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:	202-080
Drug Name:	Acurox® Tablets (oxycodone HCl, USP)
Study number:	K234-10-1002
Applicant:	King Pharmaceuticals Research and Development, Inc.
Date(s):	Submission date: 12/17/10 PDUFA date: 06/17/11 Completion date: 04/01/2011
Review Priority:	P
Biometrics Division:	DB VI
Statistical Reviewer:	Ling Chen, Ph.D., Mathematical Statistician, Special Project Team.
Concurring Reviewers:	Stella Machado, Ph.D., Division Director, and Acting Team Leader,
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Keywords: Crossover design; Drug abuse potential study; Self-reported endpoint; Multiple endpoints

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1. Executive Summary

Study K234-10-1002 in NDA 202080 was a randomized, double-blind, active-controlled crossover study to evaluate the relative abuse potential and safety of intranasally administered crushed Acurox® Tablets in comparison with crushed Roxicodone Tablets in non-dependent recreational opioid users.

There were two treatments in the study. These treatments were 2 crushed Acurox® Tablets each containing oxycodone HCl 7.5 mg, and 3 crushed Roxicodone® Tablets each containing oxycodone HCl 5 mg. The primary abuse potential measure was Drug Liking on the visual analog scale (VAS). Overall Drug Liking VAS and Take Drug Again VAS were considered as secondary measures. All measures were on a bipolar scale.

After Naloxone Challenge Phase (ensuring that subjects were not physically dependent on opioids) and Drug Discrimination Phase (ensuring that subjects could differentiate between intranasally self-administered crushed Roxicodone® Tablets 15 mg and placebo (weight-equivalent crushed Lactose tablets)), 40 eligible subjects were enrolled in the Treatment Phase and completed the study as planned.

Because 2 crushed Acurox® Tablets (weight 980 mg) had more than 3 times the weight of 3 crushed Roxicodone® Tablets (weight 300 mg), the study was not truly blind to opioid users. Serious sequence effects were found in this study. Thus, only data collected in the first period were used in this reviewer's analysis.

The reviewer's analysis showed that for crushed Acurox® Tablets, 11 subjects (>50%) had scores 90 to 100 for Emax of Drug Liking VAS. For Overall Drug Liking VAS and Take Drug Again VAS, 40% of subjects had scores between 90 and 100. In addition, 65%, 55% and 45% of subjects in Acurox® group had scores 80 or above for Emax of Drug Liking VAS, Overall Drug Liking VAS, and Take Drug Again VAS, respectively. Even though these percentages were similar to or lower than those of crushed Roxicodone® Tablets, the median response of crushed Acurox® Tablets was not significantly lower than that of crushed Roxicodone® Tablets in the Wilcoxon-Mann-Witney test for the primary and secondary measures based on data from the first period.

In conclusion, the study did not demonstrate that Acurox® Tablets have a lower abuse potential than Roxicodone® Tablets when crushed and administered intranasally to non-dependent recreational opioid users.

2. Review Report on Study K234-10-1002

2.1 Overview

2.1.1 Objectives of the study

Primary objective

The primary objective of this study was to compare the relative abuse potential of crushed Acurox® Tablets with crushed Roxicodone® Tablets when administered intranasally to non-dependent recreational opioid users.

Secondary objective

The secondary objective was to evaluate the single-dose safety of crushed and intranasally administered Acurox® Tablets in non-dependent recreational opioid users.

Reviewer's comment: This review is for the primary objective only.

2.1.2 Study design

This study used a single-center, single-dose, randomized, double-blind, active-controlled, 2-way crossover design to assess the relative abuse potential of intranasally administered crushed Acurox® Tablets in non-dependent recreational opioid users.

Treatments evaluated are noted below and were administered intranasally in the fasted or fed state.

Treatment A: 2 crushed Acurox® Tablets each containing oxycodone HCl 7.5 mg (total dose of oxycodone HCl 15 mg)

Treatment B: 3 crushed Roxicodone® Tablets each containing oxycodone HCl 5 mg (total dose of oxycodone HCl 15 mg)

Besides Screening Phase (a standard out patient medical screening visit conducted up to 28 days), study subjects participated in a Naloxone Challenge Phase, a Drug Discrimination Phase, and a Treatment Phase. The Naloxone challenge Phase was for ensuring that subjects were not physically dependent on opioids, and the Drug Discrimination Phase was for ensuring that subjects could differentiate between intranasally self-administered crushed Roxicodone® Tablets 15 mg and placebo (weight-equivalent crushed Lactose tablets). The Treatment Phase consisted of 2 dosing periods. The washout period in the Treatment Phase was 48 (±1) hours.

