CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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:	207621/0000
Drug Name:	Troxyca (oxycodone hydrochlorid and naltrexone hydrochlorid ER Capsules)
Indication:	(ALO-02) is a combination opioid agonist/opioid antagonist product indicated for the management of pain severe enough to require daily, around-the-clock, long term opioid treatment and for which alternative treatment options are inadequate.
Study number:	B4531002, B4531008, B4531009
Applicant:	Pfizer
Date(s):	Date of Document: 12/19/2014 PDUFA date:10/19/2015 Completion date: 09/22/2015
Review Priority:	P
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Keywords: Abuse Deterrent Formulation; Crossover design; Clinical abuse potential study; Co-primary endpoints; Self-reported endpoint;

Table of Contents

List of Tables

List of Figures

1. Executive Summary

The applicant, Pfizer, submitted the results from three clinical abuse potential studies b4531008 (oral), b4531009 (intranasal), and b4981002 (intravenous) in support of the claim for abuse-deterrent properties of TROXYCA ER. This reviewer used statistical methodologies recommended in the 2015 FDA Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling, to assess abuse-deterrent properties of TROXYCA ER. (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf)

Study b4531008 was a randomized, double-blind, double-dummy, placebo-controlled, 6-way crossover oral study. Treatments in this study were intact TROXYCA ER 60 mg/7.2 mg, crushed TROXYCA ER 60 mg/7.2 mg, crushed TROXYCA ER 40 mg/4.8 mg, crushed oxycodone HCl IR 60 mg, crushed oxycodone HCl IR 40 mg, and placebo. Thirty two subjects completed all treatment sessions. The study results show that crushed TROXYCA ER 40 mg/4.8 mg and 60 mg/7.2 mg had statistically significantly 20% reduction in means of maximum liking, and 25% reduction in means of maximum high compared to crushed oxycodone HCl IR. The majority of subjects had at least 10% reduction in maximum liking for both doses of crushed TROXYCA ER 40 mg/4.8 mg and 60 mg/7.2 mg, and at least 10% and 5% reduction in maximum high for crushed TROXYCA ER 40 mg/4.8 mg and TROXYCA ER 60 mg/7.2 mg respectively compared to crushed oxycodone HCl IR. The abuse potential of the intact TROXYCA ER 60 mg was not similar to placebo.

Study b4531009 was a randomized, double-blind, placebo-controlled, 4-way crossover study. Treatments in this study were crushed TROXYCA ER 30 mg/3.6 mg, crushed oxycodone HCl IR 30 mg, crushed placebo (sugar spheres) weight match to TROXYCA ER 30 mg/3.6 mg, crushed placebo (lactose tablets) weight matched to oxycodone HCl IR 30 mg. Twenty eight subjects completed all treatment sessions. The study results show that compared to crushed oxycodone HCl IR 30 mg, crushed TROXYCA ER 30 mg/3.6 mg had statistically significantly 60% and 55% reduction in means of maximum liking and high, and the majority of subjects had at least 60% and 40% reduction in maximum liking and high, respectively.

Study b4981002 was a randomized, single-dose, placebo-controlled, double-blind, 3-way crossover study. Treatments in this study were simulated TROXYCA ER 20 mg/2.4 mg IV, oxycodone HCl 20 mg IV, and placebo. Twenty nine subjects completed all treatment sessions. The study results show that compared to oxycodone HCl 20 mg IV, stimulated TROXYCA ER 20 mg/2.4 mg IV had statistically significantly 65% and 70% reduction in means of maximum liking and high, and the majority of the subjects had at least 65% reduction in both maximum liking and high.

The statistically significant differences between each dose of positive control and placebo for both Drug Liking VAS and High VAS validated all three studies.

In conclusion, the abuse-deterrent properties of TROXYCA ER are evident.

2. Review report on Study b4531008 (oral study)

2.1 Overview

Study b4531008 is a randomized, double-blind, double-dummy, placebo-controlled, single-dose, 6-way crossover study to determine the relative abuse potential of ALO-02 (oxycodone hydrochloride and naltrexone hydrochloride extended-release capsules) compared to oxycodone immediate-release and placebo when administered orally to non-dependent, recreational opioid users.

2.1.1 Objectives of the study

Primary Objectives:

- To determine the relative abuse potential of intact and crushed ALO-02 60 mg/7.2 mg compared to crushed oxycodone HCl IR 60 mg and placebo administered orally to non-dependent, recreational opioid users.
- To determine the relative abuse potential of crushed ALO-02 40 mg/4.8 mg compared to crushed oxycodone HCl IR 40 mg and placebo when administered orally to non-dependent, recreational opioid users.

Secondary Objectives:

- To evaluate the PK profile of oxycodone, noroxycodone, oxymorphone, naltrexone, and
- 6-β-naltrexol following oral administration of (crushed and intact) ALO-02, and crushed oxycodone HCl IR in non-dependent, recreational opioid users.
- To compare the safety of intact and crushed ALO-02 with crushed oxycodone HCl IR when administered orally in non-dependent, recreational opioid users.

Exploratory Objective:

To determine the oxycodone exposure-response relationship with respect to select pharmacodynamic (PD) endpoints (Drug Liking visual analogue scale [VAS], High VAS, and pupillary diameter) in the presence and absence of naltrexone, as data permitted.

2.1.2 Study design

This study consisted of the following phases:

- Screening Visit (Visit 1; 2 to 28 days prior to Visit 2; Day 0);
- Naloxone Challenge Phase (Visit 2; Day 0);
- Drug Discrimination Phase (Visit 2; Days 1 to 3);
- Randomization and entry into the 6 period Treatment Phase (Visits 3 to 8);
- End-of-Study Visit (Visit 9; 3 to 7 days following last study drug administration or at the time of early discontinuation).

During the Drug Discrimination Phase (Visit 2; Days 1 to 3), subjects received 1 of the 2 treatments, 1 treatment per day over 2 consecutive days (Days 1 and 2), assigned in random order, in a fasted state and double blind fashion:

- Oxycodone IR 40 mg (2 × 20 mg oxycodone IR tablets crushed in solution);
- Placebo solution.

The eligibility criteria are as followings:

- Distinguish oxycodone IR from placebo on select subjective drug measures (i.e., ≥ 15 point peak increase for Drug Liking and Take Drug Again, and ≥ 30 point peak increase for High within 2 hours following dosing with oxycodone IR relative to placebo). A peak score of ≥ 65 was required to be indicated on bipolar measures of Drug Liking within 2 hours postdose and Take Drug Again at 5 hours postdose in response to oxycodone IR.

- Display an acceptable placebo response, defined as a VAS response between 0 to 10 inclusive for High or 40 to 60 inclusive for Drug Liking and Take Drug Again.

- Tolerate study treatments (e.g., no episodes of vomiting within the first 4 hours postdose).

- Demonstrate general behavior suggestive that the subject could successfully complete the study, as judged by the study center staff.

Treatment Phase (Treatment Periods 1-6) addressed the study objectives and consisted of 6 treatment periods (Visits 3 to 8) each with a 2-night confined stay, where each dosing was separated by a washout period of a minimum of 120 hours (5 days) and did not exceed 14 days.

In the Treatment Phase, subjects were randomly assigned to one of treatment sequence according to a Williams Square design, and received a single dose of the following treatments in a double-blind, double –dummy crossover manner:

- Placebo;
- Intact ALO-02 60 mg/7.2 mg;
- Crushed ALO-02 60 mg/7.2 mg;
- Crushed oxycodone HCl IR 60 mg;
- Crushed ALO-02 40 mg/4.8 mg;
- Crushed oxycodone HCl IR 40 mg.

The pharmacokinetics (PK) of oxycodone in ALO-02 is characterized by a slow absorptive phase, as evidenced by a prolonged time to reach maximum observed (drug) concentration [Tmax] (12 hours versus [vs] 4 hours). The washout period of a minimum of 120 hours (5 days) and did not exceed 14 days.

An End-of Study Visit was scheduled to be between 3 to 7 days following the last study drug administration, or time of early discontinuation.

2.1.3 Abuse potential measures

Primary measures

Drug Liking VAS, and High VAS

Other measures

Other VAS items (i.e., Good Drug Effects, Any Drug Effects, Bad Drug Effects, Feel Sick, Nausea, Sleepy, and Dizzy), Take Drug Again, and Overall Drug Liking.

Pupillometry Assessment

Measurement of pupil diameter in millimeters were made using a pupillometer under standardized conditions following each dose during the Drug Discrimination Test and Treatment Phase to evaluate oxycodone exposure. This test was used to measure change in pupil diameter as an indicator of opioid pharmacological properties. Since pupils constrict in response to opioids and the effect was a reduction in pupil size, the Emax was expected to be a smaller unit number relative to baseline.

The same eye for each subject was to be used for all measurements during the study.

2.1.4 Study subjects

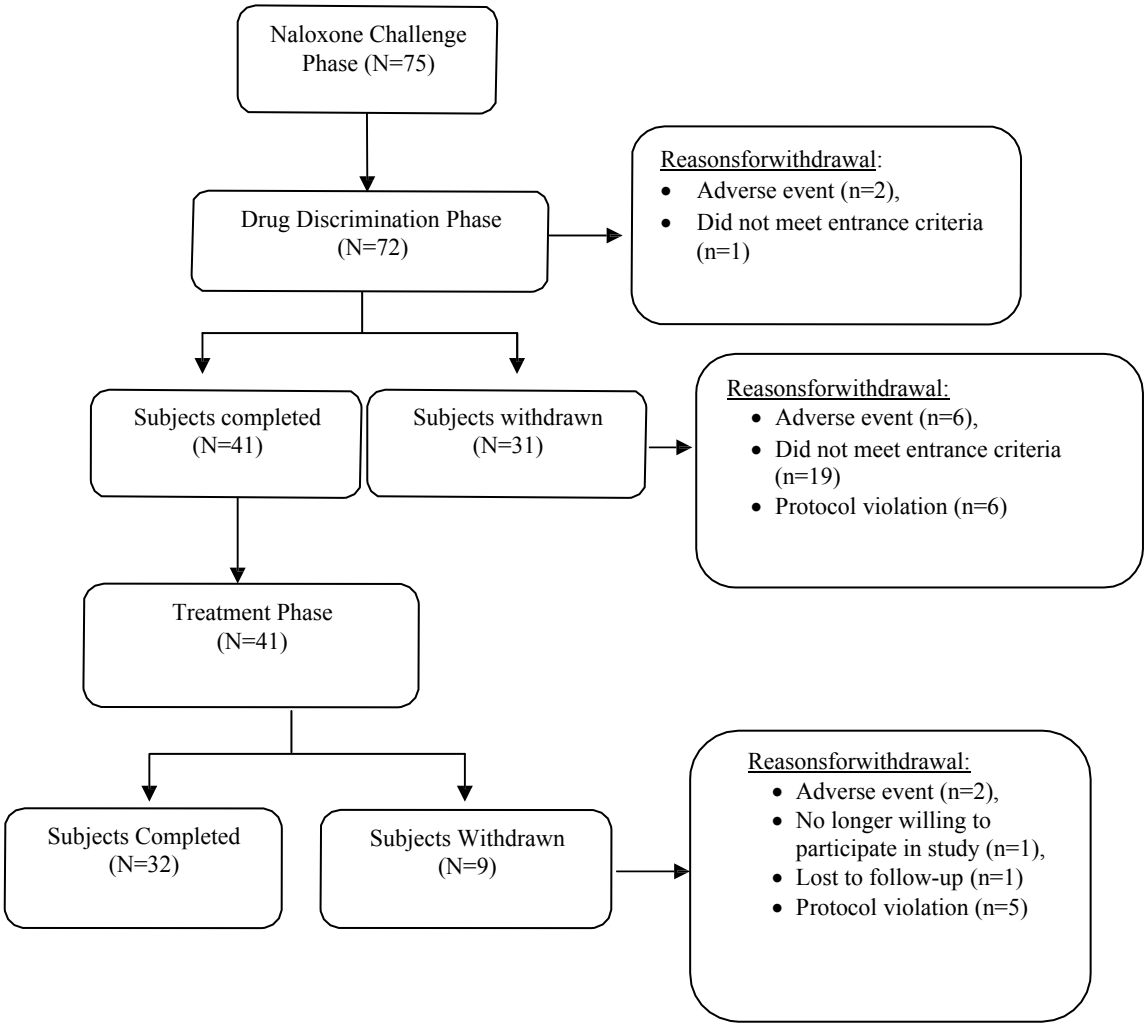
Of the 81 subjects screened, 75 eligible subjects participated in the Naloxone Challenge Phase, of which 72 subjects completed and 3 subjects were discontinued; 2 subjects due to AEs not related to study drug and 1 subject discontinued because the entrance criteria were not met.

Seventy-two (72) subjects entered the Drug Discrimination Phase, of which, 31 subjects discontinued and 41 subjects successfully completed the Drug Discrimination Phase.

Forty one subjects were randomized to the Treatment Phase. A total of 32 subjects completed the Treatment Phase and constituted the Completer Population used for primary PD analysis.

Figure 1 is for summary of subject disposition, which is on the page 66 of the study report.

Figure 1: Summary of Subject Disposition



N=total number of subjects in each group

n=number of subjects in each category

2.1.5 Statistical methodologies used in the Sponsor's analyses

All PD analyses were performed using the Completer Population and all available postdose data; these were the primary PD analyses. Key PD analyses (analyses of the primary endpoints of the primary measures) were repeated on the Evaluable Population using all available postdose data.

Precision of the estimate of PD parameters were determined by constructing 95% confidence intervals (CIs) around the estimated difference between the Test and Reference treatments using a mixed effects model. The mixed effects model was implemented using SAS Proc Mixed, with restricted maximum likelihood estimation method and Kenward-Roger degrees of freedom algorithm.

Study validation

Study validity was confirmed through the comparison of mean Emax for Drug Liking, High, and Take Drug Again between crushed oxycodone IR 40 mg and placebo administered during the Treatment Phase. This comparison was made using a mixed-effect model with treatment, period, and sequence as fixed effect, and subject nested within the sequence as a random effect.

Primary Analysis

The primary endpoints were summarized by treatment using descriptive statistics (mean, SD, median, first and third quartiles, minimum and maximum). These endpoints were analyzed using a mixed-effect model with treatment, period, and sequence as fixed effects, and subject nested within the sequence as a random effect. Analyses of endpoints with baseline (predose) measurements included the baseline measurement as a covariate in the model. LS means, standard errors, and 95% CIs were provided for each treatment and for the difference between treatments. Data were summarized graphically, where appropriate. The primary treatment comparisons were:

- Intact ALO-02 60 mg/7.2 mg vs oxycodone IR 60 mg;
- Intact ALO-02 60 mg/7.2 mg vs placebo;
- Crushed ALO-02 60 mg/7.2 mg vs oxycodone IR 60 mg;
- Crushed ALO-02 60 mg/7.2 mg vs placebo;
- Crushed ALO-02 40 mg/4.8 mg vs oxycodone IR 40 mg;
- Crushed ALO-02 40 mg/4.8 mg vs placebo.

To control for Type I errors arising from multiple comparisons, the Benjamini-Hochberg procedure was used across the primary treatment comparisons of the primary endpoints.

Regression diagnostics were performed to verify model assumptions and adequacy of the fitted linear models for the primary endpoints. The Shapiro–Wilk test was used to diagnose potential non-normality of the model residuals, and Levene's test was used to diagnose potential heterogeneity of variance. If assumptions were violated (p-value from either test was ≤ 0.05), a robust regression

model was fit with the same covariates as in the linear model, as a sensitivity analysis. Unadjusted pairwise treatment comparisons were made and M-estimates provided.

The numbers of subjects with Emax lower for intact ALO-02 and for crushed ALO-02 than for the same dose of oxycodone IR were presented for Drug Liking and High.

Secondary analysis

Analyses similar to those described in the primary analysis were performed on all secondary PD endpoints without adjustment for multiplicity.

2.1.6 Sponsor's Summary and Conclusions

The overall abuse potential of crushed ALO-02 40 mg/4.8 mg, crushed ALO-02 60 mg/7.2 mg and intact ALO-02 60 mg/7.2 mg taken orally was significantly lower than crushed oxycodone IR 40 mg and 60 mg across multiple measures including Drug Liking, High, Good Drug Effects, Any Drug Effects, and negative subjective effects for all doses, and global subjective effects. The subject's inability to discriminate between crushed oxycodone IR 40 mg and 60 mg as evidenced by a lack of significant difference for global subjective effects of Overall Drug Liking and Take Drug Again may be attributed to a plateau effect. This may be further substantiated by the crushed ALO-02 60 mg/7.2 mg vs crushed oxycodone IR 60 mg contrast not reaching statistical significance although directional in favor of crushed ALO-02 60 mg/7.2 mg. As expected, placebo showed the lowest scores for all measures. Intact ALO-02 60 mg/7.2 mg showed the lowest abuse potential among the active treatments, reflecting the PK profile of an ER formulation of oxycodone contributing to a reduced abuse potential when taken as directed.

The global subjective effects (Take Drug Again and Overall Drug Liking) for crushed ALO-02 60 mg/7.2 mg as compared to crushed oxycodone IR 60 mg were not statistically significant, although scores were numerically lower for crushed ALO-02 60 mg/7.2 mg. This supports that the abuse-deterrent effects of crushed ALO-02 40 mg/4.8 mg and ALO-02 60 mg/7.2 mg are likely to be sustained beyond the immediate dosing.

The global subjective effects for placebo and intact ALO-60 mg/7.2 mg were in the same range and the lowest as compared to all the other treatments.

The results of the objective measure of pupillometry were also supportive of the primary measure in showing lower physiologic opioid activity for crushed ALO-02 40 mg/4.8 mg and crushed ALO-02 60 mg/7.2 mg compared to crushed oxycodone IR 40 mg and 60 mg.

The pupillometry effects for intact ALO-02 60 mg/7.2 mg were consistent with an ER profile.

The effect of naltrexone was clear and consistent across multiple measures and also occurred primarily during the first 2 hours after ingestion when it would be expected to have the greatest antagonistic effect on the activity of oxycodone.

