ARIR
Treatment D – Intact Oxycodone ARIR	Placebo powder (microcrystalline cellulose) matching Roxicodone (low volume, 100 mg)	Intact 30 mg Oxycodone ARIR

Pharmacodynamic Endpoints:

Primary Endpoint:

The primary endpoint was Drug Liking measured using the Bipolar Visual Analog Scale (VAS).

Secondary Endpoints:

- Drug Effects Questionnaire (DEQ; VAS for Any Drug Effects, Good Effects, High, Bad Effects, Sick, Nausea, Sleepy and Dizzy)
- Ease of Snorting measured using VAS
- Overall Drug Liking measured using VAS

- Take Drug Again measured using VAS
- Pupillometry
- Nasal Effect Asssessments (intranasal irritation, burning, need to blow nose, runny nose/nasal discharge, facial pain/pressure, and nasal congestion) – using Likert Scale (Exploratory).

The following PD endpoints were calculated for Drug Liking, DEQ, and pupillometry:

- Peak effect (Emax)
- Time of peak effect (TEmax)
- Area under the effect curve to 0.5 hour (AUE0-0.5h)
- Area under the effect curve to 1 hour (AUE0-1h)
- Area under the effect curve from 1 to 2 hour (AUE1-2h)
- Area under the effect curve to 2 hours (AUE0-2h)
- Area under the effect curve to 8 hours (AUE0-8h)
- Area under the effect curve to 12 hours (AUE0-12h)
- Area under the effect curve to 24 hours (AUE0-24h)
- Area under the effect curve to time of observed maximum plasma oxycodone concentration (AUE0-Tmax).

Safety Assessments: Safety was evaluated based on adverse events (AEs), Nasal Effects Assessment, clinical laboratory assessments, vital signs, 12-lead electrocardiogram, and physical examinations.

2.1.3 Number of subjects (Planned and Analyzed):

Planned: A sufficient amount of subjects were screened to complete at least 28 subjects in the Treatment Period.
Analyzed: Of 214 subjects who entered the study and underwent the Naloxone Challenge Test, all 214 subjects passed the Naloxone Challenge Test. Three subjects withdrew from the study following the Naloxone Challenge Test. Of the 211 subjects who entered the Drug Discrimination Test, 180 subjects were withdrawn from the study prior to the Treatment Phase (158 subjects failed the Drug Discrimination Test; 11 experienced emesis within 2 hours of dosing in the Drug Discrimination Test and were withdrawn due to protocol-mandated criterion; 5 withdrew consent; 3 experienced AEs other than emesis; 2 had protocol deviations; and 1 was non-compliant and withdrawn due to Investigator decision.). Of the 31 subjects who entered the Treatment Period, 29 completed the study (2 subjects withdrew consent during the Treatment Phase, both citing family emergencies). An additional 5 subjects participated in the Naloxone Challenge Test, Drug Discrimination Test, and first treatment period cohort (08 March 2014) and completed the trial prior to FDA feedback, which changed the method of study drug dosing. Data from these 5

subjects are not included in the analysis, but are included in a subgroup analysis and in the listings.

2.1.4 Pharmacodynamic Statistical Methodology used in Sponsor's analyses

The primary comparison was crushed Roxicodone to ground Oxycodone ARIR 30 mg administered intranasally (Treatment B vs Treatment C) for Drug Liking. All other comparisons were secondary. The comparison of crushed Roxicodone to ground placebo was made to confirm study validity.

Each of the 6 comparisons were made:

- Treatment B vs Treatment C – Primary Comparison
- Treatment B vs Treatment A – Validity Comparison
- Treatment C vs Treatment A
- Treatment D vs Treatment A
- Treatment B vs Treatment D
- Treatment C vs Treatment D

The PD endpoints or applicable time points were analyzed using a mixed-effect model with fixed effects for sequence, period, and treatment, and a random effect for subject nested in sequence. Least-squares (LS) means along with 95% confidence intervals (CIs) were provided for each treatment. LS mean differences along with 95% CIs were provided for the pairwise treatment comparisons defined above. The parameters or time points defined above were analyzed as defined in separate models.

- Drug Liking – All PD parameters analyzed
- DEQ VAS (for Any Drug Effects, Good Effects, High, Bad Effects, Sick, Nausea, Sleepy and Dizzy) – All PD parameters analyzed
- Ease of Snorting – 5 minute time point analyzed
- Overall Drug Liking – Emax analyzed
- Take Drug Again – Emax analyzed
- Nasal Effects Assessment – All PD parameters analyzed
- Pupillometry – All PD parameters analyzed

The distribution of the residuals from each parametric model was examined to determine whether substantial departures from normality were apparent using the Shapiro Wilk test (tested at α=0.01). If the residuals were not normally distributed, a non-parametric analysis (the same

procedure after ranked transformation) was applied. In addition, the Hodges-Lehmann estimate for the differences in two paired medians was provided and the 95% CI of the median difference.

Percent Reduction and Responder Analysis of Percent Reduction

The percent reduction in peak effect (Emax) was calculated for Drug Liking. The percent reduction was calculated as:

$$reduction = \frac{c_i - t_i}{abs(c_i - p_i)} \times 100\%, i = 1, 2, ...n,$$

where ci, ti, and pi were the Emax values for the control (crushed Roxicodone [Treatment B]), test (ground Oxycodone ARIR [Treatment C]), and Placebo (Treatment A) respectively; from the ith subject; and n is the sample size. Additionally, the percent reduction was calculated for the comparison between crushed Roxicodone and intact Oxycodone ARIR (B vs D), and between intact Oxycodone ARIR and ground Oxycodone ARIR (D vs C). An exploratory calculation was also presented for percent reduction in Emax for Drug Liking VAS as:

$$\%reduction = \begin{cases} \frac{c_i - t_i}{c_i - 50} \times \left(1 - \frac{p_i - 50}{50}\right) \times 100\%, \ i = 1, 2, ...n, \ if \ p_i > 55; \\ \frac{c_i - t_i}{c_i - 50} \times 100\%, \quad i = 1, 2, ...n, \qquad if \ p_i \le 55. \end{cases}$$

where ci, ti, and pi were the Emax values for the control (crushed Roxicodone [Treatment B]), test (ground Oxycodone ARIR [Treatment C]), and Placebo (Treatment A) respectively; from the ith subject; and n was the sample size.

Percent reduction for partial AUE PD parameters for Drug Liking was also calculated using the following formula:

$$reduction = \frac{c_i - t_i}{abs(c_i - p_i)} \times 100\%, i = 1, 2, ...n,$$

where ci, ti, and pi were the AUE values for the control (crushed Roxicodone [Treatment B]), test (ground Oxycodone ARIR [Treatment C]), and Placebo (Treatment A) respectively; from the ith subject; and n was the sample size. Additionally, the percent reduction was calculated for the comparison between crushed Roxicodone and intact Oxycodone ARIR (B vs D), and between intact Oxycodone ARIR and ground Oxycodone ARIR (D vs C).

The percent reduction was calculated if data for the active control, test product, and placebo were available. In cases where one of those values was not available percent reduction was set to missing. In cases where the control was equal to placebo, the percent reduction was set to the largest percentage observed in the study (negative or positive depending on the difference of ci-ti) for that comparison; if no large percentage existed (or it was less than 101%) then the percent reduction was set to 101% (and set to negative or positive depending on the difference of ci-ti), a large value so that the subject was still counted in the analysis and would not markedly impact the descriptive statistical results.