2.1.3 Abuse Potential Measures

The primary measure was Drug Liking VAS question assessed at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, and 8 hours post-dose. Both Overall Drug Liking VAS and Take Drug Again were the secondary measures, and assessed at 8 hours post-dose. All three measures were on a bipolar scale.

2.1.4 Number of subjects

A total of 130 subjects was screened for inclusion in this study; 60 of these subjects were randomized and dosed in the Naloxone Challenge and Drug Discrimination Phase. Forty eligible subjects were enrolled in the Treatment Phase and completed the study as planned. One completed subject was excluded from the Sponsor's analyses because of post-dose AEs (vomiting); 39 subjects were included in the evaluable population.

Reviewer's comments: Subject ID 9028 was not included in the Sponsor's statistical analysis because of vomiting during Acurox® treatment. This subject had an episode of moderate vomiting during Acurox® treatment, recorded at Hour 0 (resolved in less than 1 minute), and also had an episode of mild vomiting during Roxicodone treatment at Hour 0.9 (resolved at 0 minute). However, the subject responded to the Drug liking VAS at all planned time points. The Emax of Drug Liking, Overall Drug Liking and Take Drug Again for Acurox® were scored at 100, 93 and 100, respectively. The FDA filing letter questioned eliminating this subject in the analysis. The Sponsor responded to the FDA that they were willing to redo the analysis including this subject. Because adding this subject in the Sponsor's analysis would not change the conclusion made by the Sponsor, a repeat of the analysis was not requested by this reviewer. However, this subject was included in the reviewer's analysis.

2.1.5 Statistical Methodologies Used in the Sponsor's Analyses

The parameters of interest for the Sponsor

Drug Liking VAS — The primary parameter of interest was
- Maximum (peak) effect (Emax)

The supporting parameters of interest were:
- Effects at designated time points (E0.25h, E0.5h, E1h, E1.5h, E2h, E3h)
- Area under the effect curve (AUE) over the intervals AUE0-1h, AUE0-2h, AUE0-3h, and AUE0-8h
- Time to peak effect (TEmax)
- Minimum effect (Emin) (peak disliking effect)
- Time to minimum effect (TEmin)

Take Drug Again VAS — The primary parameter of interest was
- Response at 8 hours after drug administration

Overall Drug Liking VAS — The primary parameter of interest was
- Response at 8 hours after drug administration

Primary Pharmacodynamic Analyses

The assessment parameters for the Sponsor's primary endpoints were summarized by treatment using descriptive statistics (n, arithmetic mean, median, standard deviation [SD], range, coefficient of variation). These parameters were analyzed using a linear mixed model with fixed effects for sequence, period, and treatment and a random effect for subject nested in sequence. Least square means were provided for each treatment and for the difference between treatments.

Secondary Pharmacodynamic Analyses

Analyses like those described for the primary PD endpoints were performed on all secondary PD endpoints and assessment parameters. Analyses of pupillometry included the pre-dose measurement as a covariate in the model. Raw p-values for comparisons between treatments were presented.