Results for the secondary endpoints of Good Drug Effects showed a similar trend as Drug Liking and High measures (i.e., showing reductions for all treatments of ALO-02 relative to oxycodone IR).
Mean scores for negative subjective effects measures (e.g., Bad Drug Effects, Feel Sick, and Nausea VASs) were low throughout the time course for each treatment. The reduction in abuse potential of ALO-02 compared to oxycodone IR appeared to be primarily driven by the larger reduction in the positive subjective effects (e.g., Drug Liking, High, and Good Drug Effects) rather than the relatively smaller reduction in the negative subjective effects observed for ALO-02.

Conclusion

- The study results demonstrated that administration of crushed ALO-02 40 mg/4.8 mg, crushed ALO-02 60 mg/7.2 mg and intact ALO-02 60 mg/7.2 mg showed significantly less abuse potential as compared to crushed oxycodone IR for both Drug Liking and High for Emax and AUE0-2h. Emax and AUE0-2h for crushed ALO-02 40 mg/4.8 mg and crushed ALO-02 60 mg/7.2 mg was significantly greater as compared to the placebo.
- The placebo showed the lowest scores for Drug Liking and High and other subjective measures. Intact ALO-02 60 mg/7.2 mg was in the range of placebo with peak effects occurring later and lower than crushed ALO-02 40 mg/4.8 mg and crushed ALO-02 60 mg/7.2 mg, consistent with its ER formulation.
- The reduction in abuse potential of all crushed or intact ALO-02 treatments compared to crushed oxycodone IR treatments was sustained for an extended period of time.
- The reduction of abuse potential was consistently noted across multiple secondary measures for crushed ALO-02 40 mg/4.8 mg and crushed ALO-02 60 mg/7.2 mg and all secondary measures for intact ALO-02 60 mg/7.2 mg.

2.2 Data Location

The analysis datasets are located at

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2.3 Reviewer's Assessment

The reviewer's assessment focused on the primary endpoints Emax of Drug Liking VAS and Emax of High VAS. The following notations for the treatments were used in the analysis:

- ALO40c – Crushed ALO-02 40 mg/4.8 mg in solution;
- ALO60c – Crushed ALO-02 60 mg/7.2 mg in solution;
- ALO60i – Intact ALO-02 60 mg/7.2 mg;
- Oxy40c – Crushed IR oxycodone 40 mg in solution;
- Oxy60c – Crushed IR oxycodone 60 mg in solution;

- P – Placebo.

2.3.1 Primary Analysis

2.3.1.1 Descriptive statistics

Table 1 summarizes the mean, standard error, minimum, the first quartile (Q_1), median, the third quartile (Q_3), and maximum for the 6 treatments in the study for the primary endpoints Emax of Drug Liking VAS and Emax of High VAS. The similar table for VAS measures Any Drug Effects, Good Drug Effects, Bad Drug Effects, Overall Drug Liking, and Take Drug Again, as well as Dizzy, Feel sick, Nausea and Sleepy can be found in Appendix I.

Table 1: Summary statistics for Emax of Drug Liking VAS and Emax of High VAS (N=32)

Abuse Potential Measure	TRT	Mean	StdErr	Min	Q1	Median	Q3	Max
Drug Liking VAS	ALO40c	70.1	3.40	50	51.5	64.5	91.25	100
	ALO60c	74.4	3.20	50	56.75	73	94	100
	ALO60i	59.3	2.67	50	51	51	60	100
	Oxy40c	85.5	2.85	50	74.25	90.5	100	100
	Oxy60c	89.7	2.40	57	78.25	99.5	100	100
	P	51.6	0.66	50	50	50.5	51	68
High VAS	ALO40c	47.3	6.52	0	4.5	58	83	100
	ALO60c	53.4	6.13	0	16.25	60	88.5	100
	ALO60i	21.7	6.25	-46	0	4	36.75	100
	Oxy40c	77.9	4.50	0	65.75	87	99.25	100
	Oxy60c	84.7	4.18	21	75.25	95.5	100	100
	P	10.9	3.64	0	0	0	2	54

From Table 1 one may notice that the minimum of Emax of High VAS for ALO60i is - 46. This is because one of subjects had predose response of 50, and post-dose Emax of 4. Emax of High VAS was calculated based on change from predose responses.

Figure 2 is the mean time course profiles by treatment for Drug Liking VAS. The peak mean responses of ALO40c, ALO60c and ALO60i reach at hours 1.5, 1 and 8, respectively. The profile of ALO60i stays between 45 and 55. Compared to Oxy40c and Oxy60c, the peak mean responses of ALO40c and ALO60c are more than15 points lower.

Figure 3 is the mean time course profiles by treatment for High VAS. ALO60i reaches peak mean response around 10 at hour 14. The peak mean responses of ALO40c and ALO60c are 38.3 and 48.1 and reach at hour 1.5 and 1, respectively. The reductions in the peak mean response for ALO40c and ALO60c relative to Oxy40c and Oxy60c are 35.8 and 29.1, respectively.

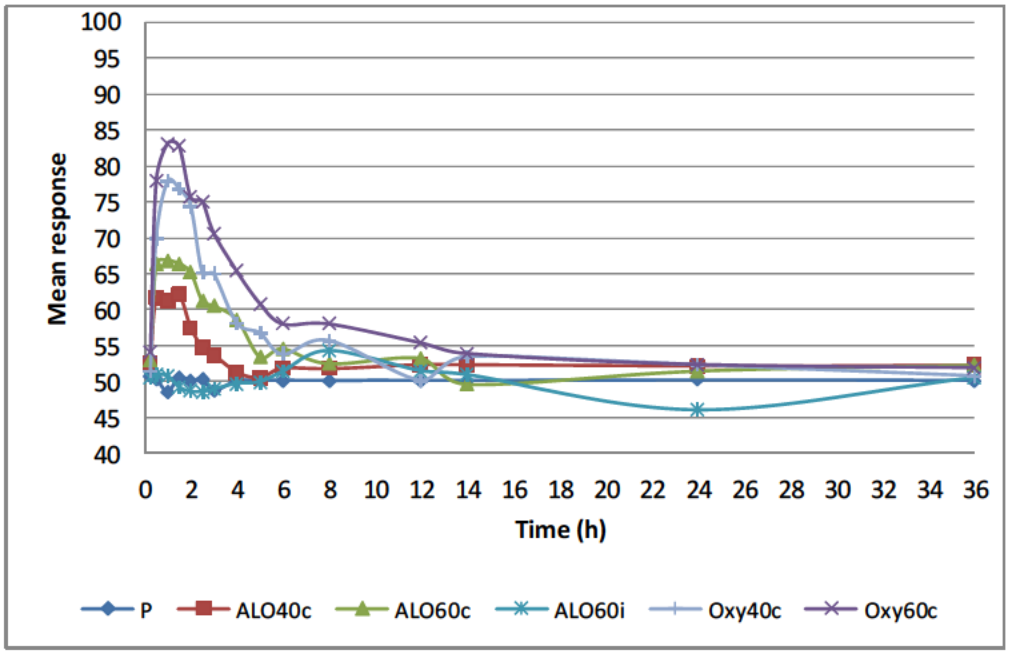


Figure 2: The mean time course profiles on Drug Liking VAS by treatment (N=32)

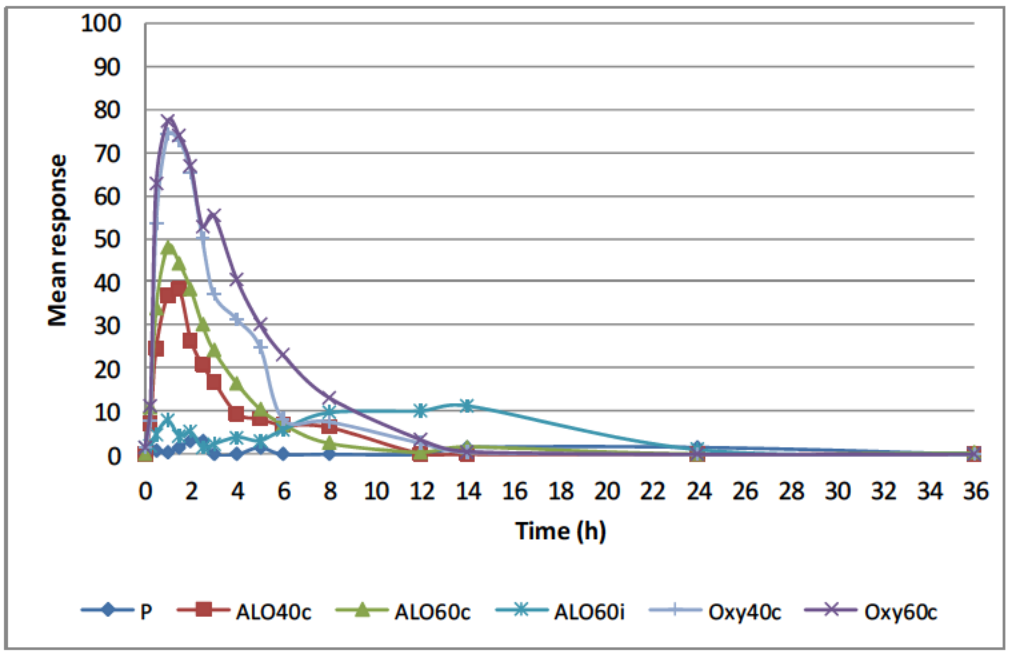


Figure 3: The mean time course profiles on High VAS by treatment (N=32)

The heat maps by treatment for two primary endpoints are presented in Figures 4 and 5.

Figure 4: **Heat Map by Treatment for Drug Liking VAS (Study 1008)**

Figure 5: Heat Map by Treatment for High VAS (Study 1008)

The heat maps show that among 32 completers approximately 6% (2) and 22% (7) of subjects had a placebo response for Drug Liking VAS and High VAS, respectively. Among 7 subjects who had a placebo response for High VAS, 5 subjects have a maximum high score around 50. In addition, three subjects (ID: 1052, 1101, and 167) had predose response to High VAS with a score of 50 for ALO60i, Oxy60c and Oxy40c, respectively.

2.3.1.2 Statistical Testing

For examining the abuse deterrent properties of ALO-02, the reviewer studied the following comparisons.

1. ALO40c versus Oxy40c
2. ALO60c versus Oxy60c
3. ALO60i versus P
4. Oxy40c versus P
5. Oxy60c versus P

The comparisons #4 and #5 are for the study validation. Because intact ALO60i is an ER product and Oxy60c is a crushed IR product, this reviewer does not believe that the comparison between ALO60i and Oxy60c is a fair and meaningful comparison for assessing abuse deterrent effect of ALO-02. Therefore, this comparison was not included in the reviewer's primary analysis.

The statistical model used in the reviewer's primary analysis was a mixed-effects model which included sequence, treatment, and period as fixed effects, and subject as a random effect. For High VAS, the model also included predose response as a covariate. The model assumption of the normality of error terms was checked using Shapiro-Wilk W-test on the residuals. The test results were not significant with p-values 0.1555 and 0.7574 for Drug Liking VAS and High VAS, respectively. The model assumption for homogeneity of variance was examined using Levene's test. The test results were significant for both primary endpoints ($p < 0.001$ for Drug Liking VAS, $p = 0.0013$ for High VAS). Therefore, a statement "Repeated/group=trtname sub=subjid R;" was included in the proc mixed to adjust heteroskedasticity. Table 2 shows the least square mean, standard error and confidence interval for each treatment for Drug Liking VAS and High VAS.

Table 2: The Least Square Means for Drug Liking VAS and High VAS

Abuse Potential Measure	Least Square Means				
	TRT	Estimate	StdErr	LCL	UCL
Drug Liking VAS	ALO40c	70.1	3.46	63.0	77.2
	ALO60c	74.4	3.14	68.0	80.8
	ALO60i	59.2	2.67	53.8	64.7
	Oxy40c	85.4	2.81	79.6	91.1
	Oxy60c	89.8	2.34	85.0	94.5
	P	51.5	0.67	50.1	52.9
High VAS	ALO40c	46.6	6.28	33.9	59.2
	ALO60c	52.8	5.70	41.4	64.3
	ALO60i	22.3	5.93	10.4	34.3
	Oxy40c	78.6	4.41	69.6	87.5
	Oxy60c	85.6	4.37	76.7	94.5
	P	10.2	4.94	0.1	20.3

The 2015 FDA Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling suggests testing the hypotheses for the difference between test drug and positive control and for the difference between positive control and placebo for Drug Liking VAS. These hypotheses were extended to High VAS as follows,

$H_0 : \mu_C - \mu_T \le \delta_1$ vs. $H_a : \mu_C - \mu_T > \delta_1$,

where μ_C and μ_T denote means of positive control and test drug, respectively; $\delta_1 = \delta^*(\mu_C - x)$, $0 < \delta^* < 1$, x=50 and 0 for Drug Liking VAS and High VAS, respectively. It is equivalent to testing

$H_0 : \mu_T - (1-\delta^*)\mu_C \ge \delta^* x$ vs. $H_a : \mu_T - (1-\delta^*)\mu_C < \delta^* x$.

For study validation, test

$H_0 : \mu_C - \mu_P \le \delta_2$ vs. $H_a : \mu_C - \mu_P > \delta_2$,

where μ_P denotes placebo mean; δ_2=15 and 30 for Drug Liking VAS and High VAS, respectively.

For the comparison between ALO60i and placebo, the reviewer used the Chen-Bonson's equivalence test for Drug Liking VAS, and also extended this test for High VAS as follows:

$$H_0 : \mu_T - \mu_P \ge \delta_3 \text{ versus } H_a : \mu_T - \mu_P < \delta_3 .$$

where δ_3 = 11 and 22 for Drug Liking VAS and High VAS, respectively.

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

Based on hypotheses recommended in the FDA 2015 Guidance, the δ^* in the hypothesis for the comparison between test drug and positive control should be pre-specified in the protocol. Because this NDA was submitted before the final guidance was published, the reviewer used δ^* =0.1 with 0.05 increment for each primary comparison, and stopped testing as soon as an insignificant result was obtained. The test results are listed in Table 3 for both primary measures.

Table 3: Summary of primary analysis results for Drug Liking VAS and High VAS

Abuse Potential Measure	Comparison	δ	Estimate* Diff	StdErr	t-value	p-value	LCL	UCL
Drug Liking VAS	ALO40c vs. Oxy40c	0.20(δ^*)	1.8	4.09	-2.00	0.0253	-6.4	-10.0
	ALO60c vs. Oxy60c	0.20(δ^*)	-1.9	3.67	-2.04	0.0234	-4.6	9.9
	Oxy40c vs. P	15(δ_2)	33.9	2.82	6.70	<.0001	28.2	39.7
	Oxy60c vs. P	15(δ_2)	38.3	2.35	9.91	<.0001	33.5	43.1
	ALO60i vs. P	11(δ_3)	7.7	2.68	-1.21	0.1174	2.3	13.2
High VAS	ALO40c vs. Oxy40c	0.25(δ^*)	-12.4	5.95	-2.08	0.0226	-24.4	-0.3
	ALO60c vs. Oxy60c	0.25(δ^*)	-11.4	5.31	-2.14	0.0193	-22.1	-0.6
	Oxy40c vs. P	30(δ_2)	68.3	4.89	7.84	<.0001	58.5	78.2
	Oxy60c vs. P	30(δ_2)	75.4	4.85	9.36	<.0001	65.6	85.2
	ALO60i vs. P	22(δ_3)	12.1	6.29	-1.57	0.0619	-0.5	24.8

*: Least square mean estimate of the difference on the left side hand of the null hypothesis.

Table 3 shows that ALO40c and ALO60c had statistically significantly 20% reduction in means of maximum liking (p=0.0253, and p=0.0234) and 25% reduction in means of maximum high (p=0.0226, and p=0.0193) compared to Oxy40c and Oxy60c, respectively. The comparisons between ALO60i and P (with a margin 11 and 22 for Drug Liking VAS and High VAS, respectively) were not significant (p=0.1174, and 0.0619). This indicates that the abuse potential of ALO60i is not similar to P. The significant results of the comparison between each dose of crushed oxycodone HCl IR and placebo for both Drug Liking VAS and High VAS validated the study.

Note that the p-value from the comparison between ALO40c and Oxy40c in maximum liking is 0.0253. This reviewer believe that p-value of 0.0253 can be round off to 0.025. Thus 20% reduction in mean of maximum liking for ALO40c relative to Oxy40c is reported.

The results from all possible pairwise comparisons among treatments including the comparison between ALO60i and Oxy60c for Drug Liking VAS and High VAS are presented in Appendix II.

2.3.2 Secondary Analysis

The secondary analysis is on the percent reduction in Emax for the test drug relative to the positive control. The sponsor defines percent reduction as follows:

$$\%\ \text{reduction} = \frac{E_{\max,ref} - E_{\max,test}}{E_{\max,ref} - X}$$

where X=50 for Drug Liking and X=0 for High.

This reviewer extended the definition for % reduction proposed by L.Chen, M. Klein and S. Calderon at the CPDD 74th Annual Meeting for Drug Liking VAS to the unipolar scale High VAS. By using the sponsor's notation for subject responses to different treatments, the calculation formulas for % reduction are defined as follows:

$$\%\ \text{reduction} = \begin{cases} \dfrac{E_{\max,ref} - E_{\max,test}}{E_{\max,ref} - X} \times \left(1 - \dfrac{E_{\max,P} - X}{Y}\right) \times 100\%, & \text{if } E_{\max,P} > Z; \\ \dfrac{E_{\max,ref} - E_{\max,test}}{E_{\max,ref} - X} \times 100\%, & \text{if } E_{\max,P} \le Z. \end{cases}$$

where X=50, Y=50, and Z=55 for Drug Liking VAS, and X=0, Y=100 and Z=10 for High VAS.

2.3.2.1 Descriptive Statistics

Descriptive statistics for the percent reductions can be found in Tables 4 and 5, and Figure 6 for Drug Liking VAS.

Table 4 shows the frequency distribution of subjects in terms of their responses to Oxy40c as well as their percent reductions for ALO40c relative to Oxy40c for Drug Liking VAS. Among 32 completers, approximate 28% (9) of subjects had no reduction in maximum liking, and 63% (20) and 53% (17) of subjects had at least 30% and 50% reduction in maximum liking for ALO40c compared to Oxy40c.

Table 5 shows 25% (8) of subjects had no reduction in maximum liking, and 59% (19) and 44% (14) of subjects had at least 30% and 50% reduction in maximum liking for ALO60c compared to Oxy60c.