Note, the reviewer doesn't agree to set the percent reduction the largest percentage observed in the study in the case of the control was equal to placebo. If the control was equal to placebo, a negative value or zero should be set to the percent reduction.

2.1.5 Sponsor's Pharmacodynamic Conclusions

The primary endpoint of interest for this study was the 0-100 point bipolar VAS scores for Drug Liking; larger values indicate greater liking. The primary comparison was crushed Roxicodone vs ground Oxycodone ARIR. The primary parameter was Emax.

Study validity was confirmed with the comparison of LS mean for Emax for Drug Liking being significantly higher for crushed Roxicodone than crushed placebo (82.67 vs 53.16 mm, $p < 0.0001$). The differences between crushed Roxicodone and crushed placebo were also statistically significantly higher ($p < 0.0001$) for all AUE intervals. That is, subjects were successfully able to distinguish between placebo and 30 mg Roxicodone.

Drug Liking Emax was significantly lower for ground Oxycodone ARIR than for crushed Roxicodone ($p < 0.0001$) as were all other PD parameters. TEmax was significantly longer for ground Oxycodone ARIR than crushed Roxicodone with the LS median difference of -0.52 hours ($p = 0.0148$). Results for the secondary endpoints supported results for Drug Liking. Overall Drug Liking and Take Drug Again Assessment both suggested significantly lower abuse potential for ground Oxycodone ARIR than crushed Roxicodone ($p < 0.0001$). Each of the positive effects for the DEQ, that is Any Effects, Good Effects, and High were significantly lower for ground Oxycodone ARIR than crushed Roxicodone; no differences were seen in the negative DEQ effects including Sleepy, Bad Effects, Sick, Nausea, and Dizzy. Ground Oxycodone ARIR was significantly more difficult to snort than crushed Roxicodone ($p < 0.0001$) and produced significantly worse nasal effects for all 5 assessments (Irritation, Burning, Runny Nose/Nasal Discharge, Facial Pain/Pressure, and Nasal Congestion; $p < 0.0001$).

Most subjects had a reduction in Drug Liking Emax with ground Oxycodone ARIR compared with crushed Roxicodone. Twenty-five subjects (86.2%) had a reduction in Drug Liking for ground Oxycodone ARIR compared with crushed Roxicodone. Twenty subjects (69%) had at least a 30% reduction on Emax and 31% had at least a 50% reduction. Findings for AUE parameters were consistent with findings for Emax. Most subjects also had a reduction in Drug Liking AUE parameters especially at the time points within 2 hours (93.1% to 96.6% of subjects had a reduction in Drug Liking AUE0-0.5h, AUE0-1h, and AUE0-2h), but also from 8 through 24 hours (72.4% through 75.9% of subjects had a reduction in Drug Liking AUE0-8h, AUE0-12h, and AUE0-24h).

Intact Oxycodone ARIR vs Ground Oxycodone ARIR. The Emax for Drug Liking was significantly ($p < 0.0001$) lower for ground Oxycodone ARIR than intact Oxycodone ARIR. For percent reduction in peak effect between ground and intact Oxycodone ARIR, 75.9% of subjects had a reduction in Drug Liking Emax with ground Oxycodone ARIR compared with intact Oxycodone ARIR. Emax for Overall Drug Liking and Take Drug Again Assessment was lower for ground Oxycodone ARIR than intact Oxycodone ARIR ($p \leq 0.0014$). For DEQ Any Effects, Emax and most AUE parameters were significantly lower for ground Oxycodone ARIR than intact Oxycodone ARIR ($p \leq 0.0268$); exceptions were AUE0-0.5h ($p = 0.0738$) and AUE0-1h ($p = 0.5640$). For Good Effects, Emax and most AUE parameters were significantly lower for ground Oxycodone ARIR than intact Oxycodone ARIR ($p \leq 0.0276$). For High, Emax and most AUE parameters were significantly lower for ground Oxycodone ARIR than intact Oxycodone

ARIR ($p \leq 0.0358$). For Bad Effects, AUE0-05h and AUE0-Tmax values for were significantly lower for ground Oxycodone ARIR than intact Oxycodone ARIR and Tmax was significantly longer for intact Oxycodone ARIR than ground Oxycodone ARIR. No other significant treatment differences were observed for any of the negative DEQ Effects including Sleepy, Sick, Nausea, and Dizzy.

Crushed Roxicodone vs Intact Oxycodone ARIR. Emax for Drug Liking was not significantly different ($p = 0.5301$) for crushed Roxicodone and intact Oxycodone ARIR. Slightly more than half of subjects (55.2%) had a reduction in Drug Liking Emax with intact Oxycodone ARIR compared with crushed Roxicodone. However, for AUE0-0.5h and AUE0-1h, 93.1% of subjects had a reduced Drug Liking for intact Oxycodone ARIR compared with crushed Roxicodone. All AUE parameters at later time points also showed reduced Drug Liking in $\geq 69.0\%$ of subjects with intact Oxycodone compared with crushed Roxicodone. Emax for Overall Drug Liking and Take Drug Again Assessment was not significantly different between intact Oxycodone ARIR and crushed Roxicodone. For DEQ Any Effects, neither Emax ($p = 0.7328$) nor any of the AUE parameters fom 8 hours through 24 hours ($p \geq 0.0709$) were significantly different. For

Good Effects, Emax was not significantly different ($p = 0.4474$), however, AUE0-0.5h, AUE0-1h, AUE0-2h, AUE0-8h, and AUE0-Tmax were significantly lower for intact Oxycodone ARIR than crushed Roxicodone ($p \leq 0.0489$). For High, Emax was not significantly different ($p = 0.9536$), however, AUE0-0.5h, AUE0-1h, AUE0-2h, and AUE0-Tmax were significantly lower for intact Oxycodone ARIR than crushed Roxicodone ($p \leq 0.0071$). For the negative DEQ Effects of Sleepy, Bad Effects, Sick, Nausea, and Dizzy there were no significant treatment differences except that Tmax for Bad Effects was significantly longer for intact Oxycodone ARIR than crushed Roxicodone ($p = 0.0172$).

All comparisons in which the tampered intranasal dose was the ground placebo Oxycodone ARIR (high volume) vs the crushed placebo tablet matching Roxicodone (low volume), the difference in the Ease of Snorting was statistically significant ($p < 0.0001$) with the ground Oxycodone ARIR tablets (active or placebo) being significantly more difficult to snort than the crushed Roxicodone tablets (active or placebo). Results of the Nasal Effects Assessment also demonstrated increased difficulty subjects had snorting the ground Oxycodone ARIR treatments (active and placebo) compared with the crushed Roxicodone treatments (active and placebo) with Emax and all AUE parameters showing significantly more irritation, burning, runny nose/nasal discharge, facial pain/pressure, and nasal congestion with the ground Oxycodone ARIR treatments.

2.2 Data Location

The analysis datasets are located at

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2.3 Reviewer's Assessment

All analyses were conducted from the stand point of the pharmacodynamics analysis.

2.3.1 Descriptive Statistics

The descriptive statistics of E_{max} and TE_{max} for the primary PD endpoint Drug Liking, and secondary PD endpoints, Drug Liking AUE [0-1h], Drug Liking AUE [0-2h], High, Overall Drug

Liking and Take Drug Again are provided in Table 1 and Table 2. E_{max} is calculated as the maximum effect in the first 24 hours in the review's analysis. Table 1 summarizes the mean, standard deviation, minimum, the first quartile (Q1), median, the third quartile (Q3), and maximum of E_{max} for the four treatments in the study. Similarly table 2 summarizes results for TE_{max}.