2.1.6 Sponsor's results and conclusion

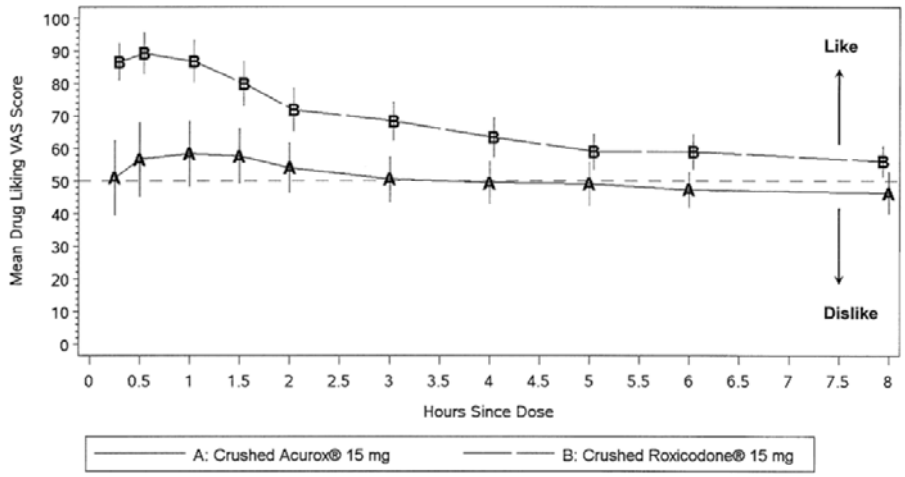
Drug Discrimination Phase

The Drug Discrimination Phase demonstrated that all subjects randomized to the Treatment Phase were able to distinguish crushed Roxicodone® Tablets (positive control) from crushed placebo using the endpoints and parameters specified for the study. This demonstrated that subjects were appropriately qualified for subsequent testing of crushed Roxicodone® Tablets and crushed Acurox® Tablets, and supported assay sensitivity.

Treatment Phase

The sponsor illustrated a figure to show the difference in mean time course profiles between two treatments on Drug Liking VAS (See Sponsor's Figure 1 below).

Synopsis Figure 1. Mean (± 95% CI) Drug Liking VAS Score Over Time – Evaluable Population (N=39)



The Sponsor also provided summary of their primary analyses results (See Sponsor's Table 1 below).

Synopsis Table 1. Summary of Primary Analyses: Acurox® Tablets Compared With Roxicodone® Tablets – Evaluable Population (N=39)

	Least Square Mean Difference[1] (SE)	95% Confidence Interval	P-value
Drug Liking VAS E_{max}	-22.6 (4.67)	-32.0, -13.3	<0.0001
Overall Drug Liking VAS E_{8h}	-39.5 (6.25)	-52.0, -27.1	<0.0001[2]
Take Drug Again VAS E_{8h}	-45.4 (7.28)	-59.9, -30.9	<0.0001[2]

E_{max} = maximum effect or greatest liking; E_{8h} = effect at 8 hours; SE = standard error; VAS = visual analogue scale.
[1] Least square mean differences were estimated from a linear mixed-effect analysis of variance with treatment sequence, period, and treatment as fixed effects, and subject within treatment sequence as a random effect. Treatment effects were significant for all 3 parameters ($p<0.0001$). Sequence effects were also significant for all parameters ($p\leq0.0054$); however, period effects were not significant ($p\geq0.1556$).
[2] P-values were adjusted using the Hochberg procedure.

The sponsor also examined pupillometry parameters, and did responder analysis. The sponsor stated that

Analysis of responders indicated that the majority of subjects (72%) had a reduction in Drug Liking VAS Emax with Acurox® Tablets compared with Roxicodone® Tablets. There was considerable individual variability in the degree of reduction in Drug Liking VAS Emax scores, ranging between 4% and 100%. Similar effects were seen with Overall Drug Liking VAS and Take Drug Again VAS assessments.

Reviewer's comments: If a subject had a score 100 to Roxicodone® treatment, with a 10% reduction, the subject would have a score 90 to Acurox® treatment. These two scores are both indicative of abuse potential.

Analysis of pupillometry parameters demonstrated that the pharmacological response to oxycodone was similar between the 2 treatments.

Based on above results, the Sponsor concluded that

Acurox® Tablets have a lower abuse potential than Roxicodone® Tablets when crushed and administered intranasally to non-dependent recreational opioid users. Results are consistent across all primary and secondary endpoints and are in the expected direction (i.e., Acurox® Tablets showed less effect than Roxicodone® Tablets).

Reviewer's comment: All results were based on 39 subjects. As this reviewer indicated earlier, addition of Subject 9028 into the Sponsor's analysis would not make significant difference in the Sponsor's conclusions. Thus, repeating the Sponsor's analysis based on 40 subjects was not requested by this reviewer.

2.2 Data Location

The analysis dataset is located

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2.3 Reviewer's Analysis

The weight of 2 crushed Acurox® Tablets (weight 980 mg) is more than 3 times the weight of 3 crushed Roxicodone® Tablets (weight 300 mg). Because of the difference in weight, the study could not be truly blind to opioid users. Also, serious sequence effects were found in this study.

According to the Sponsor's report, 21 subjects (53%) were unable to completely insufflate Acurox® Tablets. The most common reason for incomplete insufflation was blocked nasal passages (reported by 18 subjects) followed by drug falling from the nose immediately after snorting (2 subjects). One subject vomited during dosing (Subject #9028). All subjects were able to completely insufflate the entire dose of crushed Roxicodone® Tablets.