Table 4: Contingency Table for Emax of Drug Liking VAS of the positive control by percent reduction (ALO40c vs. Oxy40c)

Oxy40c (Emax)	Percent of Reduction (%)													total
	<0	0	(0, 10)	[10, 20)	[20, 30)	[30, 40)	[40, 50)	[50, 60)	[60, 70)	[70, 80)	[80, 90)	[90, 100)	≥100	
≤55		2												2
(55, 60]													1	1
(60, 65]							1							1
(65, 70]	1									1	1			3
(70, 75]											1	1		2
(75, 80]	1							1		1				3
(80, 85]	2							1						3
(85, 90]				1										1
(90, 95]								1	1					2
(95, 100]		3		2		1	1		2	1		1	3	14
Total	4	5		3		1	2	3	3	3	2	2	4	32
pct (%)	12.50	15.63		9.38		3.13	6.25	9.38	9.38	9.38	6.25	6.25	12.50	100.0
Cpct (%)	100.0	87.5	71.9	71.9	62.5	62.5	59.4	53.1	43.8	34.4	25.0	18.8	12.5	

Note: The pct, and cpct denote the percentage of subjects and the cumulative percentage of subjects, respectively.

Table 5: Contingency Table for Emax of Drug Liking VAS of the positive control by percent reduction (ALO60c vs. Oxy60c)

Oxy60c (Emax)	Percent of Reduction (%)													total
	<0	0	(0, 10)	[10, 20)	[20, 30)	[30, 40)	[40, 50)	[50, 60)	[60, 70)	[70, 80)	[80, 90)	[90, 100)	≥100	
≤55														
(55, 60]				1										1
(60, 65]														
(65, 70]	1					1			1		1	1		5
(70, 75]							1							1
(75, 80]		1						1						2
(80, 85]													1	1
(85, 90]						1				1	1			3
(90, 95]														
(95, 100]	1	5		3	1		2	4	1			1	1	19
Total	2	6		4	1	2	3	5	2	1	2	2	2	32
ptr (%)	6.25	18.75		12.50	3.14	6.25	9.38	15.63	6.25	3.13	6.25	6.25	6.25	100.0
Cptr (%)	100.0	93.8	75.0	75.0	62.5	59.4	53.1	43.8	28.1	21.9	18.8	12.5	6.3	

Figure 6 is the percent reduction profiles for ALO40c, and ALO60c compared to Oxy40c and Oxy60c for Drug Liking VAS, respectively. Even though the Sponsor and the reviewer used different calculation formulas for the percent reductions, because only two subjects whose maximum liking is greater than 55 (62, 68), Figure 2 has no noticeable difference compared to Figure 1 in proposed label by the sponsor for these two profiles.

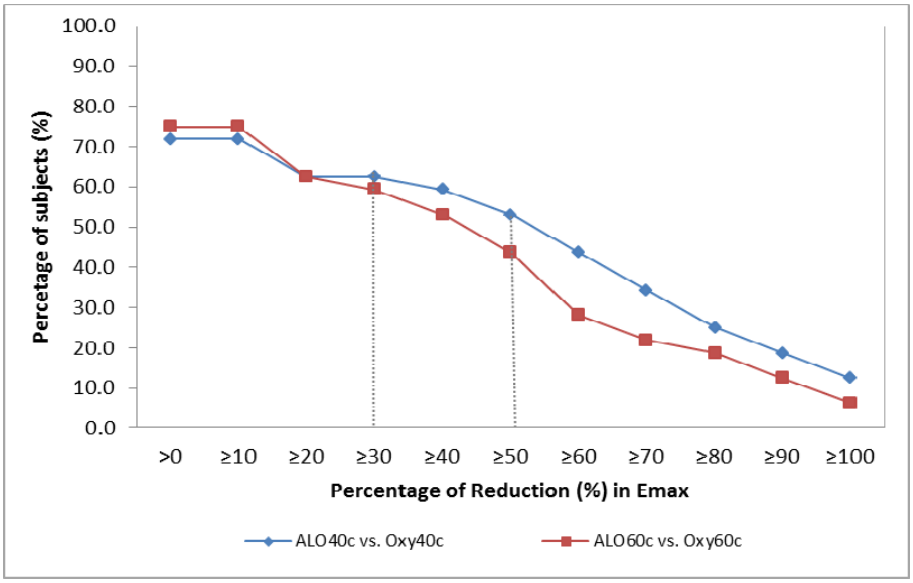


Figure 6: Percent Reduction Profiles for Emax of Drug Liking VAS for ALO40c vs. Oxy40c, and ALO60c vs. Oxy60c (N=32)

Tables 6 and 7 are contingency tables for Emax of High VAS of the positive control by percent reduction for ALO40c vs. Oxy40c, and ALO60c vs. Oxy60c, respectively.

Table 6: Contingency Table for Emax of High VAS of the positive control by percent reduction (ALO40c vs. Oxy40c crushed)

Oxy40c (Emax)	Percent of Reduction (%)													total
	<0	0	(0, 10)	[10, 20)	[20, 30)	[30, 40)	[40, 50)	[50, 60)	[60, 70)	[70, 80)	[80, 90)	[90, 100)	≥100	
≤10		1												1
(10, 20]											1			1
(20, 30]														
(30, 40]										1				1
(40, 50]		1											1	2
(50, 60]														
(60, 70]	2											1	1	4
(70, 80]	2			1			1		1		1			6
(80, 90]			1			1			1					3
(90, 100]		1	2	2	2	3		2				1	1	14
Total	4	3	3	3	2	4	1	2	2	1	2	2	3	32
ptr (%)	12.50	9.38	9.38	9.38	6.25	12.50	3.13	6.25	6.25	3.13	6.25	6.25	9.38	100.0
Cptr (%)	100.0	87.5	78.2	68.8	59.4	53.1	40.6	37.5	31.3	25.0	21.9	15.6	9.4	

Note: The pct, and cpct denote the percentage of subjects and the cumulative percentage of subjects, respectively.

Table 7: Contingency Table for Emax of High VAS of the positive control by percent reduction (ALO60c vs. Oxy60c)

Oxy60c (Emax)	Percent of Reduction (%)													total
	<0	0	(0, 10)	[10, 20)	[20, 30)	[30, 40)	[40, 50)	[50, 60)	[60, 70)	[70, 80)	[80, 90)	[90, 100)	≥100	
≤10														
(10, 20]														
(20, 30]								1						1
(30, 40]														
(40, 50]	2									1				3
(50, 60]														
(60, 70]	1										1			2
(70, 80]	1												1	2
(80, 90]				1				1		1				3
(90, 100]	1	2	4	3	2	1		2	1	1	2	1	1	21
Total	5	2	4	4	2	1		4	1	3	3	1	2	32
ptr (%)	15.63	6.25	12.50	12.50	6.25	3.13		12.50	3.13	9.38	9.38	3.13	6.25	
Cptr (%)	100.0	84.4	78.2	65.7	53.2	46.9	43.8	43.8	31.3	28.1	18.8	9.4	6.3	

Note: The pct, and cpct denote the percentage of subjects and the cumulative percentage of subjects, respectively.

Table 6 shows the frequency distribution of subjects in terms of their responses to Oxy40c as well as their percent reductions for ALO40c relative to Oxy40c for High VAS. Among 32 completers, 22% (7) had no reduction, and 53% (17) and 38% (12) of subjects had at least 30% and 50% reduction in maximum high for ALO40c compared to Oxy40c. Table 7 shows that 22% (7) had no reduction, and 47% (15) and 44% (14) of subjects had at least 30% and 50% reduction in maximum high for ALO60c relative to Oxy60c.

Figure 7 is the percent reduction profiles for ALO40c and ALO60c compared to Oxy40c and Oxy60c for High VAS, respectively.

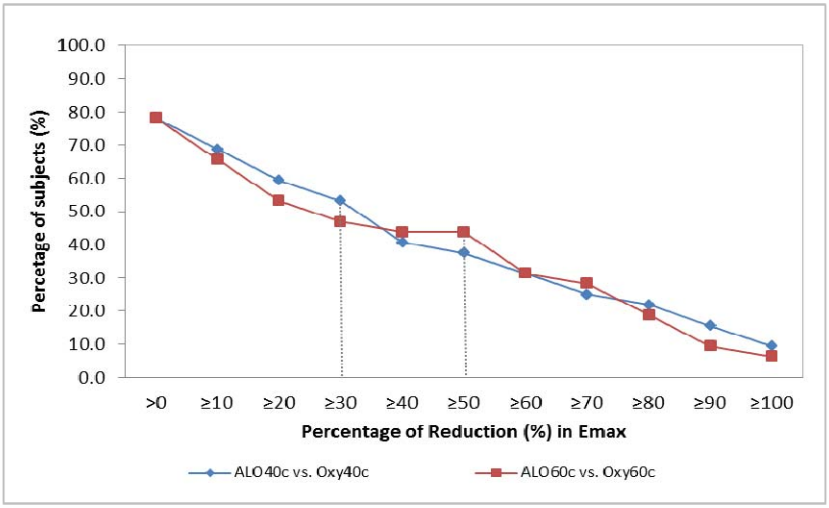


Figure 7: Percent Reduction Profiles for Emax of High VAS for ALO40c vs. Oxy40c, and ALO60c vs. Oxy60c (N=32)

Note that the Sponsor did not provide this graph in their proposed label.

2.3.2.2 Responder Analysis

The recommended responder analysis in the 2015 FDA guidance is to test

$H_0 : p^* \leq 50\%$ versus $H_a : p^* > 50\%$

at the 2.5% significance level where p^* denotes the true responder rate.

Because the Sponsor did not define a responder, the reviewer used cut off point in the order from small percent to large percent with 5% increment to define a responder, and used the binomial test for testing the null hypothesis: the majority of subjects were not responders, and stopped testing when an insignificant result was obtained. The reviewer found that

- The majority subjects had at least 10% reduction in maximum liking for ALO40c compared to Oxy40c with a p-value of 0.0067. The 95% confidence interval of the responder rate was (0.56, 0.87).
- For ALO60c, the majority subjects had at least 10% reduction in maximum liking compared to Oxy60c with a p-value of 0.0023. The 95% confidence interval of the responder rate was (0.060, 0.090).
- The majority subjects had at least 10% reduction in maximum high for ALO40c compared to Oxy40c with a p-value of 0.0169. The 95% confidence interval of the responder rate was (0.53, 0.85).
- For ALO60c, the majority subjects had at least 5% reduction in maximum high compared to Oxy60c with a p-value of 0.0169. The 95% confidence interval for the responder rate was (0.53, 0.85).

2.4 Conclusion

The oral study 1008 shows that

- TROXYCA ER has mild abuse-deterrent property if crushed and taken it orally. Compared to crushed oxycodone HCl IR, 1) crushed TROXYCA ER 40 mg /4.8 mg and 60 mg/7.2 mg had statistically significantly 20% reduction in means of maximum liking and 25% reduction in means of maximum high; 2) the majority of subjects had at least 10% reduction in maximum liking for both crushed TROXYCA ER 40 mg/4.8 mg and crushed TROXYCA ER 60 mg/7.2 mg, and had at least 10% and 5% reduction in maximum high for crushed TROXYCA ER 40 mg/4.8 mg and TROXYCA ER 60 mg/7.2 mg, respectively.
- Abuse potential of intact TROXYCA ER was not similar to that of placebo for either Drug Liking VAS or High VAS.
- The statistically significant differences between each dose of crushed oxycodone HCl IR and placebo for both Drug Liking VAS and High VAS validated study.

3. Review report on Study b4531009 (Intranasal Study)

3.1 Overview

Study b4531009 was a randomized, double-blind, placebo-controlled, single-dose, 4-way crossover study to determine the relative abuse potential of ALO-02 (oxycodone hydrochloride and naltrexone hydrochloride extended-release capsules) compared to oxycodone immediate-release, and placebo when administered intranasally to non-dependent, recreational opioid users.

3.1.1 Objectives of the study

Primary Objectives:

- To determine the relative abuse potential of crushed ALO-02 (oxycodone hydrochloride [HCl] and naltrexone HCl extended release capsules) compared to crushed oxycodone HCl immediate release (IR) and placebo administered intranasally in non-dependent, recreational opioid users.

Secondary Objectives:

- To estimate the bioavailability of oxycodone and determine the pharmacokinetic (PK) profile of oxycodone, noroxycodone, oxymorphone, naltrexone and 6-β-naltrexol following intranasal (IN) administration of crushed ALO-02 and crushed oxycodone HCl IR in non-dependent, recreational opioid users.
- To compare the safety of ALO-02 with oxycodone HCl IR when crushed and administered intranasally in non-dependent, recreational opioid users.

Exploratory Objective:

- To determine the oxycodone exposure-response relationship with respect to select pharmacodynamic (PD) endpoints (Drug Liking Visual Analogue Scale [VAS], High VAS, pupillary diameter) in the presence and absence of naltrexone, as data permitted.

3.1.2 Study design

This study consisted of the following phases:

- Screening Visit (Visit 1; 2-28 days prior to Visit 2, Day 0);
- Naloxone Challenge Phase (Visit 2; Day 0);
- Drug Discrimination Phase (Visit 2; Days 1-3);
- Treatment Phase: Treatment Periods 1-4 (Visits 3-6; Days 0-2);
- End-of-Study Visit (Visit 7; Days 3-7 following last study drug administration or at the time of early discontinuation).

During the Drug Discrimination Phase (Visit 2; Days 1 to 3), subjects randomly received either oxycodone HCl IR 30 mg or placebo (crushed lactose tablets matched to oxycodone HCl IR tablets)

i.e. 1 treatment per day over 2 consecutive days (Days 1 and 2), in a fasted state and double-blind fashion.

In the Treatment Phase, single doses of the following treatments were administered to subjects on Day 1 of each Treatment Period in a randomized, double-blind, 4-way crossover fashion (Table 8). Subjects were required to fast for at least 8 hours before and 2 hours after each drug administration in the Treatment Phase (Visits 3-6).

Table 8: Study Treatments Administered

Treatment Arm	Treatment	Total Treatment Weight
Treatment A	Placebo (sugar spheres) crushed, weight matched to ALO-02 capsule fill weight	273 mg
Treatment B	ALO-02 30 mg/3.6 mg (1 × 30 mg/3.6 mg capsule crushed)	273 mg
Treatment C	Placebo (lactose tablets) crushed, weight matched to oxycodone IR (3 × 10 mg)	510 mg
Treatment D	Oxycodone IR 30 mg (3 × 10 mg tablets crushed	510 mg

Source: Sponsor's Table 3 on page 44 of the study report.

3.1.3 Abuse potential measures

Primary measures

Drug Liking VAS, and High VAS

Secondary VAS measures

Any Drug Effects, Good Drug Effects, Bad Drug Effects, Feel Sick, Nausea, Sleepy, Dizzy, Take Drug Again, and Overall Drug Liking.

3.1.4 Study subjects

Of the 45 subjects screened, all subjects completed the Naloxone Challenge Phase. There were no discontinuations in the Naloxone Challenge Phase.

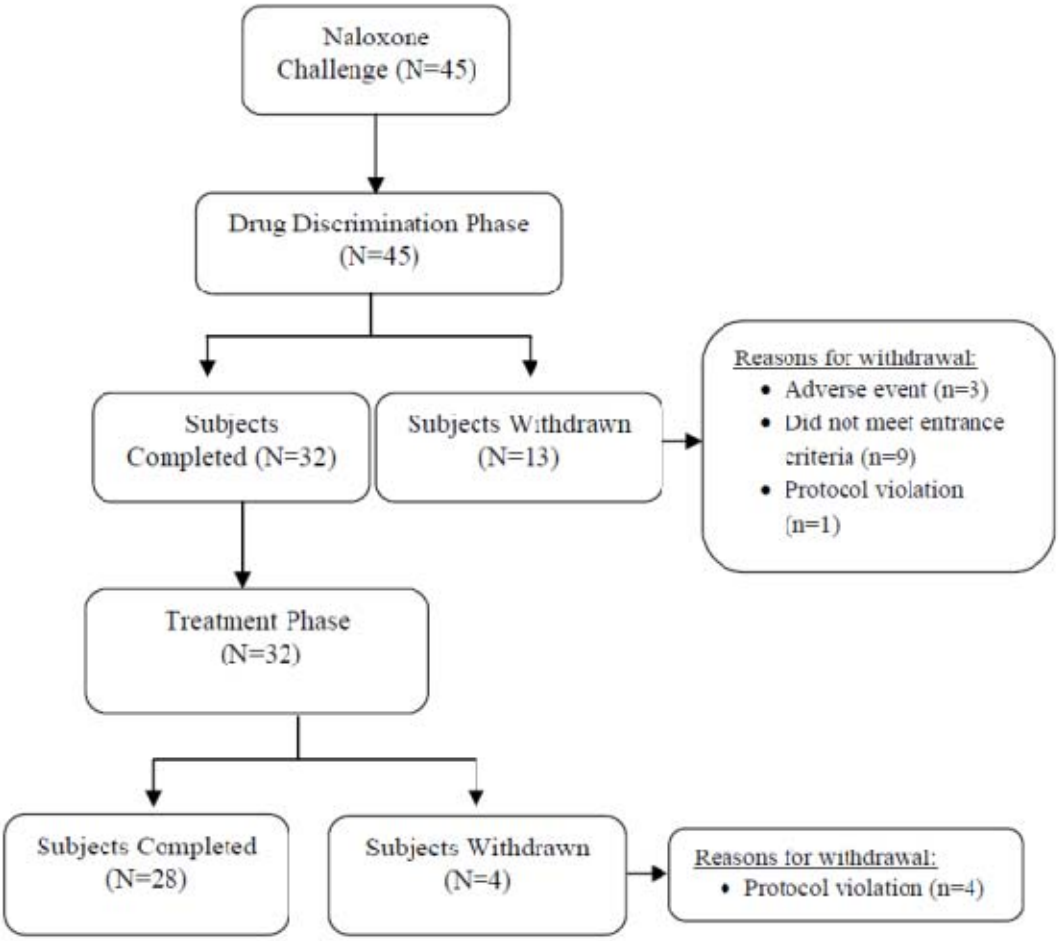
Forty five subjects entered the Drug Discrimination Phase and a total of 32 subjects successfully completed the Drug Discrimination Phase. Three subjects were discontinued after treatment with oxycodone HCl IR due to an AE and 1 subject was discontinued after treatment with placebo lactose due to a protocol violation. Nine subjects completed drug discrimination procedures, but were discontinued because they did not meet the entrance criteria.