Table 1. E_{max} Descriptive Statistics for Drug Liking, Drug Liking AUE [0-1h], Drug Liking AUE [0-2h], High, Overall Drug Liking and Take Drug Again, PD population (N=29)

Parameter	Treatment	Mean	Std Dev	Min	Q1	Median	Q3	Max
Drug Liking	A-Ground Placebo	53.41	6.34	50.00	50.00	51.00	52.00	77.00
	B-Crushed Roxicodone	82.86	11.55	50.00	79.00	82.00	91.00	100.00
	C-Ground Oxycodone ARIR	71.14	12.01	50.00	65.00	71.00	78.00	100.00
	D-Intact Oxycodone ARIR	81.48	11.49	56.00	75.00	82.00	89.00	100.00
Drug Liking AUE [0-1h]	A-Ground Placebo	0.90	3.84	-9.50	-0.13	0.00	1.00	14.50
	B-Crushed Roxicodone	19.42	8.53	0.00	14.10	21.00	27.23	31.25
	C-Ground Oxycodone ARIR	6.27	5.70	-4.75	1.38	5.50	10.88	17.50
	D-Intact Oxycodone ARIR	7.07	6.34	-0.75	2.13	5.25	10.88	24.63
Drug Liking AUE [0-2h]	A-Ground Placebo	2.46	8.86	-14.00	-0.38	0.00	1.88	38.00
	B-Crushed Roxicodone	43.11	17.86	0.00	34.25	44.35	57.75	68.00
	C-Ground Oxycodone ARIR	21.41	15.42	-1.49	7.50	20.88	32.50	57.50
	D-Intact Oxycodone ARIR	31.79	18.13	-0.25	21.88	30.75	41.00	66.25
High	A-Ground Placebo	7.52	14.93	0.00	0.00	1.00	5.00	57.00
	B-Crushed Roxicodone	66.34	25.69	0.00	56.00	74.00	84.00	96.00
	C-Ground Oxycodone ARIR	39.38	25.88	0.00	18.00	40.00	57.00	100.00
	D-Intact Oxycodone ARIR	66.66	25.92	1.00	49.00	72.00	85.00	100.00
Overall Drug Liking	A-Ground Placebo	47.59	15.73	0.00	50.00	50.00	50.00	85.00
	B-Crushed Roxicodone	80.86	14.60	35.00	73.00	85.00	90.00	100.00
	C-Ground Oxycodone ARIR	64.21	21.64	4.00	52.00	70.00	77.00	99.00
	D-Intact Oxycodone ARIR	78.55	17.41	13.00	73.00	83.00	89.00	100.00
Take Drug Again	A-Ground Placebo	41.86	20.09	0.00	49.00	50.00	50.00	78.00
	B-Crushed Roxicodone	82.14	16.44	37.00	73.00	86.00	95.00	100.00
	C-Ground Oxycodone ARIR	62.24	24.51	3.00	50.00	62.00	81.00	99.00
	D-Intact Oxycodone ARIR	77.31	18.11	13.00	70.00	81.00	89.00	100.00

The Emax descriptive statistics for Drug Liking VAS, as can be seen in table 1, for placebo, the mean 53.41 and median 51 were slightly above neutral. Crushed Roxicodone had mean 82.86 and median 82 closed to Intact Oxycodone ARIR which had mean 81.48 and median 82. Ground Oxycodone ARIR had mean equal to 71.14 and median equal to 71.

For Drug Liking AUE [0-1h] and Drug Liking AUE [0-2h], Crushed Roxicodone had the highest mean and median among the four treatments.

For High VAS, the mean Emax scores were <10 for the placebo. The mean Emax score of 39.38 for Ground Oxycodone ARIR was low compared to the mean scores of 66.34 for Crushed Roxicodone.

For Overall Drug Liking VAS, mean Emax was lowest for placebo (47.59), followed by Ground Oxycodone ARIR (64.21) and Intact Oxycodone ARIR (78.55), while Crushed Roxicodone had the highest mean Emax score (80.86).

For Take Drug Again VAS, mean Emax was lowest for placebo (41.86), followed by Ground Oxycodone ARIR (62.24) and Intact Oxycodone ARIR (77.31), while Crushed Roxicodone had the highest mean Emax score (82.14).

Table 2. TE_{max} Descriptive Statistics for Drug Liking and High, PD population (N=29)

Parameter	Treatment	Mean	Std Dev	Min	Q1	Median	Q3	Max
Drug Liking	A-Ground Placebo	1.91	4.65	0.08	0.08	0.50	1.50	24.00
	B-Crushed Roxicodone	1.64	1.98	0.08	0.50	1.00	2.00	10.00
	C-Ground Oxycodone ARIR	2.25	1.97	0.08	1.00	1.50	3.00	10.00
	D-Intact Oxycodone ARIR	1.71	0.88	1.00	1.00	1.50	2.00	4.00
High	A-Ground Placebo	2.02	4.94	0.00	0.00	0.50	1.00	24.00
	B-Crushed Roxicodone	1.57	1.28	0.00	0.50	1.50	2.00	6.00
	C-Ground Oxycodone ARIR	1.71	1.00	0.00	1.00	1.50	2.00	4.00
	D-Intact Oxycodone ARIR	1.74	0.69	1.00	1.50	1.50	2.00	4.00

TEmax is a secondary PD parameter, the larger the TEmax value, the longer for a subject to reach the Emax. So longer time to reach peak TEmax indicates the treatment has potential abuse-deterrence.
From table 2, for Drug Liking VAS, Ground Oxycodone ARIR reached TEmax at 2.25 hour longer than the TEmax of Crushed Roxicodone which was at 1.64 hour. Similarly for High VAS, Ground Oxycodone ARIR had TEmax (1.71) longer than the TEmax of Crushed Roxicodone (1.57).

Figure 1 shows the mean drug liking VAS over time, Crushed Roxicodone reached the mean peak score (~76) at hour 1. By 1.5 hours, Drug Liking for intact Oxycodone ARIR was similar to that for crushed Roxicodone (mean 76.7 vs 74.6 mm, respectively) with Drug Liking scores for ground Oxycodone ARIR at 1.5 hours of 66.2 mm and for placebo of 51.5 mm. By 4 hours, the Drug Liking scores for the active treatments narrowed and decreased in parallel and by 10 hours there was little difference among any of the treatments.