Table 1 lists the data from 40 subjects for primary endpoint Emax of Drug Liking VAS, and percentages of dose insufflated for subjects with complete or incomplete crushed Acurox® Tablets insufflation.

Table 1: Emax of Drug Liking VAS and Percentage of Dose Insufflated for Subjects with Complete or Incomplete crushed Acurox® Tablets Insufflation

Subject (AB)**	Crushed Acurox®	Pct*	Crushed Roxicodone®	Subject (BA)**	Crushed Acurox®	Pct*	Crushed Roxicodone®
9004	100	98.7	100	9001	96	100	100
9005	74	100	100	9003	67	75.4	88
9011	67	100	78	9010	82	98.5	100
9012	100	88.9	100	9015	51	48.5	88
9017	86	100	100	9016	51	27.7	97
9023	100	100	100	9025	99	28.7	51
9024	95	97.8	100	9026	51	100	100
9028	100	71.9	100	9046	90	97.9	87
9038	100	59.3	100	9048	100	100	100
9039	66	100	81	9051	71	100	86
9052	100	52.7	100	9058	58	100	76
9057	90	100	100	9062	51	100	56
9067	54	41.6	100	9063	51	100	100
9070	100	96.2	93	9081	71	100	100
9071	83	100	88	9086	87	44.2	100
9088	4	40.3	100	9089	51	100	100
9094	100	47.1	100	9093	20	51.6	98
9095	50	100	100	9098	8	85.4	100
9108	100	100	100	9106	61	93.5	92
9110	68	100	100	9019	0	100	100

*: Percentage of dose insufflated for subjects with incomplete crushed Acurox® Tablets insufflation
**: AB and BA are two sequences. A and B represent the crushed Acurox® Tablets and the crushed Roxicodone Tablets, respectively.

From Table 1 one may see the following:

- More subjects gave high score to crushed Roxicodone® Tablets when administered intranasally in the second period than that in the first period. Sixteen subjects in the second period (see column 4) versus 10 subjects in the first period (see column 8) had a score 100 for crushed Roxicodone® Tablets.
- More subjects gave lower score to crushed Acurox® Tablets when administered it intranasally in the second period than that in the first period. Three subjects in the first period (see column 2) versus 10 subjects in the second period (see column 6) had a score below 60 for crushed Acurox® Tablets.
- There were 21 subjects with incomplete crushed Acurox® Tablets insufflation.
- Some subjects had low insufflation percentage for crushed Acurox® Tablets, but had score higher than 90 (See subjects 9038, 9052, 9094, and 9025).

For those subjects who had low insufflation percentage but high score, the interpretation may be that the small amount of crushed Acurox® Tablets may make some subjects like the drug a lot, presuming oxycodone is uniformly distributed in crushed Acurox® Tablets. There is no placebo in this study. Thus, it is difficult to determine if the responses from these subjects are reliable.

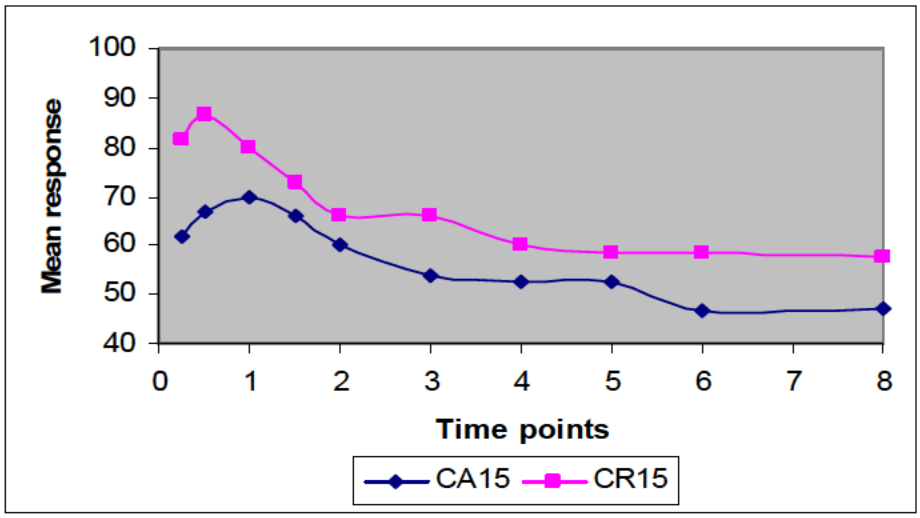
The difference in weights between two treatments made the study not truly blind. Severe sequence effects in the study were observed (See Table 1) Because of these problems in the study, the data are usable only from the first period. Thus, this reviewer's analysis used two independent samples from the first period.