In the Treatment Phase, 32 subjects were randomized to the Treatment Phase and constituted both the Safety and PK populations. A total of 28 subjects completed the Treatment Phase and constituted the Completer Population used for primary PD analysis. Four discontinuations were

observed during the Treatment Phase, all were due to positive drug screens, none of which were related to study drug. A total of 26 subjects were included in the Evaluable Population, which excluded 2 additional subjects with major protocol deviations, as described in Section 10.2 of the study report.

Figure 8 is for summary of subject disposition, which is on page 64 of the study report.

Figure 8: Summary of Subject Disposition



Source: Sponsor's Figure 1 on page 64 of the study report. N = total number of subjects in each group; n = number of subjects in each category

The Sponsor reports:

Two of the protocol deviations were considered significant/major for Subjects 10011028 and 10011095. Subject 10011028 had a positive drug screen for benzodiazepines and THC at Visit 3 Day 1 and was dosed although the protocol prohibited subjects from continuing if they had a positive UDS for drugs other than THC. Subject 10011095 was only able to insufflate 79.9% of oxycodone IR 30 mg dose and therefore was deemed as having incomplete dosing. Four subjects were discontinued in the Treatment Phase due to protocol violations. Subjects 10011118, 10011107 and 10011114 were discontinued for testing positive for cocaine and Subject 10011108 for amphetamine.

3.1.5 Statistical methodologies used in the Sponsor's analyses

All PD analyses were performed using the Completer Population and all available postdose data; these were the primary PD analyses. Key PD analyses (analyses of the primary endpoints of the primary measures) were repeated on the Evaluable Population without adjustment using all available postdose data.

The Completer Population included all randomized subjects who completed all 4 periods of the Treatment Phase and who contributed postdose PD data from each period. This population was analyzed as randomized.

The Evaluable Population included all randomized subjects in the Completer Population who did not have major protocol violations or AEs that would interfere with drug absorption such as vomiting within 1 hour of study drug administration or sneezing within 30 minutes of dosing. Major protocol violations, including deviations related to study drug intake were defined as those that could potentially affect the PD conclusions of the study. Prior to unblinding the Treatment Phase data, the Sponsor (or designee) identified protocol violations or AEs that could disqualify a subject from the Evaluable Population and determined which subjects or subject visits could be excluded. This population was analyzed as randomized.

Precision of the estimate of PD endpoints was determined by constructing 95% confidence intervals (CIs) around the estimated difference between the Test and Reference treatments using a mixed effects model. The mixed effects models were implemented using SAS Proc Mixed, with Restricted Maximum Likelihood (REML) estimation method and Kenward-Roger degrees of freedom algorithm.

Study validation

Study validity was confirmed through the comparison of mean Emax for Drug Liking, High, and Take Drug Again between oxycodone IR and weight-matched lactose placebo administered.

Primary Analysis

The primary endpoints were summarized by treatment using descriptive statistics (N, mean, SD, median, first and third quartiles, minimum and maximum). These endpoints were analyzed using a mixed-effect model with treatment, period, and sequence as fixed effects, and subject nested within the sequence as a random effect. Analyses of endpoints with baseline (predose) measurements included the baseline measurement as a covariate in the model. LS means, standard errors, and 95% CIs were provided for each treatment and for the difference between treatments. Data was summarized graphically, where appropriate. The primary treatment comparisons were:

- ALO-02 30 mg versus oxycodone IR 30 mg;
- ALO-02 30 mg versus weight-matched placebo.

To control for Type I errors arising from multiple comparisons, the Benjamini-Hochberg procedure was used across the primary treatment comparisons of the primary endpoints. Regression diagnostics were performed to verify model assumptions and adequacy of the fitted linear models for the primary endpoints. The Shapiro–Wilk test was used to diagnose potential non-normality of the model residuals, and Levene's test was used to diagnose potential heterogeneity of variance. If assumptions were violated (p-value from either test was ≤0.05), a robust regression model was fitted with the same covariates as in the linear model, as a sensitivity analysis. Unadjusted pairwise treatment comparisons were made and M-estimates provided.

Secondary analysis

The sponsor defined the secondary analysis different from what defines in the FDA 1015 guidance. Basically, it includes the analyses on the secondary endpoints.

The sponsor provided descriptive statistics for the percent reduction. The percent reduction was defined as follows:

$$\text{Reduction \%} = \frac{E_{\max,ref} - E_{\max,test}}{E_{\max,ref} - X}$$

where X=50 for Drug Liking VAS and X=0 for High VAS. The reference was oxycodone IR 30 mg and the test was ALO-02 30 mg/3.6 mg.

3.1.6 Sponsor's Summary and Conclusions

Pharmacodynamics summary

- Crushed ALO-02 30 mg/3.6 mg significantly reduced the abuse potential compared to oxycodone IR 30 mg across multiple pharmacodynamic measures including Drug Liking, High, Take Drug Again, and Overall Drug Liking.
- The primary endpoint results demonstrated that IN administration of crushed ALO-02 30 mg/3.6 mg resulted in significantly less Drug Liking and High compared to crushed IR 30 mg oxycodone (active control). Crushed ALO-02 30 mg/ 3.6 mg and oxycodone IR 30 mg treatment resulted in a significantly greater Emax and AUE0-2h compared to both placebo treatments.
- The secondary endpoints support the results of the primary endpoints. The onset of mitigation of the opioid effects with crushed ALO-02 30 mg/3.6 mg was primarily in the first 2 hours after dosing, when abusers typically desire euphoric effects. Lasting effects were observed as evidenced by a significant reduction in Emax and Emean on the global measures of Overall Drug Liking and Take Drug Again with crushed ALO-02 compared to crushed oxycodone IR. These global measures were assessed when the acute pharmacological effects of the opioids had disappeared, which indicates sustained mitigation of liking with crushed ALO-02 30 mg/3.6 mg.

- There was no evidence of any difference in the performance of the placebo treatments. The placebo lactose tablet and the placebo sugar spheres had similar scores on all measures and were not significantly different from each other.
- The results of the Good Drug Effects VAS measures support those of the primary endpoints, and peak effects on Sleepy and Dizzy VAS were similar in direction showing generally greater effects for crushed oxycodone IR 30 mg and less effect for crushed ALO-02 30 mg/ 3.6 mg and the placebo treatments.
- Bad Drug Effects, and Nausea VAS were minimal for all treatments and followed a similar pattern as the primary endpoints with the highest scores occurring with crushed oxycodone IR 30 mg followed by crushed ALO-02 30 mg/3.6 mg and then by the placebo treatments.
- Crushed ALO-02 30 mg/3.6 mg resulted in less miosis than crushed oxycodone IR 30 mg. Decreased opioid receptor activation as evidenced by reduced miosis further indicates less opioid effect with ALO-02 30 mg/3.6 mg, supporting the conclusions drawn from the subjective measures.
- Overall, crushed ALO-02 30 mg/3.6 mg had significantly lower abuse potential than crushed oxycodone IR when administered intranasally to non-dependent recreational opioid users.

Conclusion

- Overall, crushed ALO-02 30 mg/3.6 mg showed reduced abuse potential compared to an equivalent dose of crushed oxycodone IR 30 mg. The abuse potential of the placebo treatments was less than crushed ALO-02 30 mg/3.6 mg.

- The study results demonstrated that IN administration of crushed ALO-02 showed significantly less Drug Liking and High compared to crushed oxycodone IR 30 mg documenting a decreased abuse potential of ALO-02 30 mg/3.6 mg compared to IR oxycodone 30 mg. The primary comparisons between ALO-02 30 mg/3.6 mg and oxycodone IR 30 mg showed significant reductions with ALO-02 30 mg/3.6 mg for both

- Drug Liking and High for the primary endpoints of Emax and AUE0-2h. Emax and AUE0-2h was significantly greater with ALO-02 30 mg/3.6 mg compared to the placebo treatments with the exception of Drug Liking AUE0-2h.

- The reduction in secondary endpoints, Take Drug Again and Overall Drug Liking up to 24 hours postdose was supportive of the primary endpoint.

3.2 Data Location

The analysis datasets are located at

\\cdsesub1\evsprod\nda207621\0000\m5\datasets\b4531009\analysis\legacy\datasets\adpdfda.xpt

3.3 Reviewer's assessment

The reviewer's assessment focused on the primary endpoints Emax of Drug Liking VAS and Emax of High VAS. The following notations for the treatments were used in the reviewer's analyses:

ALO30c – ALO-02 30 mg/3.6 mg;
Oxy30c – Oxycodone IR 30 mg;
Palo – Placebo sugar spheres;
Poxy – Placebo lactose.

3.3.1 Insufflation

Because this is an intranasal study, this reviewer examined the dose insufflation first.

Two subjects had less than 100% insufflation. Subject 10011013 insufflated 95.4% of ALO30c and subject 10011095 insufflated 79.9% of Oxy30c. Descriptive summary of dose insufflated is presented in Table 9.

Table 9: Summary of Dose Insufflation (%)

Treatment	N	Mean	Std	Median	Min	Max
Palo	29	100	0	100	100	100
ALO30c	30	99.9	0.84	100	95.4	100
Poxy	30	100	0	100	100	100
Oxy30c	32	99.4	3.55	100	79.9	100

Table 10 lists Emax of Drug Liking VAS and Emax of High VAS from Subject 10011095 who only insufflated 79.9% Oxy30c.

Table 10: Emax for Drug Liking VAS and High VAS from Subject 10011095

Abuse Potential Measure	ALO30c	Oxy30c	Palo	Poxy
Drug Liking VAS	51	92	51	50
High VAS	26	94	0	0

Table 10 shows that even though Subject 10011095 insufflated 79.9% of Oxy30c, the subject's maximum like and high are above 90.

3.3.1 Primary Analysis

3.3.1.1 Descriptive Statistics

Table 11 summarizes the mean, standard error, minimum, the first quartile (Q1), median, the third quartile (Q3), and maximum for the 4 treatments in the study for the primary endpoints Emax of Drug Liking VAS and Emax of High VAS. The similar table for VAS measures Any Drug Effects, Good Drug Effects, Bad Drug Effects, Overall Drug Liking, and Take Drug Again, as well as Dizzy, Feel sick, Nausea and Sleepy can be found in Appendix III.

Table 11: Summary statistics for Emax of Drug Liking VAS and Emax of High VAS (N=28)

Abuse Potential Measure	TRT	Mean	StdErr	Min	Q1	Median	Q3	Max
Drug Liking	ALO30c	60.5	2.28	50	51	57	69.5	100
	Oxy30c	92.8	2.26	50	91.25	98.5	100	100
	Palo	50.9	0.22	50	50	51	51	56
	Poxy	51.3	0.63	50	50	51	51	68
High	ALO30c	26.6	5.37	0	0.25	19	40	100
	Oxy30c	85.8	4.60	0	88	93.5	100	100
	Palo	2.2	1.89	0	0	0	0	53
	Poxy	6.0	4.13	-50	0	0	0	60

Table 11 shows that for ALO30c approximate 75% of subjects had a maximum liking at most 69.5 with a median of 57, while approximate 75% of subjects had a maximum liking at least 91.3 with a median of 98.5 for Oxy30c. Similarly, for ALO30c approximate 75% of subjects had a maximum high at most 40 with a median of 19, while approximate 75 % of subjects had a maximum high at least 88 with a median of 93.5 for Oxy30c.

Figures 9 and 10 are the mean time course profiles by treatment for Drug Liking VAS and High VAS respectively. These two figures show that the mean time course profiles for two placebos are very similar. The peak mean response of ALO30c is around 56 and 17 while the peak mean response of Oxy30c is approximately 88 and 80 for Drug Liking VAS and High VAS, respectively.

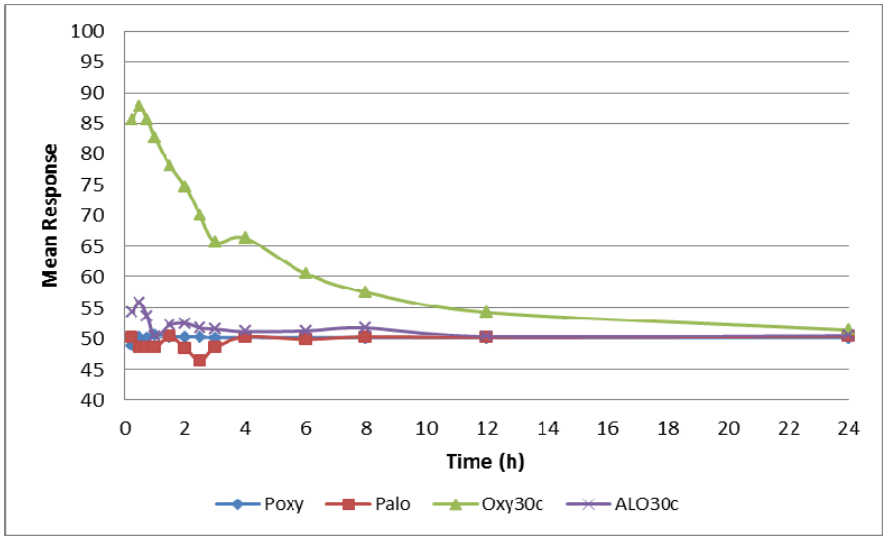


Figure 9: The mean time course profiles on Drug Liking VAS by treatment (N=28)

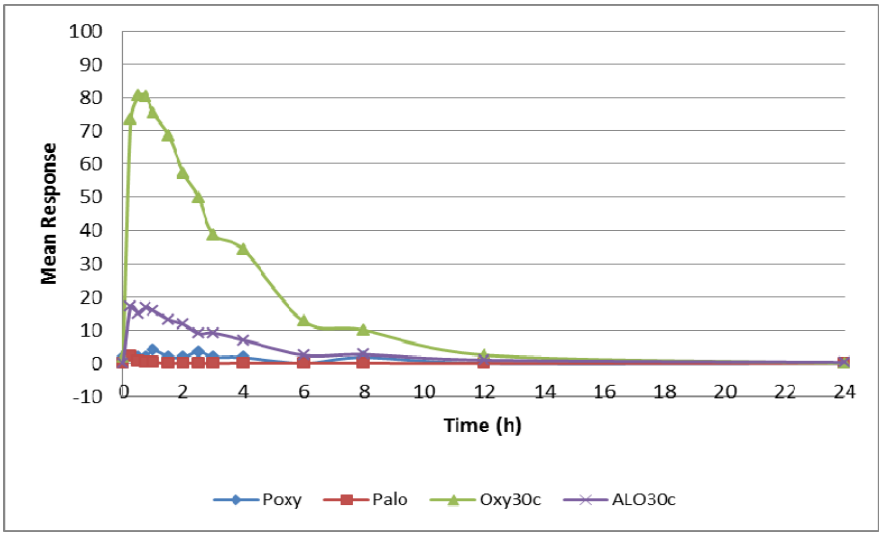


Figure 10: The mean time course profiles on High VAS by treatment (N=28)

Figures 11 and 12 are the heat maps by treatment for Drug Liking VAS and High VAS, respectively. These two figures show individual maximum responses to each treatment for these two primary measures. Note that 4 (14.3%) subjects had placebo response for Poxy for High VAS. Comparing individual maximum responses for ALO30c to those for Oxy30c in these two graphs, one may clearly see the abuse-deterrent effects of ALO30c.

Figure 11: Heat map by treatment for Drug Liking VAS (Study 1009)

Figure 12: Heat map by treatment for High VAS (Study 1009)

3.3.1.2 Statistical testing

For examining the abuse deterrent properties of ALO-02, the reviewer studied the following comparisons:

1. ALO30c versus Oxy30c (Primary)
2. Oxy30c versus Poxy (Study validation)

Because the volume of Oxy30c is almost doubled the volume of ALO30c, the volume of the test drug is not an issue in this intranasal study.

The hypotheses for these comparisons are listed below:

Primary comparison

$$H_0 : \mu_{Oxy30c} - \mu_{ALO30c} \le \delta^*(\mu_{Oxy30c} - x) \text{ versus } H_a : \mu_{Oxy30c} - \mu_{ALO30c} > \delta^*(\mu_{Oxy30c} - x),$$

where $0 < \delta^* < 1$, x=50 and 0 for Drug Liking VAS and High VAS, respectively. It is equivalent to testing

$$H_0 : \mu_{ALO30c} - (1-\delta^*)\mu_{Oxy30c} - \delta^* x \ge 0 \text{ versus } H_a : \mu_{ALO30c} - (1-\delta^*)\mu_{Oxy30c} - \delta^* x < 0.$$

Study validation

$$H_0 : \mu_{Oxy30c} - \mu_{Poxy} \le \delta_2 \text{ versus } H_a : \mu_{Oxy30c} - \mu_{Poxy} > \delta_2,$$

where δ_2 =15 and 30 for Drug Liking VAS and High VAS, respectively. It is equivalent to testing

$$H_0 : \mu_{Oxy30c} - \mu_{Poxy} - \delta_2 \le 0 \text{ versus } H_a : \mu_{Oxy30c} - \mu_{Poxy} - \delta_2 > 0.$$

Because there is no pre-specified δ^*, using the mean listed in Table 12 for each treatment, the reviewer calculated the ratio of $(\bar{x}_{Oxy30c} - \bar{x}_{ALO30c})$ to $(\bar{x}_{Oxy30c} - x)$ to determine the starting δ^* for the primary comparisons. This ratio is equal to 0.75 for Drug Liking VAS and 0.70 for High VAS. Therefore, the reviewer used δ^* started from 0.5 with 0.05 increment for the test, and stopped testing when an insignificant result was obtained.

For the comparison between ALO30c and Poxy, the Chen-Bonson's test was used.

The same statistical model used in the oral study 1008 was also used in this study. The results from the W test for examining the normality assumption of the statistical model for both primary endpoints were highly significant with p-value <0.0001. Note that the distributions of $ALO30c - (1-\delta^*)Oxy30c - \delta^* x$ and $ALO30c - Poxy - \delta_3$ were positively skewed and these tests are lower-tailed tests. In addition, note that the distribution of $Oxy30c - Poxy - \delta_2$ was

negatively skewed, and the test for this comparison is an upper-tailed test. Therefore, t-test was used for all comparisons. The results are presented in Table 12.