Figure 1. Mean Drug Liking VAS Scores over time (PD Population, N=29)

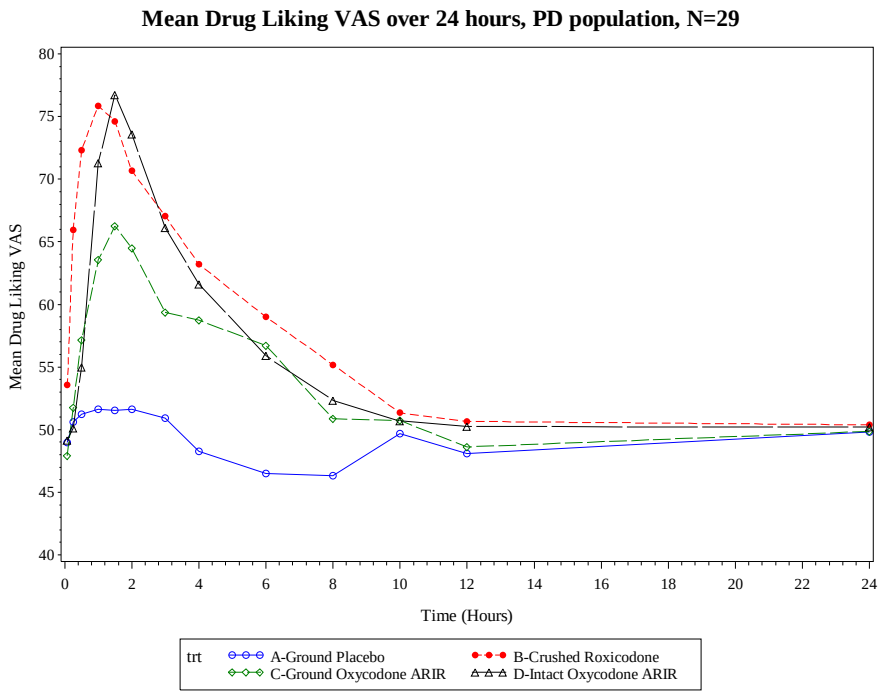
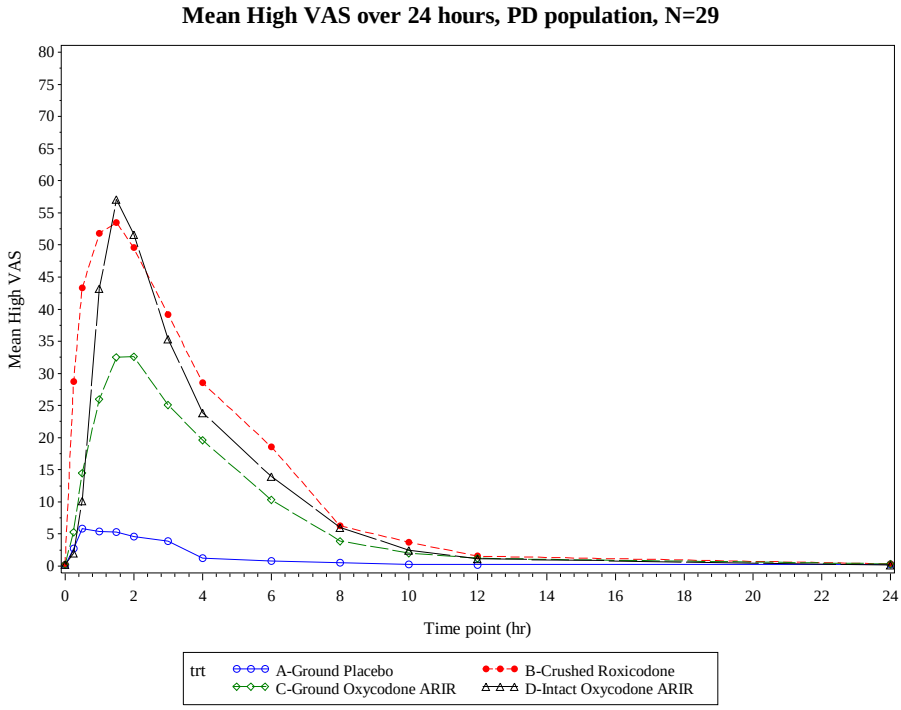


Figure 2 presented the Mean High VAS scores over time. Crushed Roxicodone started earlier and reached the mean peak (~54) at hour 1.7, however, intact Oxycodone ARIR reached a higher maximum (~60) at hour 1.7, and ground Oxycodone ARIR had mean peak (~33). There were no differences in these treatment effects after hour 10. Mean High VAS scores for placebo treatment was low throughout the 24-hours.

Figure 2. Mean High VAS Scores over time (PD Population, N=29)



Individual E_{max} scores are displayed by subject for all treatments from Figure 3 to Figure 6, each row represent one patient with four treatments, the darker color means the more like. We can compare the E_{max} score for each patient at different treatment. The heatmaps show general more like for Crushed Roxicodone and intact Oxycodone ARIR comparing with Ground Oxycodone ARIR, placebo mostly remained neutral.