2.3.1 Descriptive Statistics

Figures 1 gives the mean time course profiles for Drug Liking VAS.

Figure 1 shows that the peak mean responses for crushed Acurox® Tablets and crushed Roxicodone® Tablets were at hour 0.5 and hour 1.0, respectively. The mean response to crushed Acurox® Tablets was consistently lower than that of crushed Roxicodone® Tablets for the entire 8 hour time course. The peak mean response to crushed Roxicodone® Tablets was approximately 86, and reached at 30 minutes after dosing. The peak mean response to crushed Acurox® Tablets was approximately 70, and reached at 1 hour after dosing.

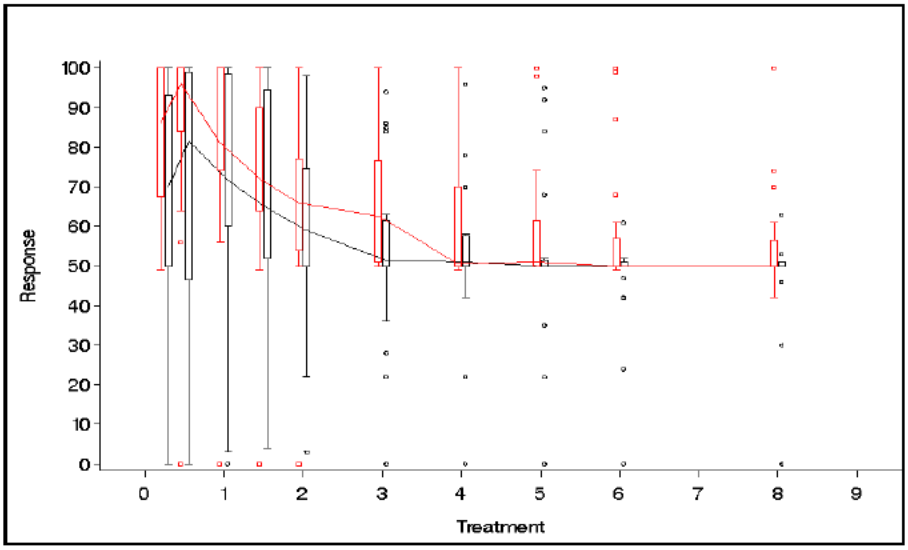
Figure 1: Mean Time Course Profiles for Drug Liking VAS



CA15 and CR 15 denote crushed Acurox® 15 mg Tablets and crushed Roxicodone® 15 mg Tablets, respectively.

Figure 2 shows the boxplots for Drug Liking VAS at each time point by treatments. The curves connected medians of the data distributions. Crushed Acurox® Tablets had lower median at each time point during the first 3 hours than crushed Roxicodone® Tablets. Variability in responses to crushed Acurox® Tablets was large in early hours, and the 75th percentiles of responses to the crushed Acurox Tablets at hours 0.25, 0.5, 1.0 and 1.5 were above score 90 for Drug Liking VAS.

Figure 2: Boxplots for Drug Liking VAS by Treatments



Note: CR15 is in red and CA 15 is in black.

This reviewer categorized the data into six categories: [0, 40), [40, 60), [60, 80), [80, 90), [90, 100], and listed the frequencies in Table 2. Note that these measures were on bipolar scale, and 50 was a neutral score.

Table 2: Categorical Summary for Abuse Potential Measures

Abuse Potential Measures	Treatment	[0. 40)	[40, 60)	[60, 70)	[70. 80)	[80, 90)	[90, 100]
Emax of Drug Liking VAS	CA15	1	2	3	1	2	11
	CR15	0	2	0	1	4	13
Overall Drug Liking VAS	CA15	6	0	3	1	2	8
	CR15	1	1	2	5	4	7
Take Drug Again VAS	CA15	6	0	3	2	1	8
	CR15	1	1	2	1	2	13

It can be seen from Table 2 that for crushed Acurox® Tablets, 11 subjects (>50%) had Emax of Drug Liking VAS 90 to 100; and 40% of subjects were in the same category for Overall Drug Liking VAS and Take Drug Again VAS. In addition, 65% of subjects in Acurox® group had

Emax of Drug Liking VAS 80 or above; 55% and 45% subjects had score 80 or above to Overall Drug Liking VAS and Take Drug Again VAS, respectively.
Table 3 lists the quantiles of responses for Emax of Drug Liking VAS, Overall Drug Liking VAS, and Take Drug Again VAS.