Table 12: Summary of results from the primary analysis (n=28)

Abuse Potnetial Measure	Comparison	δ	Mean* Diff	StdErr	t-value	p-value	LCL	UCL
Drug Liking VAS	ALO30c vs. Oxy30c	0.6 (δ*)	-6.6	2.54	-2.59	0.0217	-11.8	-1.4
	Oxy30c vs. Poxy	15 (δ_2)	26.5	2.21	11.97	0.0000	21.9	31.0
	ALO30c vs. Poxy	11(δ_3)	-1.8	2.41	-0.74	0.2324	-6.7	3.2
High VAS	ALO30c vs. Oxy30c	0.55(δ*)	-16.3	5.92	-2.06	0.0246	-23.9	-0.04
	Oxy30c vs. Poxy	20 (δ_2)	49.8	4.42	11.27	0.0000	40.8	58.9
	ALO30c vs. Poxy	22(δ_3)	-1.4	7.74	-0.18	0.4311	-17.2	14.5

*: Estimate of the difference on the left hand side of the null hypothesis.

Table 12 shows that ALO30c had statistically significantly 60% reduction in mean of maximum liking compared to Oxy30c (p=0.0217), and statistically significantly 55% reduction in mean of maximum high compared to Oxy30c (p=0.0246). Abuse potential of ALO30c is not similar to placebo (p=0.2324 for liking; p=0.4311 for high). The significant difference between Oxy30c and Poxy for both Drug Liking VAS (p=0.0000) and High VAS (p=0.0000) validated study.

3.3.2 Secondary Analysis

3.3.2.1 Descriptive Statistics

The same methods used in Study 1008 for calculating the percent reduction were used in this study. Tables 13 and 14 show the frequency distributions of subjects in terms of their responses to Oxy30c and their percent reductions for ALO30c relative to Oxy30c for Drug Liking VAS and High VAS, respectively. Among 28 completers, approximately 7% (2) and 11% (3) of subjects did not have any reduction in maximum liking and maximum high for ALO30c compared to Oxy30c, respectively. Approximately 89% (25) and 82% (23) of subjects had at least 30% and 50% reduction in maximum liking for ALO30c relative to Oxy30c, respectively, and approximately 79% (22) and 61% (17) of subjects had at least 30% and 50% reduction in maximum high for ALO30c relative to Oxy30c, respectively.

Table 13: Contingency Table for Emax of Drug Liking VAS of the positive control by percent reduction (ALO30c vs. Oxy30c)

Oxy30c (Emax)	Percent of Reduction (%)													total
	<0	0	(0, 10)	[10, 20)	[20, 30)	[30, 40)	[40, 50)	[50, 60)	[60, 70)	[70, 80)	[80, 90)	[90, 100)	≥100	
≤55														1
(55, 60]														
(60, 65]														
(65, 70]			1											1
(70, 75]										1				1
(75, 80]														
(80, 85]										1		1		2
(85, 90]														
(90, 95]	1					2		1	1			1	1	7
(95, 100]								2	2	1	2	8	1	16
Total	1	1	1			2		3	3	3	2	10	2	28
pct (%)	3.57	3.57	3.57			7.14		10.71	10.71	10.71	7.14	35.71	7.14	100.0
Cpct (%)	100.0	96.4	92.8	89.3	89.3	89.3	82.1	82.1	71.4	60.7	50.0	42.9	7.1	

Note: The pct, and cpct denote the percentage of subjects and the cumulative percentage of subjects, respectively.

Table 14: Contingency Table for Emax of High VAS of the positive control by percent reduction (ALO30c vs. Oxy30c)

Oxy30c (Emax)	Percent of Reduction (%)													total
	<0	0	(0, 10)	[10, 20)	[20, 30)	[30, 40)	[40, 50)	[50, 60)	[60, 70)	[70, 80)	[80, 90)	[90, 100)	≥100	
≤10		1												1
(10, 20]	1													1
(20, 30]														
(30, 40]														
(40, 50]								1						1
(50, 60]														
(60, 70]														
(70, 80]											2			2
(80, 90]					1			1		2				4
(90, 100]	1				2	2	3			3	4		4	19
Total	2	1			3	2	3	2		5	6		4	28
pct (%)	7.14	3.57			10.71	7.14	10.71	7.14		17.86	21.43		14.29	100.0
Cpct (%)	100.0	92.9	89.3	89.3	89.3	78.6	71.4	60.7	53.6	53.6	35.7	14.3	14.3	

Figure 13 is the percent reduction profiles for ALO30c vs. Oxy30c for Drug Liking VAS and High VAS.

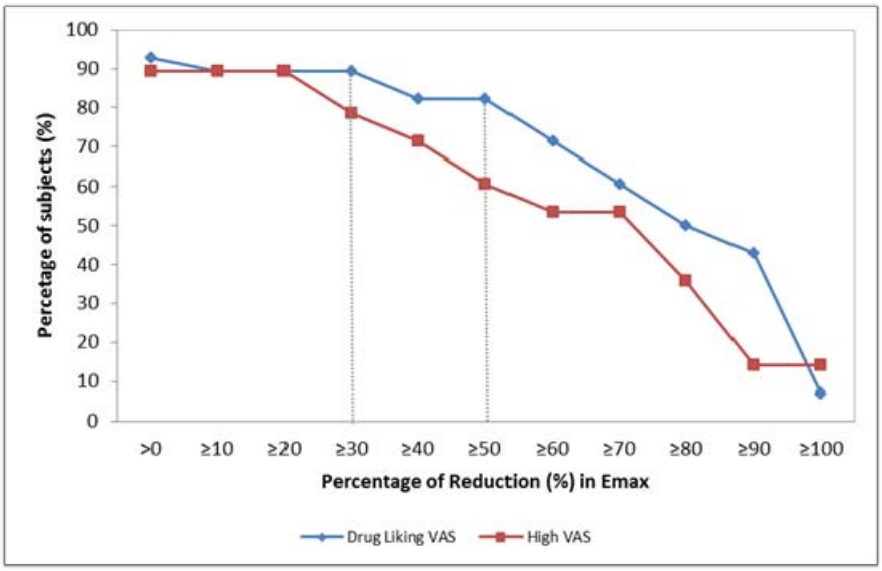


Figure 13: Percent Reduction Profiles for ALO30c vs. Oxy30c for Drug Liking VAS and High VAS (N=28).

3.3.2.2 Responder analysis

Because the Sponsor did not define a responder, the reviewer used cut off point in the order from small percent to large percent with 5% increment to define a responder, and used the binomial test to test the null hypothesis: the majority subjects are not responders. The testing procedure was stopped when an insignificant result was obtained. The reviewer found that

- The majority of the subjects had at least 60% reduction in maximum liking for ALO30c compared to Oxy30c with a p-value of 0.0117. The 95% confidence interval of the responder rate was (0.55, 0.88).
- The majority subjects had at least 40% reduction in maximum high for ALO30c compared to Oxy30c with a p-value of 0.0117. The 95% confidence interval of the responder rate was (0.55, 0.88).

3.4 Conclusion

The intranasal study 1009 shows that

- TROXYCA ER has abuse deterrent property if crushed and administered through nasal route. Compared to crushed IR oxycodone 30 mg, crushed TROXYCA ER 30 mg/3.6 mg had statistically significantly 60% and 55% reduction in means of maximum liking and maximum high respectively, at least 60% and 55% reduction in maximum liking and maximum high respectively for the majority of subjects.
- Abuse potential of crushed TROXYCA ER 30 mg/ 3.6 mg was not similar to that of placebo for the nasal route.
- The statistically significant difference between crushed oxycodone IR and placebo for both Drug Liking VAS and High VAS validated the study.

4. Review report on Study b4531002 (Intravenous Study)

4.1 Overview

Study b4531002 was a randomized, single-dose, placebo-controlled, double-blind, 3-way crossover study to determine the relative abuse potential of intravenous oxycodone hydrochloride alone or in combination with intravenous naltrexone hydrochloride in opioid experienced non-dependent subjects

4.1.1 Objectives of the study

Primary Objectives:

- To determine the relative abuse potential of intravenous (IV) oxycodone hydrochloride (HCl) when combined with IV naltrexone HCl (i.e., simulated IV administration of ALO-02) compared with an equivalent IV dose of oxycodone HCl alone and with IV placebo, when administered to non-dependent, recreational opioid users.

Secondary Objectives:

- To evaluate the pharmacokinetics (PK) of oxycodone, oxymorphone, noroxycodone, naltrexone, and 6-β-naltrexol following administration of IV oxycodone HCl combined with IV naltrexone HCl and IV oxycodone alone, when administered IV to non-dependent, recreational opioid users.
- To evaluate the overall systemic exposure of oxycodone in the presence and absence of naltrexone.
- To assess the safety and tolerability of single doses of IV oxycodone and IV oxycodone combined with IV naltrexone in non-dependent, recreational opioid users.

Exploratory Objective:

- To determine the oxycodone exposure-response relationship with respect to select pharmacodynamics (PD) and safety endpoints (e.g., visual analog scales [VAS] Drug Liking, VAS High, pupil diameter, oxygen saturation of hemoglobin [SpO2], end tidal carbon dioxide [EtCO2]) in the presence and absence of naltrexone.

4.1.2 Study design

This study consisted of the following phases:

- Screening Visit (Visit 1; 2-28 days prior to Visit 2, Day 0);

- Naloxone Challenge Phase (Visit 2; Day 0);
- Drug Discrimination Phase (Visit 2; Days 1 to 3);
- Randomization and entry into the 6 period Treatment Phase (Visits 3 to 5, Days 0-2);
- End-of-Study Visit (Visit 6; 3 to 7 days following last study drug administration or at the time of early discontinuation).

During the Drug Discrimination Phase (Visit 2; Days 1 to 3), Subjects randomly received either oxycodone HCl 20 mg or placebo, i.e., 1 treatment per day over 2 consecutive days (Days 1 and 2), in a fasted state and double-blind fashion.

During the Treatment Phase (Visits 3-5, Days 0-2), subjects received single doses of treatments in randomized, double-blind, placebo-controlled, 3-way crossover fashion on Day 1 of each Treatment Period as described in Table 15.

Table 15: Study Treatment Administered

Treatment A	Treatment	Formulation
Treatment A	Placebo	0.9% sodium chloride IV push over 4 minutes±15 seconds
Treatment B	Simulated parenteral dose of ALO-02 20 mg/2.4 mg	Oxycodone HCl 20 mg IV + naltrexone HCl 2.4 mg simultaneously IV push over 4 minutes±15 seconds
Treatment C	Oxycodone HCl 20 mg	Oxycodone HCl 20 mg IV push over 4 minutes±15 seconds

Abbreviations: ALO-02 = oxycodone hydrochloride and naltrexone hydrochloride extended-release capsules; HCl = hydrochloride; IV = intravenous.
Source: Sponsor's Table S1 on page 2 of the synopsis of the study report.

4.1.3 Abuse potential measures

Primary measures

Drug Liking VAS, and High VAS

Other VAS measures

Any Drug Effects, Good Drug Effects, Bad Drug Effects, Feel Sick, Nausea, Sleepy, and Dizzy, Take Drug Again, and Overall Drug Liking.

Pupillometry Assessment: Pupil size.

4.1.4 Study subjects

Of the 60 subjects screened, all subjects completed the Naloxone Challenge Phase. There were no discontinuations in the Naloxone Challenge Phase.

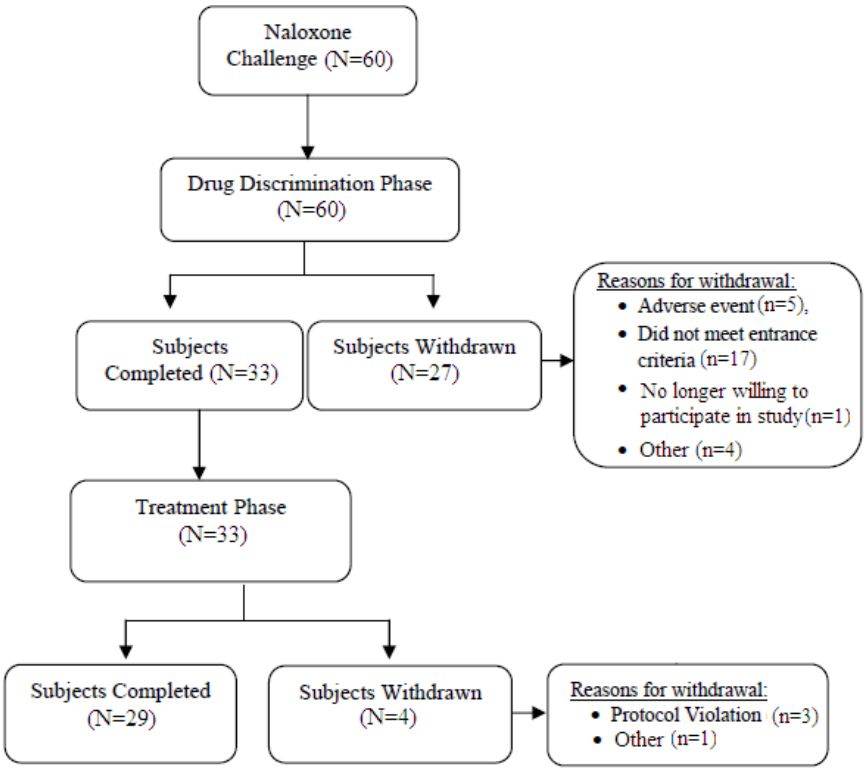
Sixty (60) subjects entered the Drug Discrimination Phase and a total of 33 subjects successfully completed the Drug Discrimination Phase. Five (5) subjects were discontinued after treatment with oxycodone HCl 20 mg IV due to treatment-related AEs. Seventeen (17) subjects completed drug discrimination procedures, but were discontinued because they did not meet randomization criteria for the Treatment Phase (Section 9.1.3). One (1) subject was discontinued after treatment with placebo due to unwillingness to participate in the study. Four (4) subjects were discontinued due to other reasons un-related to the study drug: 1 subject was withdrawn at the discretion of the site as he presented a likelihood that he would not complete the study; 1 subject withdrew from the study due to family emergency; 2 subjects discontinued as the number of randomized subjects required for this study had been fulfilled.

In the Treatment Phase, 33 subjects were randomized to the Treatment Phase and constituted both the Safety and PK populations (Section 11.1). A total of 29 subjects completed the Treatment Phase and constituted the Completer Population used for primary PD analysis. Three (3) discontinuations due to positive drug screens were observed during the Treatment Phase, none of which were related to study drug. One (1) subject was discontinued due to work conflict.

A total of 26 subjects were included in the Evaluable Population, which excluded 1 subject (10011026) with major protocol deviations (Section 10.2) and 2 subjects who had an emesis episode within 2 hours of study drug administration (Section 11.1).

Figure 14 is for summary of subject disposition, which is on page 68 of the study report.

Figure 14: Summary of Subject Disposition



Source: Sponsor's Figure 1 on page 68 of the study report.

N = total number of subjects in each group; n = number of subjects in each category

4.1.5 Statistical methodologies used in the Sponsor's analyses

The Completer Population included all randomized subjects who completed all 3 Periods of the Treatment Phase and who contributed post-dose PD data from each period. This population was analyzed as randomized.

Primary endpoints

The primary endpoints were summarized by treatment using descriptive statistics (mean, SD, median, first and third quartiles, minimum and maximum). These parameters were analyzed using a mixed-effect model with treatment, period, and sequence as fixed effects, and subject nested within the sequence as a random effect. Analyses of endpoints with baseline (pre-dose) measurements included the baseline measurement as a covariate in the model. LS means, standard errors (SEs), and 95% CIs were provided for each treatment and for the difference between treatments.

The primary treatment comparisons were:

- Simulated IV dose of ALO-02 20 mg/2.4 mg versus oxycodone HCl 20 mg IV;
- Simulated IV dose of ALO-02 20 mg/2.4 mg versus placebo.

Statistical significance of all treatment differences was reported; all statistical tests were conducted using one-tailed significance criteria. To control for Type I errors arising from multiple comparisons, the Benjamini-Hochberg procedure was used across the primary treatment comparisons of the primary endpoints. These comparisons were used to assess the primary study objective.

Regression diagnostics were performed to verify model assumptions and adequacy of the fitted linear models for the primary endpoints. Levene's test was used to diagnose potential heterogeneity of variance and the Shapiro–Wilk test was used to diagnose potential non-normality of the model residuals.
If the resulting p-value from Levene's test was ≤0.05, the null hypothesis of equal variances was rejected and it was concluded that there was a difference between the treatment group variances. An unequal variance model was then applied using the Satterthwaite method in order to produce an accurate F-approximation.

If the resulting p-value from the Shapiro-Wilk test was ≤0.05, symmetry of the distribution of paired differences was tested and either the Wilcoxon Signed Rank Test or Friedman Test was performed.
If needed (Shapiro-Wilk test had a p-value ≤0.05), symmetry was tested for each of the primary comparisons using the Kolmogorov-Smirnov test.

The test for median of differences for each treatment comparison and endpoint (Emax and AUC0-2h), was determined by the Wilcoxon Signed Rank Test if the paired differences were symmetric, or by the Friedman Test if the paired differences were asymmetric.
As a post hoc analysis, symmetry was tested using the Triples Test instead of the Kolmogorov-Smirnov test, and the testing procedure was continued as described above.

The numbers of subjects with Emax lower for simulated ALO-02 20 mg/2.4 mg than for oxycodone HCl were also presented for Drug Liking and High.

The analysis for percent reduction in Emax for Drug Liking and High used the following formulas for the responder analysis:

- For Drug Liking, Percent Reduction (%) was calculated as:

$$\frac{\text{Emax(reference)} - \text{Emax (test)}}{\text{Emax (reference)} - 50} \text{X } 100\%, \text{if P} \leq 60$$

$$\frac{\text{Emax(reference)} - \text{Emax (test)}}{\text{Emax (reference)} - 50} \text{X} \cdot 1 - \frac{\text{P} - 50}{50} \text{ X } 100\%, \text{if P} > 60$$

- For High, Percent Reduction(%) was calculated as:

$$\frac{\text{Emax(reference)} - \text{Emax (test)}}{\text{Emax (reference)}} \text{X } 100\%, \text{if P} \leq 10$$

$$\frac{\text{Emax(reference)} - \text{Emax (test)}}{\text{Emax (reference)}} \text{X } \quad 1 - \frac{\text{P}}{100} \text{ X } 100\%, \text{if P} > 10$$

where P was the response for Placebo; the reference was oxycodone HCl 20 mg IV and the test was simulated IV dose of ALO-02 20 mg/2.4 mg.