Figure 3. Heatmap for Emax of Drug Liking VAS by treatment

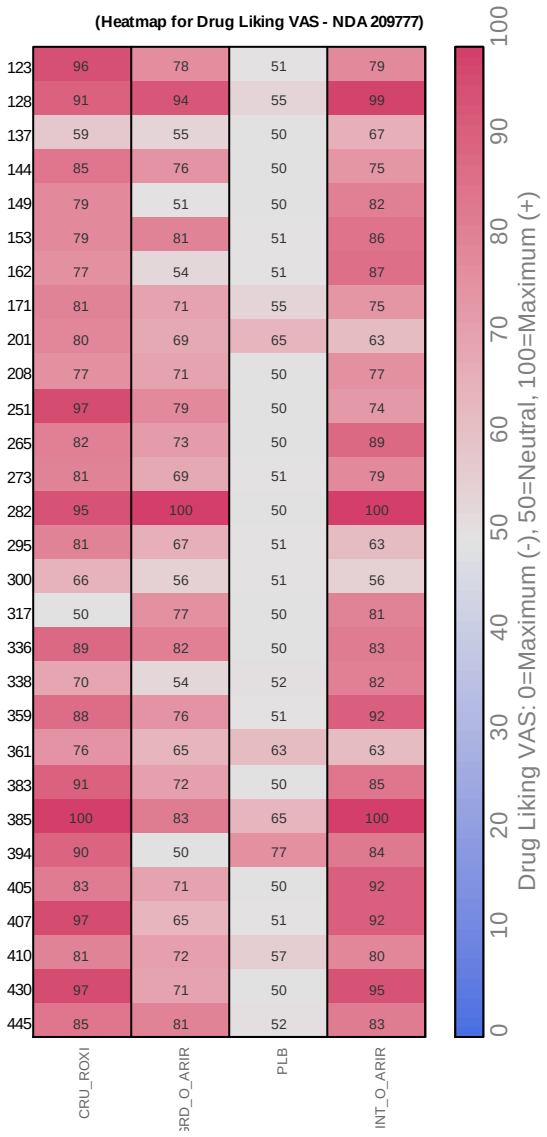


Figure 4. Heatmap for Emax of High VAS by treatment

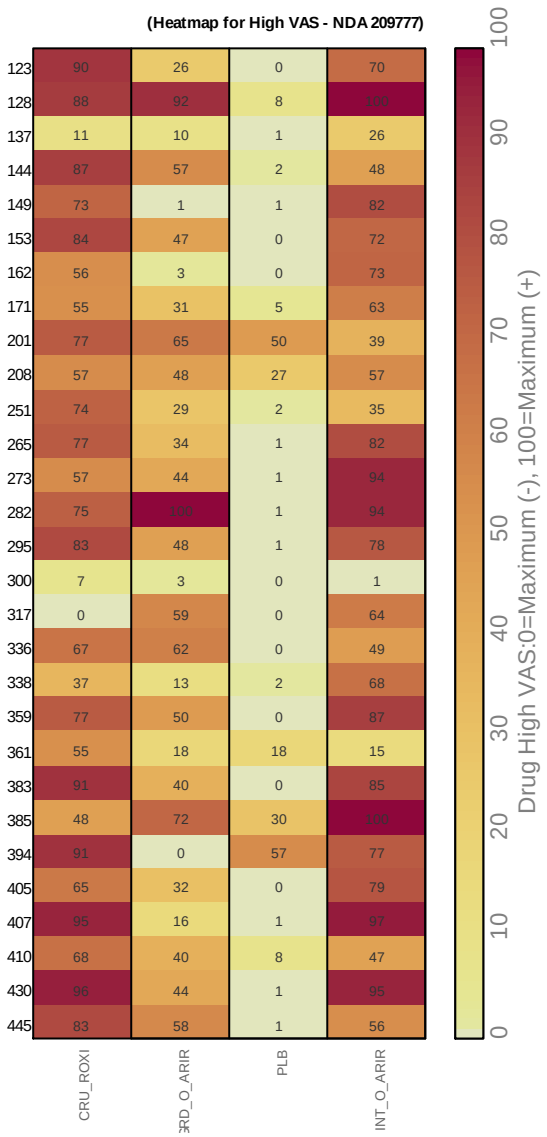


Figure 5. Heatmap for Emax of Overall Drug Liking VAS by treatment

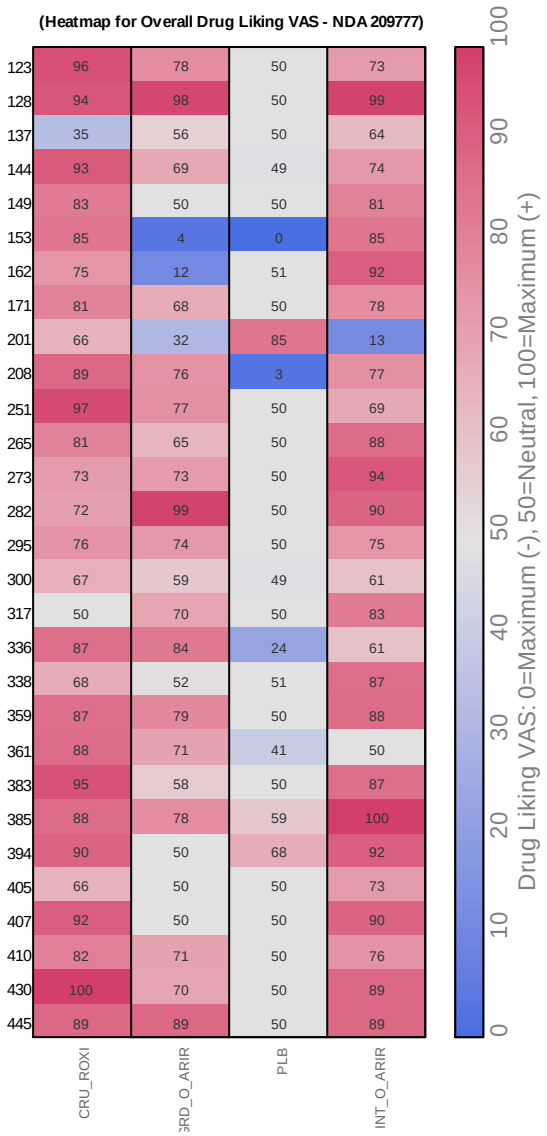
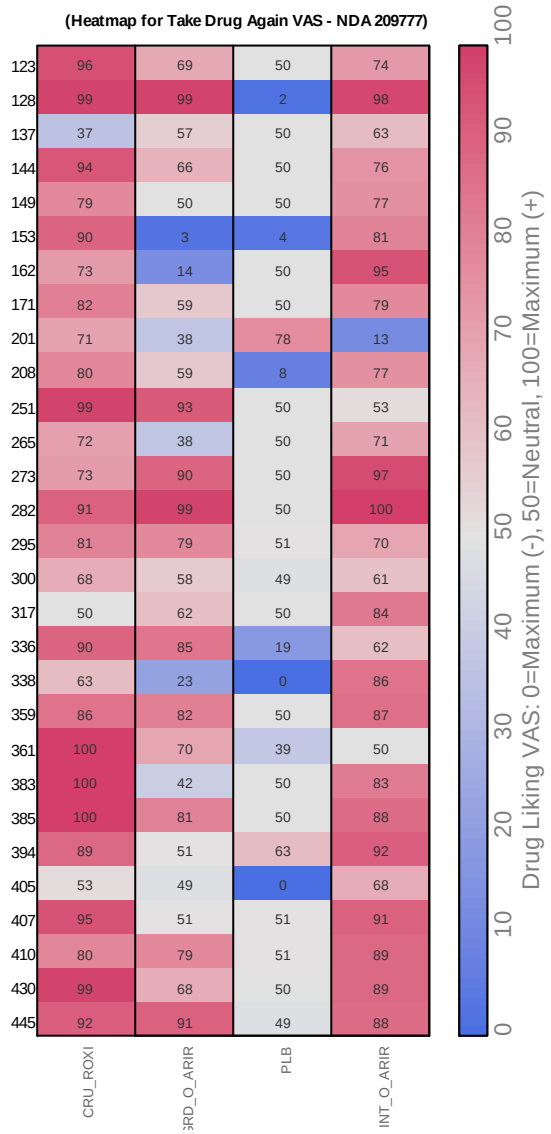


Figure 6. Heatmap for Emax of Take Drug Again VAS by treatment



2.3.2 Statistical Analysis

Analysis of Primary Endpoints for Primary Comparisons

PD parameters of interest for the Treatment Phase will be analyzed using a mixed-effect model if the data is normally distributed. Parameters that don't meet these criteria will be analyzed non-parametrically.

In this study, for Drug Liking, Drug Liking AUE [0-1h], Drug Liking AUE [0-2h] and High, the normality assumption tests were met, the reviewer analyzed the hypotheses of the primary objective using the mixed-effect model, with period, sequence and treatment as fixed effects, and subject nested within treatment sequence as random effect. For Overall Drug Liking and Take Drug Again, the normality assumption test was not met, so non-parametric method was conducted. TEmax of Drug liking VAS and High VAS were also conducted by non-parametric

method. Table 3 to table 8 are the statistical analysis results for Emax of Drug Liking, Drug Liking AUE [0-1h], Drug Liking AUE [0-2h], High, Overall Drug Liking and Take Drug Again respectively. Table 9 is the statistical analysis results for TEmax of Drug Liking and High.

Table 3. Statistical Analysis of the mean difference in Emax for Drug Liking VAS, PD Population.

	LS Mean	StdE	Pr > |t|	Lower	Upper
Treatments					
A-Ground Placebo	53.16	1.98	<.0001	49.23	57.09
B-Crushed Roxicodone	82.67	1.98	<.0001	78.74	86.60
C-Ground Oxycodone ARIR	70.74	1.98	<.0001	66.81	74.67
D-Intact Oxycodone ARIR	81.16	1.98	<.0001	77.23	85.09
Contrasts (difference)					
Crushed Roxicodone vs. Ground Oxycodone ARIR (B-C) – **Primary Test**	11.93	2.40	<.0001	7.16	16.70
Crushed Roxicodone vs. Ground Placebo (B-A)- **Validation Test**	29.50	2.40	<.0001	24.74	34.27
Intact Oxycodone ARIR vs. Ground Oxycodone ARIR (D-C)	10.42	2.40	<.0001	5.65	15.18
Crushed Roxicodone vs. Intact Oxycodone ARIR (B-D)	1.51	2.40	0.53	-3.26	6.28
Ground Oxycodone ARIR vs. Ground Placebo (C-A)	17.58	2.40	<.0001	12.81	22.34
Intact Oxycodone ARIR vs. Ground Placebo (D-A)	27.99	2.40	<.0001	23.22	32.77

The Emax for Drug Liking was significantly (p <0.0001) lower for ground Oxycodone ARIR than crushed Roxicodone. The LS mean Emax for Drug Liking for ground Oxycodone ARIR was 70.74 compared with 82.67 for crushed Roxicodone. There was no significant difference between Crushed Roxicodone and Intact Oxycodone ARIR (P value=0.53).