Table 3: Quantiles of Responses to the Primary and Secondary Endpoints by Treatments

Quantiles	Emax of Drug Liking VAS		Overall Drug Liking VAS		Take Drug Again VAS	
	CA15	CR15	CA15	CR15	CA15	CR15
0.0%	4	51	0	0	0	0
0.5%	4	51	0	0	0	0
2.5%	4	51	0	0	0	0
10.0%	50.4	58	0	51.1	0	52.2
25.0%	67.25	86	30.75	72.25	6.75	76.5
50.0%	92.5	97.5	78.5	83	77	100
75.0%	100	100	95.25	100	100	100
90.0%	100	100	100	100	100	100
97.5%	100	100	100	100	100	100
99.5%	100	100	100	100	100	100
100.0%	100	100	100	100	100	100

From Table 3, it is clear that 25% of subjects strongly like crushed Acurox® Tablets and wanted to take the drug again. Medians for crushed Acurox® Tablets were 92.5, 78.5 and 77 for Emax of Drug Liking VAS, Overall Drug Liking VAS and Take Drug Again VAS, respectively. Although the medians in Acurox® group were lower than those in Roxicodone® group, the median score 92.5 for Acurox® versus that 97.5 for Roxicodone for the primary endpoint Emax of Drug Liking VAS, and 78.5 versus 83 for Overall Drug Liking VAS did not show a meaningful difference in terms of abuse potential.

2.3.2 Inferential Statistics

Because the normality assumption on the parent distributions for the two independent samples from the first period was not satisfied, the Wilcoxon-Mann-Whitney test was used in the reviewer's analysis to test

H_0 : Acurox® Tablets has the same abuse potential as Roxicodone® Tablets, when crushed and administered intranasally to non-dependent recreational opioid user.
H_a : Acurox® Tablets has less abuse potential than Roxicodone® Tablets, when crushed and administered intranasally to non-dependent recreational opioid user.

for the primary measure and the secondary measures.

It is equivalent to testing

$H_0 : M_{CA15} = M_{CR15}$ versus $H_a : M_{CA15} < M_{CR15}$

for the primary measure and the secondary measures, where M_{CA15} and M_{CR15} denote the medians for crushed Acurox® 15 mg and crushed Roxicodone® 15 mg, respectively.

Table 4 shows that the median response of crushed Acurox® Tablets was not significantly lower than that of crushed Roxicodone® Tablets with the p-values 0.2261, 0.1254, and 0.0609 (one-sided) for Emax of Drug Liking, Overall Drug Liking VAS, and Take Drug Again VAS, respectively.

Table 4: The Results from the Wilcoxon-Mann-Witney Test ($\alpha = 0.025$)

Abuse Potential Measure	TRT	N	Sum of Scores*	Expected Under H0	StdDev Under H0	Mean Score	P-value**
Drug Liking VAS	CA15	20	383.0	410.0	35.24	19.15	0.2261
	CR15	20	437.0	410.0	35.24	21.85	
Overall Drug Liking VAS	CA15	20	367.5	410.0	36.56	18.38	0.1254
	CR15	20	452.5	410.0	36.56	22.63	
Take Drug Again VAS	CA15	20	355.5	410.0	34.90	17.78	0.0609
	CR15	20	464.5	410.0	34.90	23.23	

*: Average score were used for ties.
**: p-value was based on the normal approximation one sided Z test.

Note that the power of the test is low based on two independent samples with a sample size 20 for each treatment. Unfortunately, the data only are usable from the first period in this crossover study.

3. Conclusion

Because of the weight differences between treatments, this study was not truly blind. Therefore, the comparisons between crushed Acurox® Tablets and crushed Roxicodone® Tablets could not be adjusted by the sequence effects by statistical modeling. This resulted in the data only being usable from the first period. Based on this reviewer's descriptive and inferential statistical analyses, the study did not demonstrate that Acurox® Tablets have a lower abuse potential than Roxicodone® Tablets when crushed and administered intranasally to non-dependent recreational opioid users.

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/s/

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04/01/2011

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04/01/2011