Secondary endpoints

Analyses similar to those described in Section 9.7.3.1.2 were performed on all secondary PD endpoints and assessment parameters without adjustment for multiplicity.

4.1.6 Sponsor's Results and Conclusions

Study Validation

- Validity of the study was evaluated through statistical comparison of Emax for Drug Liking and High between oxycodone HCl 20 mg IV (active control) and placebo administered during the Treatment Phase. The Emax for Drug Liking and High for oxycodone HCl 20 mg IV were significantly greater ($p < 0.0001$) than that observed with placebo and 95% Cis showed differences >15 for Drug Liking and >30 for High between oxycodone HCl 20 mg and placebo, therefore confirming sensitivity of the study.

Primary Pharmacodynamic Measures

Drug Liking VAS

- The Shapiro-Wilk test for normality was statistically significant for all primary comparisons and therefore the primary statistical comparisons were made using median differences using either the Wilcoxon Signed Rank Test or Friedman Test depending on the results from the Kolmogorov-Smirnov test for symmetry. For Drug Liking Emax and AUE0-2h, simulated ALO-02 20 mg/2.4 mg IV was significantly lower compared to oxycodone HCl 20 mg IV (median difference = -38.0 and -49.9, respectively, both adjusted p <0.0001).

- The Emax and AUE0-2h for simulated ALO-02 20 mg/2.4 mg IV were slightly higher in comparison to placebo. The median Emax for simulated ALO-02 20 mg/2.4 mg IV was significantly higher in comparison to placebo (median difference = 1.0, adjusted p = 0.0097), whereas the median difference from placebo in AUE0-2h was not statistically significant (median difference = 0.6, adjusted p = 0.0682).
- The Triples Test used for the post hoc analysis showed different results when determining symmetry compared to the Kolmogorov-Smirnov test for some treatment comparisons. However, the results of the post hoc nonparametric analyses showed no qualitative differences in statistical significance when compared to the results of the primary analysis.
- The overall mean percentage reduction was 75%. Relative to oxycodone HCl 20 mg IV, a majority of subjects (26 [90%]) had some degree (any reduction) of reduced Drug Liking Emax after receiving simulated ALO-02 20 mg/2.4 mg IV. Twenty six (90%) subjects had at least a 30% reduction (equivalent to a 15-point decrease on this bipolar scale) and 24 (83%) subjects had at least 50% reduction. Three (10%) subjects had no reduction, whereas 5 (17%) subjects had at least 100% reduction in Drug Liking Emax compared to oxycodone HCl 20 mg IV, indicating full abatement of liking.

High VAS

- The Shapiro-Wilk test for normality was statistically significant for all primary comparisons and therefore the primary statistical comparisons were made using median differences using either the Wilcoxon Signed Rank Test or Friedman Test depending on the results from the Kolmogorov-Smirnov test for symmetry. For High Emax and AUE0-2h, simulated ALO-02 20 mg/2.4 mg IV was significantly lower compared to oxycodone HCl 20 mg IV (median difference = -86.0 and -126.3, respectively, both adjusted p <0.0001).
- The Emax and AUE0-2h for simulated ALO-02 20 mg/2.4 mg IV were significantly higher in comparison to placebo (median difference = 2.0, adjusted p = 0.0083 for Emax; median difference = 1.1, adjusted p <0.0001 for AUE0-2h).
- The Triples Test used for the post hoc analysis showed different results when determining symmetry compared to the Kolmogorov-Smirnov test for some treatment comparisons. However, the results of the post hoc nonparametric analyses showed no qualitative differences in statistical significance when compared to the results of the primary analysis.
- The overall mean percentage reduction was 77%. Relative to oxycodone HCl 20 mg IV, a majority of subjects (28 [97%]) had some degree (any reduction) of reduced High Emax after receiving simulated ALO-02 20 mg/2.4 mg IV. Twenty seven (93%) subjects had at least a 30%

reduction (equivalent to a 30-point decrease on this unipolar scale) and 27 (93%) subjects had at least a 50% reduction. One (3%) subject had no reduction; whereas 4 (14%) subjects had at least 100% reduction in High Emax compared to oxycodone HCl 20 mg IV, indicating a complete (100%) reduction in feeling high.

Secondary Pharmacodynamic Measures

The results of the positive subjective effects (Good Drug Effects VAS), other subjective effects (Any Drug Effects, Sleepy, and Dizzy VASs) and negative subjective effects (Bad Drug Effects, Feel Sick, Nausea VASs) measures supported those of the primary endpoints, showing less effect for simulated ALO-02 20 mg/2.4 mg and the placebo treatment compared to oxycodone HCl 20 mg IV.

Measurement of pupil diameter by pupillometry indicated that IV oxycodone 20 mg resulted in significantly greater pupil constriction compared to simulated IV ALO-02 20 mg/2.4 mg as well as placebo. The miotic effect was the greatest with IV oxycodone, followed by simulated IV ALO-02, and smallest with the placebo.

Conclusions from the PD study

- Overall, simulated parenteral administration of ALO-02 20 mg/ 2.4 mg IV resulted in significantly lower abuse potential compared to oxycodone HCl 20 mg IV when administered to non-dependent recreational opioid users.
- The primary endpoint results demonstrated that simulated IV crushed ALO-02 20 mg/2.4 mg showed significantly less Drug Liking and High compared to oxycodone HCl 20 mg IV.
- The secondary endpoints supported the results of the primary endpoints. The onset of mitigation of the opioid effects with simulated IV crushed ALO-02 20 mg/2.4 mg was primarily in the first 2 hours after dosing, when abusers typically desire euphoric effects. Lasting effects were observed as evidenced by a significant reduction in Emax and Emean on the global measures of Overall Drug Liking and Take Drug Again with simulated ALO-02 20 mg/2.4 mg IV compared to oxycodone HCl 20 mg IV.
- Other secondary endpoints, i.e., positive subjective effects (Good Drug Effects VAS), other subjective effects (Any Drug Effects, Sleepy, and Dizzy VASs) and negative subjective effects (Bad Drug Effects, Feel Sick, Nausea VASs) also supported that there was decreased opioid activity with simulated IV crushed ALO-02 compared to oxycodone HCl IV.

4.2 Data Location

The analysis datasets are located at

\\cdsesub1\evsprod\nda207621\0000\m5\datasets\b4981002\analysis\legacy\datasets\adpdfda.xpt

4.3 Reviewer's assessment

The reviewer's assessment focused on the primary endpoints Emax of Drug Liking VAS and Emax of High VAS. The following notations for the treatments were used in the reviewer's analyses:

ALO20IV – Simulated parental dose of ALO-02 20 mg/2.4 mg;
Oxy20IV – Oxycodone HCl IV 20 mg;
PIV - placebo.

4.3.1 Primary Analysis

4.3.1.1 Descriptive statistics

Table 16 summarizes the mean, standard error, minimum, the first quartile (Q_1), median, the third quartile (Q_3), and maximum for the 3 treatments in the study for the primary endpoints Emax of Drug Liking VAS and Emax of High VAS. The similar table for VAS measures Any Drug Effects, Good Drug Effects, Bad Drug Effects, Overall Drug Liking, and Take Drug Again, as well as Dizzy, Feel sick, Nausea and Sleepy can be found in Appendix IV.

Table 16: Summary statistics for Emax of Drug Liking VAS and Emax of High VAS (N=29)

Abuse Potential Measure	TRT	Mean	StdErr	Min	Q1	Median	Q3	Max
Drug Liking	ALO20IV	58.2	2.32	50	51	51	64	100
	Oxy20IV	92.4	1.66	69	85	97	100	100
	PIV	52.3	0.99	50	50	51	51	75
High	ALO20IV	17.4	4.53	0	1	3	25.5	92
	Oxy20IV	93.1	1.99	55	88.5	98	100	100
	PIV	3.7	1.63	0	0	0	1	33

Table 16 shows that Q3s of maximum liking and high from subjects to ALO20IV were 64 and 25.5, respectively. In the contrast, The Q1s of maximum liking and high from subjects to Oxy20IV were 85 and 88.5, respectively. The abuse-deterrent effect of ALO20IV is very large.

Figures 14 and 15 are the mean time course profiles by treatment for Drug Liking VAS and High VAS, respectively. The maximum of mean response for ALO20IV is approximately 56 for liking and 13 for high. The entitle profile of ALO20IV lays within placebo range for both primary measures.

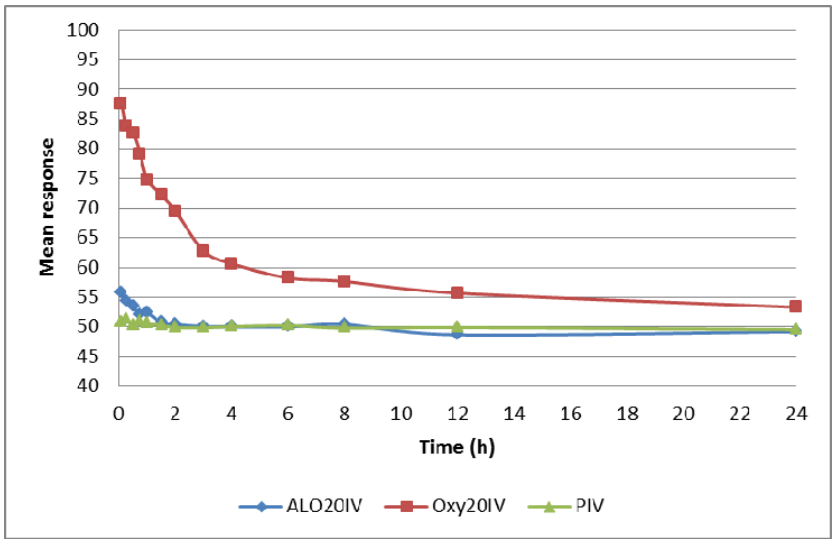


Figure 14: **The mean time course profiles on Drug Liking VAS by treatment (N=29)**

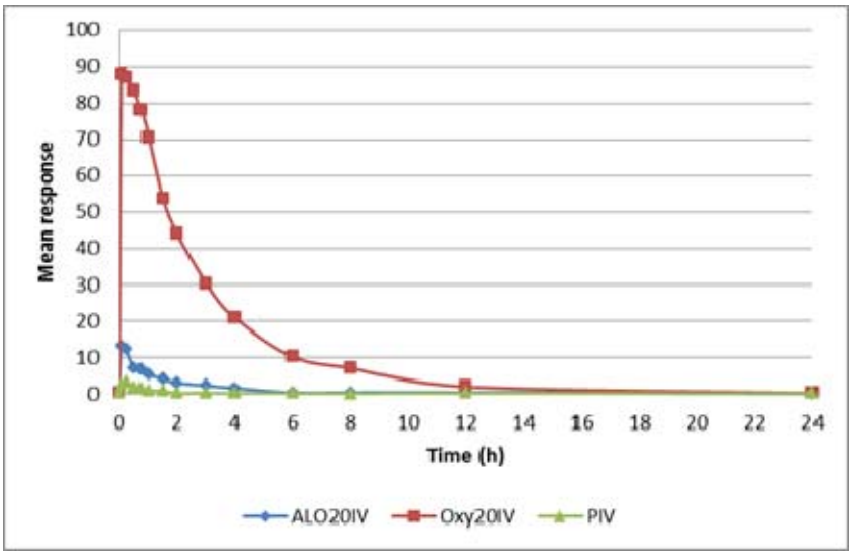


Figure 15: The mean time course profiles on High VAS by treatment (N=29)

The heat maps by treatment for two primary endpoints are presented in Figures 16 and 17.

Figure 16: **Heat Map by Treatment for Drug Liking VAS (Study 1002)**

Figure 17: Heat Map by Treatment for High VAS (Study 1002)

4.3.1.2 Statistical testing

For examining the abuse deterrent properties of ALO-02, the reviewer performed the following comparisons:

- ALO20IV versus Oxy20IV (Primary)
- Oxy20IV versus PIV (Study validation)

The hypotheses for these comparisons are listed below:

Primary comparison

$$H_0 : \mu_{Oxy20IV} - \mu_{ALO20IC} \le \delta^*(\mu_{Oxy20IV} - x) \text{ vs. } H_a : \mu_{Oxy20IV} - \mu_{ALO20IV} > \delta^*(\mu_{Oxy20IV} - x),$$

where $0 < \delta^* < 1$, x=50 and 0 for Drug Liking VAS and High VAS, respectively. It is equivalent to testing

$$H_0 : \mu_{ALO20IV} - (1-\delta^*)\mu_{Oxy20IV} - \delta^* x \ge 0 \text{ vs. } H_a : \mu_{ALO20IV} - (1-\delta^*)\mu_{Oxy20IV} - \delta^* x < 0.$$

Study validation

$$H_0 : \mu_{Oxy20IV} - \mu_{PIV} \le \delta_2 \text{ vs. } H_a : \mu_{Oxy20IV} - \mu_{PIV} > \delta_2,$$

where δ_2 =15 and 30 for Drug Liking VAS and High VAS, respectively. It is equivalent to testing

$$H_0 : \mu_{Oxy20IV} - \mu_{PIV} - \delta_2 \le 0 \text{ vs. } H_a : \mu_{Oxy20IV} - \mu_{PIV} - \delta_2 > 0.$$

For the comparison between ALO20IV and placebo, the reviewer used the Chen-Bonson's equivalence test for Drug Liking VAS, and also extended this test for High VAS as follows:

$$H_0 : \mu_{AlO20IV} - \mu_{PIV} \ge \delta_3 \text{ vs. } H_0 : \mu_{ALO20IV} - \mu_{PIV} < \delta_3,$$

where δ_3 =11 and 22 for Drug Liking VAS and High VAS, respectively. It is equivalent to test

$$H_0 : \mu_{AlO20IV} - \mu_{PIV} - \delta_3 \ge 0 \text{ vs. } H_0 : \mu_{AlO20IV} - \mu_{PIV} - \delta_3 < 0.$$

Because there is no pre-specified δ^*, the reviewer used means listed in Table 17 for each treatment to calculate the ratio of $(\bar{x}_{Oxy20IV} - \bar{x}_{ALO20IV})$ to $(\bar{x}_{Oxy20IV} - x)$ for the starting δ^* for the primary comparison. This ratio for both Drug Liking VAS and High VAS is 0.81. Therefore, the reviewer used δ^* started from 0.6 with 0.05 increment for the test, and stopped testing when an insignificant result was obtained.

The same statistical model used in Studies 1008 and 1009 was used in this study. The results from the W test for examining the normality assumption of the statistical model for both primary endpoints were highly significant with p-value <0.0001. Note that the distributions of $ALO20IV - (1-\delta^*)Oxy20IV - \delta^* x$ and $ALO20IV - Poxy$ were positively skewed and these tests

are lower-tailed tests. In addition, note that the distribution of $Oxy20IV - Poxy$ was negatively skewed, and the test for this comparison is an upper-tailed test. Therefore, t-test was used for all comparisons.

Table 17: Summary of results from the primary analysis (n=29)

Abuse Potnetial Measure	Comparison	δ	Mean* Diff	StdErr	t-value	p-value	LCL	UCL
Drug Liking VAS	ALO20IV vs.Oxy20IV	0.65(δ*)	-6.6	2.47	-2.67	0.0063	-8.6	-4.5
	Oxy20IV vs. PIV	15 (δ_2)	25.1	2.00	12.55	0.0000	23.1	27.2
	ALO20IV vs. PIV	11 (δ_3)	-5.0	2.64	-1.91	0.0334	-7.1	-3.0
High VAS	ALO20IV vs. Oxy20IV	0.70(δ*)	-10.5	4.57	-2.30	0.0146	-12.6	-8.5
	Oxy20IV vs. PIV	30 (δ_2)	59.4	2.62	22.70	0.0000	57.3	61.4
	ALO20IV vs. PIV	22 (δ_3)	-8.3	5.00	-1.66	0.0545	-10.3	-6.2

*: Estimate of the difference on the left hand side of the null hypothesis.

Table 17 shows that compared to Oxy20IV, ALO20IV had statistically significant 65% reduction in mean of maximum liking (p=0.0063), and statistically significantly 70% reduction in mean of maximum high (p=0.0146). Abuse potential of ALO20IV was not similar to PIV (p=0.0334 for liking, and p=0.0545 for high). The significantly differences between Oxy20IV and PIV for both Drug Liking VAS (p=0.0000) and High VAS (p=0.0000) validated the study.

4.3.2 Secondary Analysis

The only difference in the calculation formulas for percent reduction between the Sponsor and this reviewer is that the cutoff point for large placebo responses is 60 used by the Sponsor and 55 used by the reviewer for Drug Liking VAS. Three subjects had placebo responses greater than 55 (60, 63 and 72) for Drug Liking VAS. Therefore, percent reductions calculated by the reviewer had no much difference from those calculated by the Sponsor.

4.3.2.1 Descriptive Statistics

The same methods as used in Studies 1008 and 1009 for calculating percent reductions were used by the reviewer. Tables 19 and 20 show the frequency distributions of subjects in terms of their responses to Oxy20IV and their percent reductions for ALO20IV relative to Oxy20IV for Drug Liking VAS and High VAS, respectively. Among 29 completers, approximately 10% (3) and 3% (1) of subjects did not have any reduction for ALO20IV relative to Oxy20IV in maximum liking and maximum high, respectively. Approximately 90% (26) and 83% (24) of subjects had at least 30% and 50% reduction in maximum liking for ALO20IV relative to Oxy20IV, respectively, and approximately 93% (27) of subjects had at least 50% reduction in maximum high for ALO20IV relative to Oxy20IV.