Table 4. Statistical Analysis of the mean difference in Emax for Drug Liking AUE [0-1h], PD Population.

	LS Mean	StdE	Pr > |t|	Lower	Upper
Treatments					
A-Ground Placebo	0.71	1.17	0.54	-1.62	3.04
B-Crushed Roxicodone	19.20	1.17	<.0001	16.87	21.53
C-Ground Oxycodone ARIR	6.09	1.17	<.0001	3.75	8.42
D-Intact Oxycodone ARIR	6.85	1.17	<.0001	4.52	9.18
Contrasts (difference)					
Crushed Roxicodone vs. Ground Oxycodone ARIR (B-C) – **Primary Test**	13.12	1.51	<.0001	10.11	16.13
Crushed Roxicodone vs. Ground Placebo (B-A)- **Validation Test**	18.49	1.51	<.0001	15.48	21.50
Intact Oxycodone ARIR vs. Ground Oxycodone ARIR (D-C)	0.76	1.51	0.61	-2.24	3.77
Crushed Roxicodone vs. Intact Oxycodone ARIR (B-D)	12.35	1.51	<.0001	9.34	15.36
Ground Oxycodone ARIR vs. Ground Placebo (C-A)	5.37	1.51	0.00	2.36	8.38
Intact Oxycodone ARIR vs. Ground Placebo (D-A)	6.14	1.51	0.00	3.12	9.15

Drug Liking results for AUE [0-1h] and AUE [0-2h] showed similar results as for Emax with significantly less liking for ground Oxycodone ARIR than crushed Roxicodone ($p < 0.0001$).

Table 5. Statistical Analysis of the mean difference in Emax for Drug Liking AUE [0-2h], PD Population.

	LS Mean	StdE	Pr > |t|	Lower	Upper
Treatments					
A-Ground Placebo	2.18	2.91	0.46	-3.62	7.98
B-Crushed Roxicodone	42.91	2.91	<.0001	37.12	48.71
C-Ground Oxycodone ARIR	20.96	2.91	<.0001	15.16	26.75
D-Intact Oxycodone ARIR	31.32	2.91	<.0001	25.52	37.12
Contrasts (difference)					
Crushed Roxicodone vs. Ground Oxycodone ARIR (B-C) – **Primary Test**	21.96	3.49	<.0001	15.02	28.90
Crushed Roxicodone vs. Ground Placebo (B-A)- **Validation Test**	40.73	3.48	<.0001	33.80	47.66
Intact Oxycodone ARIR vs. Ground Oxycodone ARIR (D-C)	10.36	3.48	0.00	3.43	17.30
Crushed Roxicodone vs. Intact Oxycodone ARIR (B-D)	11.59	3.48	0.00	4.66	18.52
Ground Oxycodone ARIR vs. Ground Placebo (C-A)	18.78	3.48	<.0001	11.84	25.71
Intact Oxycodone ARIR vs. Ground Placebo (D-A)	29.14	3.49	<.0001	22.20	36.08

Table 6. Statistical Analysis of the mean difference in Emax for High VAS, PD Population.

	LS Mean	StdE	Pr > |t|	Lower	Upper
Treatments					
A-Ground Placebo	7.26	4.37	0.10	-1.44	15.96
B-Crushed Roxicodone	66.41	4.37	<.0001	57.70	75.11
C-Ground Oxycodone ARIR	38.65	4.37	<.0001	29.94	47.35
D-Intact Oxycodone ARIR	66.09	4.37	<.0001	57.38	74.79
Contrasts (difference)					
Crushed Roxicodone vs. Ground Oxycodone ARIR (B-C) – **Primary Test**	27.76	5.47	<.0001	16.88	38.63
Crushed Roxicodone vs. Ground Placebo (B-A)- **Validation Test**	59.15	5.46	<.0001	48.28	70.01
Intact Oxycodone ARIR vs. Ground Oxycodone ARIR (D-C)	27.44	5.46	<.0001	16.57	38.30
Crushed Roxicodone vs. Intact Oxycodone ARIR (B-D)	0.32	5.46	0.95	-10.55	11.18
Ground Oxycodone ARIR vs. Ground Placebo (C-A)	31.39	5.46	<.0001	20.52	42.25
Intact Oxycodone ARIR vs. Ground Placebo (D-A)	58.83	5.47	<.0001	47.95	69.70

Ground Oxycodone ARIR and Crushed Roxicodone resulted in LS mean Emax values for High VAS of 38.65 and 66.41, respectively. This reduction in maximum High VAS following Ground Oxycodone ARIR was statistically significant lower comparing Crushed Roxicodone ($p<0.0001$) and supports a deterrent effect of Ground Oxycodone ARIR to abuse. For the comparison

between intact Oxycodone ARIR and crushed Roxicodone, Emax was not significantly different (p = 0.95).

Table 7. Nonparametric Analyses of Overall Drug Liking Emax, PD Population

Treatment Difference	Median Difference	StdE	Interquartile Range	P-value
Crushed Roxicodone vs. Ground Oxycodone ARIR (B-C) – **Primary Test**	16	4.30	27	0.0004
Crushed Roxicodone vs. Ground Placebo (B-A)- **Validation Test**	32	4.32	23	<.0001
Intact Oxycodone ARIR vs. Ground Oxycodone ARIR (D-C)	9	4.67	22	0.0021
Crushed Roxicodone vs. Intact Oxycodone ARIR (B-D)	1	3.59	18	0.6313
Ground Oxycodone ARIR vs. Ground Placebo (C-A)	20	4.83	24	0.0006
Intact Oxycodone ARIR vs. Ground Placebo (D-A)	36	4.72	16	<.0001

For Overall Drug Liking, Emax was significantly higher for crushed Roxicodone than ground Oxycodone ARIR (p = 0.0004), but there was no difference between intact Oxycodone ARIR and crushed Roxicodone (p = 0.6313). Overall Drug Liking Emax was significantly higher for intact Oxycodone ARIR than ground Oxycodone ARIR (p = 0.0021).

Table 8. Nonparametric Analyses of Take Drug Again Emax, PD Population

Treatment Difference	Median Difference	StdE	Interquartile Range	P-value
Crushed Roxicodone vs. Ground Oxycodone ARIR (B-C) – **Primary Test**	21	4.54	31	<.0001
Crushed Roxicodone vs. Ground Placebo (B-A)- **Validation Test**	43	4.64	24	<.0001
Intact Oxycodone ARIR vs. Ground Oxycodone ARIR (D-C)	10	5.26	26	0.0049
Crushed Roxicodone vs. Intact Oxycodone ARIR (B-D)	3	4.09	21	0.2587
Ground Oxycodone ARIR vs. Ground Placebo (C-A)	19	5.43	40	0.0005
Intact Oxycodone ARIR vs. Ground Placebo (D-A)	37	5.48	21	<.0001

For Take Drug Again Assessment, Emax was significantly higher for crushed Roxicodone than ground Oxycodone ARIR (p < 0.0001), there was no difference between intact Oxycodone ARIR and crushed Roxicodone (p = 0.2587). Take Drug Again Assessment Emax was higher for intact Oxycodone ARIR than ground Oxycodone ARIR (p = 0.0049).