Table 18: Contingency Table for Emax of Drug Liking VAS of the positive control by percent reduction (ALO20IV vs. Oxy20IV)

Oxy20IV (Emax)	Percent of Reduction (%)													total
	<0	0	(0, 10)	[10, 20)	[20, 30)	[30, 40)	[40, 50)	[50, 60)	[60, 70)	[70, 80)	[80, 90)	[90, 100)	≥100	
≤55														
(55, 60]														
(60, 65]														
(65, 70]		1												1
(70, 75]														
(75, 80]							1	1				1		3
(80, 85]	1						1					1		3
(85, 90]								1			1	2		4
(90, 95]										1				1
(95, 100]		1						1	1	2	2	6	4	17
Total	1	2					2	3	1	3	3	10	4	29
pct (%)	3.45	6.90					6.90	10.34	3.45	10.34	10.34	34.48	13.79	100.0
Cpct (%)	100.0	96.5	89.6	89.6	89.6	89.6	89.6	82.7	72.4	69.0	58.6	48.3	13.8	

Table 19: Contingency Table for Emax of High VAS of the positive control by percent reduction (ALO20IV vs. Oxy20IV)

Oxy20IV (Emax)	Percent of Reduction (%)													total
	<0	0	(0, 10)	[10, 20)	[20, 30)	[30, 40)	[40, 50)	[50, 60)	[60, 70)	[70, 80)	[80, 90)	[90, 100)	≥100	
≤10														
(10, 20]														
(20, 30]														
(30, 40]														
(40, 50]														
(50, 60]									1					1
(60, 70]									1					1
(70, 80]									1					1
(80, 90]	1								2	1	1			5
(90, 100]				1				3	1	1	3	8	4	21
Total	1			1				3	6	2	4	8	4	29
pct (%)	3.45			3.45				10.34	20.69	6.90	13.79	27.59	13.79	100.0
Cpct (%)	100.0	96.6	96.6	96.6	93.1	93.1	93.1	93.1	82.8	62.1	55.2	41.4	13.8	

Figure 18 is the percent reduction profiles for ALO20IV relative to Oxy20IV for Drug Liking VAS and High VAS.

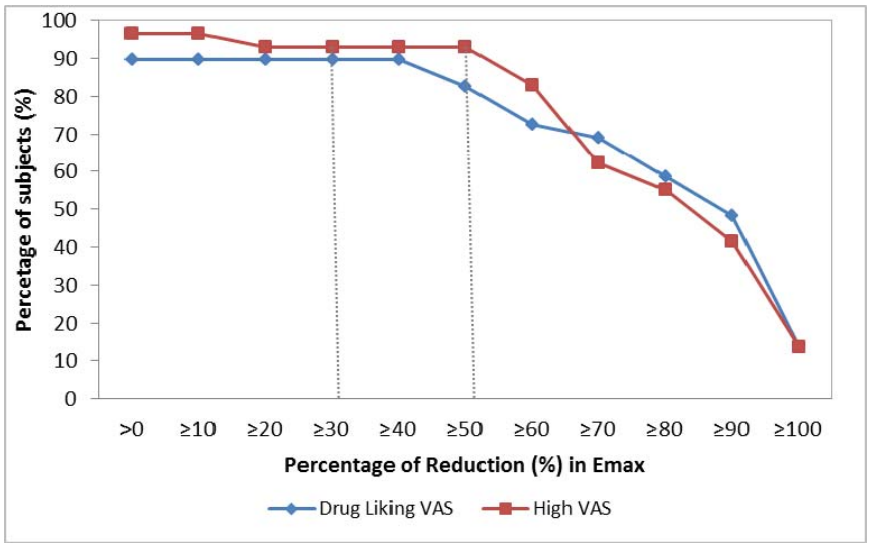


Figure 18: Percent Reduction Profiles for ALO20IV vs. Oxy20IV for Drug Liking VAS and High VAS (N=29)

4.3.2.2 Responder Analysis

Because the Sponsor did not define a responder, the reviewer used cut off point in the order from small percent to large percent with a 5% increment to define a responder, and used the binomial test to test the null hypothesis: the majority subjects are not responders. The testing procedure was stopped when an insignificant result was obtained. The reviewer found that

- The majority of the subjects had at least 70% reduction in maximum liking for ALO20IV relative to Oxy20IV with a p-value of 0.0205. The 95% confidence interval of the responder rate was (0.52, 0.86).
- The majority subjects had at least 65% reduction in maximum high for ALO20IV relative to Oxy30c with a p-value of 0.0027. The 95% confidence interval of the responder rate was (0.60, 0.91).

4.4 Conclusion

The results from the intravenous study 1002 shows that

- The stimulated parental dose of TROXYCA ER 20 mg has abuse deterrent property for intravenous route. Compared to oxycodone HCl 20 mg IV, stimulated parental dose of TROXYCA 20 mg had statistically significantly 65% and 70% reduction in means of maximum liking and maximum high respectively, and at least 65% reduction in both maximum liking and maximum high respectively for the majority of subjects.
- Abuse potential of stimulated parental dose of TROXYCA 20 mg was not similar to placebo.
- The statistically significant differences between oxycodone HCl 20 mg IV and placebo for both Drug Liking VAS and High validated the study.

Appendix I: Summary statistics for other abuse potential measures (Study 1008)

Table 20: Summary statistics for other abuse potential measures (Study 1008)

Abuse Potential Measure	TRT	Mean	StdErr	Min	Q1	Median	Q3	Max
Any Drug Effects VAS	ALO40c	47.2	6.80	0	5	60	81.75	100
	ALO60c	56.0	6.35	0	19	69.5	91.75	100
	ALO60i	27.7	6.32	0	0	4	57.5	100
	Oxy40c	82.4	4.47	0	73.5	94.5	100	100
	Oxy60c	88.7	3.63	21	87.25	100	100	100
	P	8.8	3.43	0	0	0	2.75	58
Good Drug Effects VAS	ALO40c	48.1	6.81	0	4.5	60.5	85.75	100
	ALO60c	54.7	6.39	0	14.25	63	90.5	100
	ALO60i	24.2	6.13	0	0	4	55.5	100
	Oxy40c	81.8	4.34	0	70.75	90	100	100
	Oxy60c	84.3	3.98	22	74.25	94.5	100	100
	P	11.6	4.40	0	0	0	1.75	100
Bad Drug Effects VAS	ALO40c	16.4	4.73	0	0	0	18.5	74
	ALO60c	16.9	5.10	0	0	0	21.75	100
	ALO60i	20.6	6.31	0	0	0	39.25	100
	Oxy40c	26.5	6.47	0	0	3.5	64.5	100
	Oxy60c	31.4	5.78	0	0	16.5	64.5	94
	P	5.8	2.73	0	0	0	0	50
Overall Drug Liking VAS	ALO40c	64.3	4.24	0	50.25	58.5	84.75	100
	ALO60c	74.0	3.97	22	55.5	78	98.25	100
	ALO60i	52.9	3.77	0	50	50	55.5	100
	Oxy40c	80.8	3.45	29	68.75	82.5	100	100
	Oxy60c	81.6	4.09	0	73.5	90.5	100	100
	P	50.8	2.26	0	50	50	51	100
Take Drug Again VAS	ALO40c	57.9	5.94	0	50	59	87.5	100
	ALO60c	72.0	5.01	0	52	77.5	100	100
	ALO60i	48.1	4.97	0	50	50	57	100
	Oxy40c	83.4	3.58	30	68	90.5	100	100
	Oxy60c	81.3	4.46	0	67.75	90.5	100	100
	P	45.7	3.37	0	50	50	51	92

Table 13 continued.

Abuse Potential Measure	TRT	Mean	StdErr	Min	Q1	Median	Q3	Max
Dizzy VAS	ALO40c	23.4	5.77	0	0	1	52.5	100
	ALO60c	19.5	5.58	-1	0	0	36.75	90
	ALO60i	12.0	4.99	0	0	0	1.5	92
	Oxy40c	30.6	6.47	0	0	10	55.5	100
	Oxy60c	39.3	6.70	0	0	37	75	100
	P	3.6	2.17	0	0	0	0.75	50
Feel Sick VAS	ALO40c	5.4	2.68	0	0	0	2.75	69
	ALO60c	2.6	1.25	0	0	0	0.75	27
	ALO60i	10.1	4.66	0	0	0	0	93
	Oxy40c	8.8	4.53	-17	0	0	3	100
	Oxy60c	11.7	4.98	-49	0	0	7.75	100
	P	3.1	1.91	0	0	0	0	50
Nausea VAS	ALO40c	11.5	4.43	0	0	0	5.5	89
	ALO60c	11.3	4.15	0	0	0	6	76
	ALO60i	9.5	4.63	0	0	0	2.5	94
	Oxy40c	17.8	5.68	0	0	0	22	100
	Oxy60c	22.0	5.88	0	0	0	58	100
	P	6.1	3.34	-1	0	0	0	85
Sleepy VAS	ALO40c	56.8	6.28	0	27	64.5	92.75	100
	ALO60c	59.2	6.50	0	25.5	66	97	100
	ALO60i	38.3	6.77	0	0	18	73.75	100
	Oxy40c	72.0	5.40	0	59.5	78	99.5	100
	Oxy60c	76.1	4.58	10	57.25	83.5	100	100
	P	24.7	6.02	-3	0	0.5	50.75	100

Appendix II: Other Analysis Results from Study 1008

Table 21: Summary of results of comparisons for Drug Liking VAS (Study 1008)

Differences in Least Squres Means									
NAME OF TREATMENT	*NAME OF TREATMENT*	*LSmean Diff*	*Standard Error*	*DF*	*t Value*	*Pr >|t|*	*Alpha*	*Lower*	*Upper*
ALO40c	ALO60c	-4.3392	4.6284	57.5	-0.94	0.3524	0.05	-13.6054	4.9270
ALO40c	ALO60i	10.8953	4.3257	54.8	2.52	0.0147	0.05	2.2256	19.5650
ALO40c	Oxy40c	-15.2675	4.4136	55.2	-3.46	0.0011	0.05	-24.1119	-6.4232
ALO40c	Oxy60c	-19.6660	4.1270	50.3	-4.77	<.0001	0.05	-27.9540	-11.3781
ALO40c	P	18.6447	3.4696	30.6	5.37	<.0001	0.05	11.5643	25.7250
ALO60c	ALO60i	15.2345	4.0719	56.3	3.74	0.0004	0.05	7.0785	23.3905
ALO60c	Oxy40c	-10.9283	4.1672	57.1	-2.62	0.0112	0.05	-19.2726	-2.5840
ALO60c	Oxy60c	-15.3268	3.8612	52.5	-3.97	0.0002	0.05	-23.0732	-7.5804
ALO60c	P	22.9839	3.1489	31.1	7.30	<.0001	0.05	16.5627	29.4050
ALO60i	Oxy40c	-26.1628	3.8284	57.2	-6.83	<.0001	0.05	-33.8283	-18.4973
ALO60i	Oxy60c	-30.5613	3.4941	55.2	-8.75	<.0001	0.05	-37.5630	-23.5596
ALO60i	P	7.7494	2.6829	31.1	2.89	0.0070	0.05	2.2782	13.2206
Oxy40c	Oxy60c	-4.3985	3.6035	54.6	-1.22	0.2275	0.05	-11.6211	2.8241
Oxy40c	P	33.9122	2.8239	31.7	12.01	<.0001	0.05	28.1577	39.6667
Oxy60c	P	38.3107	2.3525	31.3	16.29	<.0001	0.05	33.5149	43.1065

Table 22: Summary of results of comparisons for High VAS (Study 1008)

Differences of Least Squares Means									
NAME OF TREATMENT	*NAME OF TREATMENT*	*Estimate*	*Standard Error*	*DF*	*t Value*	*Pr > |t|*	*Alpha*	*Lower*	*Upper*
ALO40c	ALO60c	-6.2781	7.1927	44.8	-0.87	0.3874	0.05	-20.7667	8.2105
ALO40c	ALO60i	24.1991	7.3856	49.3	3.28	0.0019	0.05	9.3593	39.0388
ALO40c	Oxy40c	-31.9909	6.2374	38.1	-5.13	<.0001	0.05	-44.6168	-19.3650
ALO40c	Oxy60c	-39.0605	6.2028	40.9	-6.30	<.0001	0.05	-51.5887	-26.5324
ALO40c	P	36.3459	6.6039	46.1	5.50	<.0001	0.05	23.0536	49.6382
ALO60c	ALO60i	30.4772	6.9002	48.3	4.42	<.0001	0.05	16.6058	44.3485
ALO60c	Oxy40c	-25.7128	5.6602	40.9	-4.54	<.0001	0.05	-37.1444	-14.2812
ALO60c	Oxy60c	-32.7824	5.6192	43.6	-5.83	<.0001	0.05	-44.1098	-21.4550
ALO60c	P	42.6240	6.0588	42.5	7.04	<.0001	0.05	30.4014	54.8466
ALO60i	Oxy40c	-56.1900	5.8774	38	-9.56	<.0001	0.05	-68.0885	-44.2915
ALO60i	Oxy60c	-63.2596	5.8391	39.1	-10.83	<.0001	0.05	-75.0688	-51.4503
ALO60i	P	12.1468	6.2860	47.2	1.93	0.0593	0.05	-0.4974	24.7911
Oxy40c	Oxy60c	-7.0696	4.2986	31.4	-1.64	0.1100	0.05	-15.8322	1.6930

Appendix III: Summary statistics for other abuse potential measures (Study 1009)

Table 23: Summary statistics for other abuse potential measures (Study 1009)

Abuse Potential Measure	TRT	Mean	StdErr	Min	Q1	Median	Q3	Max
Any Drug Effects VAS	ALO30c	35.5	6.01	0	1.75	30	65	100
	Oxy30c	88.6	4.02	8	84.75	100	100	100
	Palo	0.6	0.27	0	0	0	0	5
	Poxy	6.2	3.31	0	0	0	0.75	65
Good Drug Effects VAS	ALO30c	25.6	5.59	0	0	15.5	46.75	100
	Oxy30c	87.9	3.98	9	88.25	93.5	100	100
	Palo	4.3	2.59	0	0	0	0.75	54
	Poxy	8.4	3.40	0	0	0	0.75	61
Bad Drug Effects VAS	ALO30c	13.0	4.63	0	0	0	20.25	100
	Oxy30c	18.5	4.96	0	0	9.5	18	86
	Palo	1.4	1.04	0	0	0	0	29
	Poxy	5.6	3.01	0	0	0	0	51
Overall Drug Liking VAS	ALO30c	59.9	4.10	0	50	53	74	100
	Oxy30c	85.1	4.51	0	82.5	92.5	100	100
	Palo	50.5	0.16	50	50	50	51	54
	Poxy	51.5	1.24	50	50	50	50.75	85
Take Drug Again VAS	ALO30c	58.3	6.05	0	46.25	54.5	86.5	100
	Oxy30c	87.8	5.04	0	88.5	100	100	100
	Palo	48.0	2.82	0	50	50	50.75	83
	Poxy	46.6	3.54	0	50	50	51	98

Table 17 continued.

Abuse Potential Measure	TRT	Mean	StdErr	Min	Q1	Median	Q3	Max
Dizzy VAS	ALO30c	7.4	2.98	0	0	0	9.75	64
	Oxy30c	23.5	6.92	-51	0	4.5	68	85
	Palo	4.4	2.52	0	0	0	0	50
	Poxy	4.1	2.84	-1	0	0	0	62
Feel Sick VAS	ALO30c	8.7	3.87	0	0	0	0	82
	Oxy30c	4.6	4.15	-46	0	0	0	79
	Palo	2.1	1.74	0	0	0	0.75	49
	Poxy	3.9	2.52	0	0	0	0	51
Nausea VAS	ALO30c	9.3	3.97	0	0	0	7.5	85
	Oxy30c	12.3	5.66	-35	0	0	7.5	90
	Palo	1.9	1.75	0	0	0	0	49
	Poxy	5.3	3.01	-4	0	0	0	51
Sleepy VAS	ALO30c	35.0	6.81	0	0	25.5	66.75	100
	Oxy30c	62.9	6.85	-2	30.25	77.5	90	100
	Palo	7.6	4.03	-14	0	0	2.5	70
	Poxy	11.1	5.37	-23	0	0	5.75	100

Appendix IV: Summary statistics for other abuse potential measures (Study 1002)

Abuse Potential Measure	TRT	Mean	StdErr	Min	Q1	Median	Q3	Max
Any Drug Effects VAS	ALO20IV	17.2	4.21	0	1.5	9	22.5	97
	Oxy20IV	91.3	2.30	55	89	97	100	100
	PIV	3.9	1.46	0	0	0	3	33
Good Drug Effects VAS	ALO20IV	16.4	4.15	0	1	10	25	90
	Oxy20IV	89.7	2.32	58	82	97	99.5	100
	PIV	3.4	1.42	0	0	0	1.5	32
Bad Drug Effects VAS	ALO20IV	7.6	3.28	0	0	1	6	89
	Oxy20IV	25.2	4.89	0	3	13	45	94
	PIV	1.4	0.53	0	0	0	1	12
Overall Drug Liking VAS	ALO20IV	50.2	1.18	24	50	50	51	67
	Oxy20IV	81.8	3.00	43	73.5	81	98	100
	PIV	49.9	0.88	27	50	50	50.5	56
Take Drug Again VAS	ALO20IV	51.6	2.18	18	50	50	51	100
	Oxy20IV	82.3	2.68	50	71.5	81	98	100
	PIV	49.7	0.76	29	50	50	50	55
Dizzy VAS	ALO20IV	2.3	0.80	0	0	1	1	17
	Oxy20IV	29.7	5.11	0	2	25	52.5	96
	PIV	1.2	0.70	0	0	0	1	20
Feel Sick VAS	ALO20IV	2.2	0.83	0	0	1	2	19
	Oxy20IV	17.8	4.78	0	1	5	28.5	93
	PIV	2.2	1.30	0	0	0	1	31
Nausea VAS	ALO20IV	1.8	0.66	0	0	1	1	17
	Oxy20IV	22.7	5.42	0	2	10	31.5	98
	PIV	2.5	1.68	-2	0	0	1	44
Sleepy VAS	ALO20IV	9.0	2.54	0	0	2	14.5	55
	Oxy20IV	44.2	6.29	-21	15.5	45	67	100
	PIV	4.0	1.80	-10	0	0	1	36

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/s/

LING CHEN
09/22/2015

QIANYU DANG
09/22/2015

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 207-621
Drug Name:	ALO-02 (oxycodone hydrochloride and naltrexone hydrochloride)
Indication(s):	Management of pain severe enough to require daily, around-the-clock, long term opioid treatment and for which alternative treatment options are inadequate
Applicant:	Pfizer Inc.
Date(s):	Letter date: December 19, 2014; PDUFA date: October 19, 2015
Review Priority:	Standard
Biometrics Division:	II
Statistical Reviewer:	Feng Li, Ph.D.
Concurring Reviewers:	Freda Cooner, Ph.D.
Medical Division:	Division of Anesthesia, Analgesia, and Addiction Products
Clinical Team:	Elizabeth Kilgore, M.D.
Project Manager:	Diana Walker
Keywords:	NDA review, Clinical Studies

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. EXECUTIVE SUMMARY

Pfizer, Inc. submitted a New Drug Application (NDA) for a fixed-dose combination product of oxycodone hydrochloride and naloxone hydrochloride (ALO-02) with potential abuse deterrent features, seeking an indication for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. A confirmatory phase 3 efficacy study (Study B4531002) in subjects with chronic low back pain (CLBP) was conducted to support the efficacy of ALO-02 administered twice daily in comparison to placebo. Based on this review, the study provided evidence that ALO-02 has an analgesic effect in comparison to placebo.