Table 9. Nonparametric Analyses of TEmax for Drug Liking, PD Population

Treatment Difference	Median Difference	StdE	Interquartile Range	P-value
Crushed Roxicodone vs. Ground Oxycodone ARIR (B-C) – **Primary Test**	-0.75	0.31	2	0.0622
Crushed Roxicodone vs. Ground Placebo	0.17	0.93	1.67	0.4060

(B-A)- **Validation Test**				
Intact Oxycodone ARIR vs. Ground Oxycodone ARIR (D-C)	0	0.37	0.5	0.1578
Crushed Roxicodone vs. Intact Oxycodone ARIR (B-D)	-0.5	0.34	1.5	0.1876
Ground Oxycodone ARIR vs. Ground Placebo (C-A)	1	0.94	0.92	0.0073
Intact Oxycodone ARIR vs. Ground Placebo (D-A)	0.75	0.89	0.92	0.0282

Table 10. Nonparametric Analyses of TEmax for High VAS, PD Population

Treatment Difference	**Median Difference**	**StdE**	**Interquartile Range**	**P-value**
Crushed Roxicodone vs. Ground Oxycodone ARIR (B-C) – **Primary Test**	-0.50	0.22	1.0	0.3119
Crushed Roxicodone vs. Ground Placebo (B-A)- **Validation Test**	1.0	0.97	1.5	0.0594
Intact Oxycodone ARIR vs. Ground Oxycodone ARIR (D-C)	0	0.19	1.0	0.8548
Crushed Roxicodone vs. Intact Oxycodone ARIR (B-D)	-0.5	0.21	1.5	0.2661
Ground Oxycodone ARIR vs. Ground Placebo (C-A)	1.0	0.96	2.25	0.0347
Intact Oxycodone ARIR vs. Ground Placebo (D-A)	1.0	0.93	1.0	0.0101

Table 9 and Table 10 show that no significant difference in TEmax between Crushed Roxicodone and Ground Oxycodone ARIR for Drug Liking (P=0.0622) and High VAS (P=0.3119).

Note: The reviewer's conclusion for TEmax is different from sponsor's conclusion.

Percent Reduction Analysis

Percent reduction analysis is an important abuse potential measure, and it is recommended for the clinical abuse potential studies. For the parameter of Drug Liking Emax VAS, percent reductions were calculated for each subject for both test treatments as:

$$\%\,reduction = \begin{cases} \dfrac{C-T}{C-50} \times \left(1 - \dfrac{P-50}{50}\right) \times 100\%, & if\ P > 55; \\ \dfrac{C-T}{C-50} \times 100\%, & if\ P \le 55. \end{cases}$$

where C and T were the Emax values for the control and the test product, respectively, and P was the Emax value of placebo. The percent reduction was calculated if data for the active control and test product were available. In cases where one of those values was not available or the control was equal to 50, percent reduction was to be set to 0.

Note, the reviewer doesn't agree with sponsor's percent reduction analysis method: sponsor set the percent reduction the largest percentage observed in the study in the case of the control was equal to placebo. The reviewer's suggestion: If the control was equal to placebo, a negative value or zero should be set to the percent reduction.

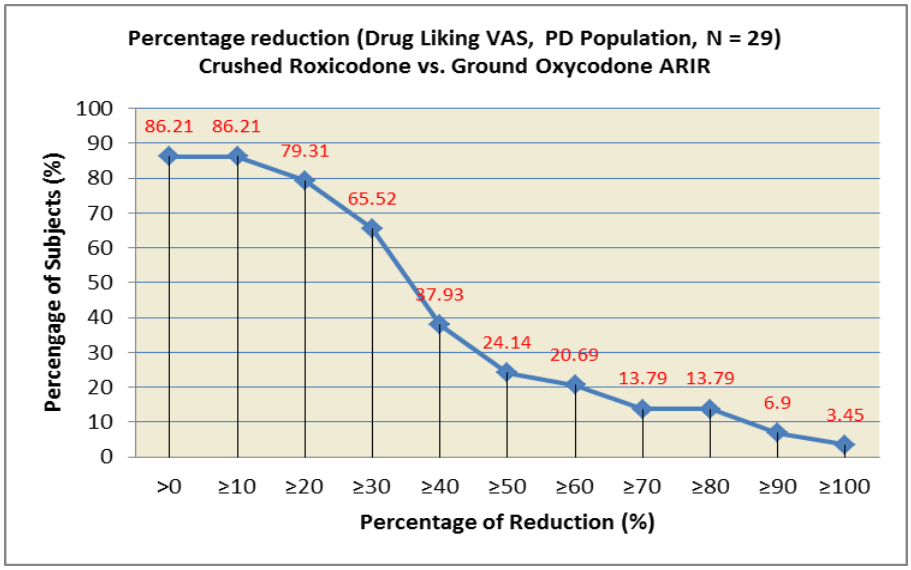
Crushed Roxicodone vs. Ground Oxycodone ARIR

From Table 9 and Figure 7, 25 out of the 29 subjects who completed the study (~86%) had some reduction in Drug Liking with Ground Oxycodone ARIR compare to Crushed Roxicodone, while 14% subjects had no reduction or negative reduction. 19 subjects (~66%) had at least 30% reduction and 7 subjects (~24%) had at least 50% reduction in Drug Liking with Ground Oxycodone ARIR compare to Crushed Roxicodone.

Table 11. %reduction, Drug Liking VAS, Crushed Roxicodone vs. Ground Oxycodone ARIR (PD Population, N=29)

Percentage of Reduction (%)	Frequency	Percentage of subjects (%)
>0	25	86.21
≥10	25	86.21
≥20	23	79.31
≥30	19	65.52
≥40	11	37.93
≥50	7	24.14
≥60	6	20.69
≥70	4	13.79
≥80	4	13.79
≥90	2	6.90
≥100	1	3.45

Figure 7. %reduction, Drug Liking VAS, Crushed Roxicodone vs. Ground Oxycodone ARIR (PD Population, N=29)



2.3.3 Primary statistical analysis using 2015 new guidance method

The 2015 FDA Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling suggests the primary analysis of abuse-deterrent effects should be based on the comparison of means between crushed, chewed, or otherwise modified T and C with an abuse deterrence margin on drug liking VAS. That is, test

$$H_0 : \mu_C - \mu_T \le \delta_1 \; vs \; H_a : \mu_C - \mu_T > \delta_1 \quad (1)$$

Where μ_C and μ_T denote means of positive control and test drug respectively, and $\delta_1 = \delta^*(\mu_C - 50), 0 < \delta^* < 1,$ formula (1) is equivalent to:

$$H_0 : \mu_T - (1-\delta^*)\mu_C \ge 50\delta^* \; vs \; H_a : \mu_T - (1-\delta^*)\mu_C < 50\delta^* \quad (2)$$

Study validation is denoted as following, Where μ_P denotes mean of placebo and $\delta_2 \ge 15$.

$$H_0 : \mu_C - \mu_P \le \delta_2 \; vs \; H_a : \mu_C - \mu_T > \delta_2 \quad (3)$$

Both tests are one-sided at the 2.5% significance level.

These hypotheses can be extended to the other PD endpoints using unipolar scale such as High VAS with $\delta_1 = \delta^* \mu_C \; (0 < \delta^* < 1)$ and $\delta_2 \ge 30$.

According to the 2015 FDA guidance, δ^* should be pre-specified in the protocol. Since this NDA study was submitted before the guidance was published, the reviewer used δ^*=0.10 with 0.05 increment for each primary comparison, and stopped once an insignificant result was obtained. Table 10 lists the test results.

Table 12. Summary of primary analysis result for Drug Liking, High, Take Drug Again and Overall Drug Liking by following 2015 FDA new guidance.

Parameter	Comparison	Test type	Estimate Diff	Std Err	T-value	Tails	P-value	Lower	Upper
Drug Liking	Crushed Roxicodone vs. Ground Placebo (B-A)	Validation	29.50	2.40	6.05	Upper	<.0001	24.74	Infty
	Crushed Roxicodone vs. Ground Oxycodone ARIR (B-C)	Primary (δ*=0.20)	4.61	2.18	10.00	Lower	0.0078	-Infty	8.95
High	Crushed Roxicodone vs. Ground Placebo (B-A)	Validation	59.15	5.46	5.34	Upper	<.0001	48.28	Infty
	Crushed Roxicodone vs. Ground Oxycodone ARIR (B-C)	Primary (δ*=0.25)	-11.16	4.86	-2.30	Lower	0.0121	-Infty	-1.49
Take Drug Again	Crushed Roxicodone vs. Ground Placebo (B-A)	Validation	40.24	4.93	5.12	Upper	<.0001	30.43	Infty
	Crushed Roxicodone vs. Ground Oxycodone ARIR (B-C)	Primary (δ*=0.35)	8.49	4.19	-2.15	Lower	0.0172	-Infty	16.82
Overall Drug Liking	Crushed Roxicodone vs. Ground Placebo (B-A)	Validation	33.25	4.47	4.09	Upper	<.0001	24.36	Infty

	Crushed Roxicodone vs. Ground Oxycodone ARIR (B-C)	Primary (δ*=0.30)	7.29	3.87	-1.99	Lower	0.0249	-Infty	14.99

Table 10 shows that Emax of Crushed Roxicodone is significantly greater than Ground placebo (P<0.0001) for Drug Liking VAS, High VAS, Take Drug Again VAS and Overall Drug Liking VAS, thereby confirming study validity. For the primary comparison between Crushed Roxicodone vs. Ground Oxycodone ARIR, Ground Oxycodone ARIR had statistically significant 20% reduction in Emax of Drug Liking VAS, 25% reduction in Emax of High VAS, 35% reduction in Emax of Take Drug Again VAS and 30% reduction in Emax of Overall Drug Liking VAS comparing with Crushed Roxicodone.

3. Conclusions

The primary objective was to assess the relative abuse potential of Ground Oxycodone ARIR to crushed Roxicodone when administered intranasally to nondependent, recreational opioid users with intranasal experience.

The reviewer analyzed the primary PD endpoint Drug Liking, and the secondary PD endpoints: Drug Liking AUE [0-1h] Emax, Drug Liking AUE [0-2h] Emax, High, Take Drug Again and Overall Drug Liking. The results from the statistical reviewer's analyses establish that:

- The Crushed Roxicodone resulted in statistically significantly greater (p<0.0001) VAS scores compared to Ground placebo for Drug Liking, Drug Liking AUE [0-1h] Emax, Drug Liking AUE [0-2h] Emax, High, Take Drug Again and Overall Drug Liking, thereby validating these pharmacodynamic measures.

- The Emax for Drug Liking VAS was significantly (p<0.0001) lower for ground Oxycodone ARIR than crushed Roxicodone. The LS mean Emax for Drug Liking VAS for ground Oxycodone ARIR was 70.74 compared with 82.67 for crushed Roxicodone. There was no significant difference between Crushed Roxicodone and Intact Oxycodone ARIR (P value=0.53). Drug Liking of AUE [0-1h] and AUE [0-2h] showed similar results in Emax with statistically significant less liking for ground Oxycodone ARIR than crushed Roxicodone (p<0.0001). These data support a possible deterrent effect of Ground Oxycodone ARIR to abuse.

- Ground Oxycodone ARIR and Crushed Roxicodone resulted in LS mean Emax values for High VAS of 38.65 and 66.41, respectively. This reduction in maximum High VAS following Ground Oxycodone ARIR was statistically significant lower comparing Crushed Roxicodone (p<0.0001) and supports a deterrent effect of Ground Oxycodone ARIR to abuse.

- For Take Drug Again VAS, the median difference between Crushed Roxicodone and Ground Oxycodone ARIR was 21 (p<0.0001). This reduction suggests that if given the opportunity again, subjects would have a greater willingness to Crushed Roxicodone, as opposed to Ground Oxycodone ARIR. This supports a deterrent effect of Ground Oxycodone ARIR to abuse.

- For Overall Drug Liking VAS, the median difference between Crushed Roxicodone and Ground Oxycodone ARIR was 16 (p=0.0004). This provides additional support for a deterrent effect of Ground Oxycodone ARIR to abuse.

- There was no significant difference in TEmax between Crushed Roxicodone and Ground Oxycodone ARIR for Drug Liking VAS (P=0.06) and High VAS (P=0.3119).

- There was no significant difference between Crushed Roxicodone and Intact Oxycodone ARIR for Drug Liking VAS, High VAS, Take Drug Again VAS and Overall Drug Liking VAS (P-values>0.05).

- 25 out of the 29 subjects who completed the study (~86%) had some reduction in Drug Liking VAS with Ground Oxycodone ARIR compare to Crushed Roxicodone, while 14% subjects had no reduction or negative reduction. 19 subjects (~66%) had at least 30% reduction and 7 subjects (~24%) had at least 50% reduction in Drug Liking VAS with Ground Oxycodone ARIR compare to Crushed Roxicodone.

By following the 2015 new guidance:

- Emax of Crushed Roxicodone is significantly greater than Ground placebo (P<0.0001) for Drug Liking VAS, High VAS, Take Drug Again VAS and Overall Drug Liking VAS, thereby confirming study validity.
- For the primary comparison between Crushed Roxicodone vs. Ground Oxycodone ARIR, Ground Oxycodone ARIR had statistically significant 20% reduction in Emax of Drug Liking VAS, 25% reduction in Emax of High VAS, 35% reduction in Emax of Take Drug Again VAS and 30% reduction in Emax of Overall Drug Liking VAS comparing with Crushed Roxicodone.

Additional comments:

- In this study, for the statistical analyses of the PD parameters, sponsor used the rank transformations analysis while the normality assumption was not met for.
  Reviewer's comments:
  The results from Rank transformation should be interpreted carefully. The mixed model uses the rankings of VAS scores instead of their values as outcome, so it is the result of testing the differences of mean rankings from two treatment arms, not the mean or median of paired differences (in VAS score values) from two treatments.

- The reviewer doesn't agree with sponsor's percent reduction analysis method: sponsor set the percent reduction the largest percentage observed in the study in the case of the control was equal to placebo. The reviewer's suggestion: If the control was equal to placebo, a negative value or zero should be set to the percent reduction.

- The new ADF guidance has published in April 2015, in the future, you should follow the new guidance regarding the hypothesis testing and pre-specifications as well as primary and secondary statistical analysis at:
  http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf

4. References

1) Guidance for Industry: Assessment of Abuse Potential for Drugs (January 2017)

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf

2) Guidance for Industry: Abuse Deterrent Opioids—Evaluation and Labeling (April 2015) http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf

3) Chen, Klein and Calderon (2012) poster presentation at the 74th College on Problems of Drug Dependence (CPDD) annual scientific meeting held in Palm Springs.

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/s/

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