Study B4531002 was a multicenter, double-blind, placebo-controlled, randomized withdrawal study to demonstrate the efficacy and safety of ALO-02 in subjects with moderate to severe CLBP. The study consisted of four study periods: screening period (up to 2 weeks), open-label conversion and titration period (4 to 6 weeks), double-blind treatment period (12 weeks), and post-treatment period (2 weeks). Subjects who demonstrated analgesic benefit and acceptable tolerability with ALO-02 treatment during the open-label titration period were eligible for entering the double-blind period.

A total of 281 eligible subjects were randomized equally to receive either ALO-02 or the matching placebo based on their ALO-02 dose strength at the end of the titration period. Subjects were permitted to administer acetaminophen up to 3000 mg per day throughout the study as the rescue medication.

The primary analgesic efficacy variable was the difference between ALO-02 and placebo in the mean changes from randomization baseline to the average of the scores from the final two weeks (Weeks 11 and 12) of the double-blind treatment period in the daily pain scores for low back pain. The primary efficacy population included all subjects who were randomized and received at least one dose of the double-blind study drug. The primary analysis was based on an analysis of covariance (ANCOVA) model with terms of treatment, prior pain analgesic (opioid or non-opioid), randomization baseline score and final total daily dose of the titration period. The primary analysis employed a hybrid multiple and single imputation strategy to impute missing data for the calculation of the primary endpoint.

Based on this review, the study demonstrated the superiority of ALO-02 over placebo in pain reduction over 12 weeks. There was a statistically significant difference in the final two-week pain between the two treatment groups based on the pre-specified analysis. Sensitivity analyses employing several different methods for handling subjects who discontinued the study drug produced generally consistent results. About 40% of the subjects randomized to placebo and 27% of the subjects randomized to ALO-02 discontinued the double-blinded treatment early.

Study B4531002 has provided evidence of analgesic efficacy for ALO-02. The review team will need to consider the totality of evidence including safety analyses and findings from abuse

deterrent studies to decide whether the benefit-risk profile justifies the approval of this combination product.

2. INTRODUCTION

2.1 Overview

Pfizer Inc. is developing ALO-02 as a combination product of oxycodone and naltrexone with potential abuse deterrent features for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The applicant claims that ALO-02 provides abuse deterrent features by introducing a combination of oxycodone with a sequestered opioid antagonist, naltrexone. When taken as directed by patients, the oxycodone is released in an extended manner to provide sustained pain relief, whereas the naltrexone remains sequestered and is excreted. When the ALO-02 capsules are manipulated by crushing for the purposes of abuse by the oral, intranasal or intravenous routes, naltrexone is released and antagonizes the positive subjective effects of oxycodone such as drug-liking and high.

The development program of ALO-02 has been discussed with the agency under IND 107,037. Issues relevant to this statistical review are summarized as below:

- At the End-of-Phase 2 meeting held on November 8, 2010, the division stated that the proposed single efficacy study and the long-term safety study may be adequate to support the efficacy and safety of ALO-02. In addition, the division recommended that the proposed efficacy study should take into account recommendations from the National Academy of Science report on missing data.

- On July 21, 2010, the division issued a No-Agreement letter for a Special Protocol Assessment (SPA) on the phase 3 efficacy Study ALO-02-10-3002 (thereafter referred to as Study B4531002). The division informed the applicant that the use of an enriched enrollment randomized withdrawal trial to demonstrate efficacy is acceptable. However, the design and planned analysis of the study did not adequately address the objectives necessary to support a regulatory submission.

- On December 2, 2011, the division issued a No-Agreement letter on the re-submission of the SPA for Study B4531002. The division stated that an agreement could not be granted for analgesic trials at that time due to lack of experience with many of the statistical methods proposed to address concerns with missing data outlined in the National Academy of Science report. The division encouraged the applicant to proceed with the proposed statistical approach without a SPA agreement.

- At the pre-NDA meeting held on March 18, 2014, the division advised the sponsor include an Integrated Summary of Efficacy in the NDA that describes the results of the

single efficacy study along with the agency's findings for the reference listed drugs and cited literature references to support the efficacy of ALO-02.

This statistical review focuses on the efficacy results from Study B4531002.

2.2 Data Sources

The efficacy data for Study B4531002 are submitted to \\Cdsesub1\evsprod\NDA207621\0000\m5\datasets\b4531002.

3.1 Data and Analysis Quality

The applicant submitted study SDTM tabulation datasets and AdaM analysis datasets in CDISC format. The submitted datasets and define documents are of acceptable quality.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study B4531002 was a multicenter, double-blind, placebo-controlled, randomized withdrawal study to demonstrate the efficacy and safety of ALO-02 in subjects with moderate to severe chronic low back pain (CLBP). The study consisted of four study periods: screening period (up to 2 weeks), open-label conversion and titration period (4 to 6 weeks), double-blind treatment period (12 weeks), and post-treatment period (2 weeks).

During the open-label conversion and titration period, all subjects were initiated on, or converted to ALO-02 and titrated to response. Only subjects who tolerated and achieved satisfactory efficacy with ALO-02 according to the protocol-defined treatment response criteria were randomized to continue ALO-02 or to switch to placebo for a comparison of the efficacy and adverse events (AEs) during the 12-week double-blind treatment period. In order to avoid opioid withdrawal signs and symptoms during the first two weeks of this period, a subject randomized to receive placebo underwent a two-week double-blind gradual tapering from the ALO-02 dose identified from the open-label conversion and titration period to placebo treatment. A subject demonstrating all of the following criteria was considered a treatment responder:

- the subject had a reduction score (to ≤ 4) in the daily average pain scores based on Numeric Rating Scale (NRS) for low back pain for at least four of the last seven days of open-label treatment prior to randomization;
- the treatment with ALO-02 was considered tolerated by the subject and corroborated as such by the investigator;
- the subject had remained on the same fixed dose of ALO-02 without a change in the dose for at least seven consecutive days prior to randomization.

Eligible subjects were randomized in a 1:1 ratio to receive either ALO-02 or the matching placebo based on their ALO-02 dose strength at the end of the open-label titration period.

Subjects were permitted to administer acetaminophen up to 3000 mg per day throughout the study as the rescue medication.

The primary efficacy assessment was the daily average low back pain. Daily average low back pain was assessed with an 11-point Numerical Rating Scale (NRS). Subjects rated their average low back pain intensity during the past 24 hours by choosing the appropriate number from 0 (no pain) to 10 (worst pain). The secondary efficacy assessments included Patient's Global Assessment (PGA), Brief Pain Inventory-Short Form (BPI-SF) and rescue medication use. The applicant did not propose any multiplicity adjustment to control overall Type I error rate.

3.2.2 Statistical Methodologies

The primary efficacy variable was the difference between ALO-02 and placebo in the mean changes from randomization baseline to the average of the scores from the final two weeks (Weeks 11 and 12) of the double-blind treatment period in the daily average NRS-pain scores for low back pain. The primary efficacy population included all subjects who were randomized and received at least one dose of double-blind study drug. The primary analysis was based on an analysis of covariance (ANCOVA) model with terms of treatment, prior pain analgesic (opioid or non-opioid), randomization baseline pain score and final total daily dose of the titration period. The primary analysis employed a hybrid multiple and single imputation strategy to impute missing data for the calculation of the primary endpoint. According to the applicant, the hybrid imputation method assumed that missing data from subjects who discontinued due to AEs or lack of efficacy, or with opioid withdrawal symptoms, were most likely to be missing not at random. Missing data from subjects who discontinued due to other reasons were assumed to be missing at random.

The imputation procedure was performed as follows. At first, multiple imputation linear regression procedures (using SAS PROC MI) were performed by treatment group 100 times to impute 100 datasets. Variables in the regression model were: prior pain analgesic (opioid or non-opioid), randomization baseline pain score, final total daily dose of the titration period, age, sex, screening period value, and weekly pain scores measured prior to the subject discontinuation. The screening period value was defined as the average of the scores from the last seven days of the screening period. If less than seven days had scores recorded, the average of available scores during the seven-day period was used. The randomization baseline pain intensity score was the average of scores from the last seven days of the open-label conversion and titration period, prior to receiving randomized study drug. If less than seven days had scores recorded, the average of the available scores during the seven-day period was used.

After the multiple imputation steps were performed, subjects who had missing endpoint data and discontinued for certain reasons had endpoint re-defined. In particular, for subjects who discontinued due to AEs or lack of efficacy, the screening period pain intensity score was used as the average of values of Weeks 11 and 12. For subjects who were randomized to placebo but discontinued with opioid withdrawal symptoms, the randomization baseline pain intensity score

was used as the average of the values of Weeks 11 and 12. Finally, the treatment comparison on the primary endpoint was performed within each of the 100 datasets using the ANCOVA methodology discussed above. The overall assessment of treatment effect on the primary endpoint was then carried out by combining results across the 100 datasets using SAS PROC MIANALYZE.

The proposed approach for handling missing data was intended to ensure that a high pain score (the screening period value) was assigned to subjects who clearly had a poor clinical outcome (adverse event or lack of efficacy) when they discontinued. The assignment of randomization baseline score to placebo subjects who experienced opioid withdrawal symptoms ensured the placebo group was not penalized for randomized withdrawal of the opioid. For subjects who did not necessarily discontinue for poor clinical outcomes (other reasons for discontinuation), multiple imputation was employed under the assumption that data from these subjects were missing at random.

The applicant performed the following sensitivity analyses to investigate the robustness of the conclusion from the primary analysis:

1. Complete-case analysis: the completer population was analyzed with the same ANCOVA model as the one used in the primary analysis.
2. Modified hybrid multiple and single imputation (pattern mixture model): the primary analysis method was repeated with changes to create a type of pattern mixture model. For subjects who discontinued due to AEs, the screening period value was used as the average value of the final two weeks (Weeks 11 and 12). For placebo subjects who discontinued with opioid withdrawal symptoms, the randomization baseline value was used as the average value of the final two weeks. For subjects who discontinued for any other reasons, including lack of efficacy, multiple imputation procedure was used to impute the missing values based on the distribution of responses of placebo subjects at each of the visits in the study. The Markov Chain Monte Carlo (MCMC) method was used for the imputation in this analysis.
3. Single imputation: for subjects who discontinued due to AEs, the screening period value was used as the average value of the final two weeks. For placebo subjects who discontinued with opioid withdrawal symptoms, the randomization baseline value was used. For subjects who discontinued due to lack of efficacy or any other reason, the average of the weekly average pain scores from the last two weeks of treatment was used.
4. Mixed model repeated measures (MMRM): a mixed model repeated measures analysis was performed utilizing all observed data up to and including Week 12. The model used for this analysis had treatment, prior pain analgesic (opioid or non-opioid), randomization baseline score, final total daily dose of the titration period, time (study week), and time-by-treatment interaction as fixed effects.
5. (Screening Observation Carried-Forward) SOCF only: the screening period value was used as the average value of the final two weeks for all subjects, regardless of treatment group and reason for discontinuation, who prematurely discontinue the study. This

allowed an assessment assigning all discontinuations as if there were no treatment benefit.

Except for sensitivity analyses 1 and 4, the other sensitivity analyses were conceptually similar: assigning high pain scores to bad outcomes.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 281 subjects were randomized to the double-blind phase of the study, 134 to placebo and 147 to ALO-02. One subject randomized to ALO-02 did not receive the double-blind study drug because the subject decided to withdraw from the study with no reason provided. Overall, approximately 33% of the subjects discontinued the double-blind period early (Table 1). The dropout rates of the placebo and ALO-02 groups were 40% and 27%, respectively. About 12% of the subjects in the placebo group and 3% of the subjects in the ALO-02 group discontinued prematurely because of insufficient clinical response. Among subjects who discontinued due to AEs, two subjects randomized to placebo and one subject randomized to ALO-02 had opioid withdrawal symptoms.

The demographic and baseline characteristics were similar between the two treatment groups (Table 2). Overall, during the double-blind treatment period, 73% and 25% of the subjects were white and black, respectively. The mean age was 50 years and 44% of the subjects were male. Overall, the average pain scores before randomization were 3 for both groups.

Table 1: Subject Disposition − Number (%) of Patients

	Placebo	ALO-02	Total
Randomized	134	147	281
Randomized and treated (full analysis population)	134	146	280
Completed double-blind period	81 (60%)	107 (73%)	188 (67%)
Discontinued study drug during double-blind period	53 (40%)	40 (27%)	93 (33%)
Insufficient clinical response	16 (12%)	4 (3%)	20 (7%)
Adverse events	9 (7%)	14 (10%)	23 (8%)
Subject died	0	0	0
Protocol violation	8 (6%)	9 (6%)	17 (6%)
Lost to follow-up	3 (2%)	6 (4%)	9 (3%)
No longer willing to participate in study	11 (8%)	6 (4%)	17 (6%)
Other	6 (4%)	1 (1%)	7 (2%)

Source: Clinical Study Report, Table 14.1.1.1.2

Table 2: Summary of Demographics and Baseline Characteristics

	Placebo (N=134)	ALO-02 (N=146)	All Subjects (N=280)
Mean age (SD)	49 (12)	51 (13)	50 (13)
Gender, n (%)			
Male	59 (44%)	65 (45%)	124 (44%)
Female	75 (56%)	81 (55%)	156 (56%)
Race, n(%)			
White	103 (77%)	102 (70%)	205 (73%)
Black	29 (22%)	41 (28%)	70 (25%)
Asia	1 (1%)	1 (1%)	2 (1%)
Other	1 (1%)	2 (1%)	3 (1%)
Body Mass Index (kg/m^2)			
Mean (SD)	31 (6)	30 (6)	31 (6)
Prior pain analgesic			
Opioid	58 (43%)	61 (42%)	119 (42%)
Non-opioid	76 (57%)	85 (58%)	161 (58%)
Screening pain intensity			
Mean (SD)	7 (1)	7 (1)	7(1)
(Min, Max)	(3, 10)	(4, 9)	(3, 10)
Pre-randomization pain intensity			
Mean (SD)	3 (1)	3 (1)	3 (1)
(Min, Max)	(0, 5)	(0, 8)	(0, 6)

Source: Clinical Study Report, Table 14.1.2.1 and Table 14.1.3.1; SD: standard deviation

3.2.4 Results and Conclusions

I replicated the applicant's results from the primary efficacy analysis (Table 3). The difference between ALO-02 and placebo for the primary efficacy endpoint was statistically significant. Except for the pattern mixture model and the completer-case analyses, the results from different sensitivities analyses (Table 4) also achieved nominal statistical significance.

Table 3: Primary Efficacy Analysis Results

Visit	Statistics	Placebo (N=134)	ALO-02 (N=146)	95% CI	P-value
Screening baseline	Mean (SD)	7.1 (1.2)	7.0 (1.1)		
Randomization baseline	Mean (SD)	3.1 (1.0)	3.0 (1.3)		
Final two weeks (Weeks 11 and 12)	Mean (SD)	4.3 (2.2)	3.6 (2.0)		
Change from randomization baseline to final two weeks	Mean (SD)	1.2 (1.9)	0.60 (1.8)		
Model-adjusted change from baseline (SE)	Difference	-0.62 (0.25)		(-1.1, -0.1)	0.01

Source: Clinical Study Report, Table 14.2.1.1; SD: stand deviation; SE: standard error; CI: confidence interval

Table 4: Sensitivity Analysis Results

Type of Analysis	Difference from Placebo (SE)	95% CI	P-value
Analyses reported by the applicant			
1. Completer-case	-0.30 (0.24)	(-0.78, 0.17)	0.2
2. Pattern mixture model	-0.45 (0.25)	(-0.94, 0.03)	0.07
3. Single imputation	-0.48 (0.22)	(-0.90, -0.05)	0.03
4. MMRM	-0.80 (0.23)	(-1.3, -0.35)	0.0005
5. SOCF only	-0.61 (0.27)	(-1.2, -0.08)	0.02
Reviewer's analysis for Week 12			
6. Primary analysis model for Week 12 only	-0.59 (0.25)	(-1.1, -0.1)	0.02

Source: Clinical Study Report and reviewer's analysis, Table 14.2.1.5; SE: standard error; CI: confidence interval

Overall, results from these sensitivity analyses supported the conclusion that there was a statistically significant difference between groups due to treatments. The SOCF method produced very similar results to those from the primary analysis, which is expected as both methods assigned the screening period value to subjects discontinued due to AEs or lack of efficacy, which accounted for the majority of the dropouts. The MMRM method yielded the most optimistic estimate of the treatment effect, which is likely due to subjects randomized to ALO-02 experienced pain relief before discontinuation due to AEs and subjects randomized to placebo experienced worse pain than randomization baseline before discontinuation.
Results from an additional analysis comparing the change from randomization baseline in pain to Week 12 value instead of the average value of Week 11 and Week 12 were similar to those from the primary analysis (Table 4, sensitivity analysis 6).

To compare the pain reduction effect over time, the average observed pain intensity score of each treatment group was depicted through Week 12 (Figure 1). On average, subjects randomized to placebo experienced an increase in pain after randomization. In contrast, the average pain of subjects randomized to ALO-02 remained roughly unchanged. It appears that the treatment effect was maintained from Week 2 to Week 12.

There is an apparent separation between the continuous responder curves of the two treatments (Figure 2). For example, about 58% of the subjects in the ALO-02 group had at least 30% improvement from screening. In contrast, approximately 44% of the placebo group had at least 30% improvement from screening. Subjects who discontinued study drug were considered as non-responders in the calculations.

Results from the secondary endpoints such as change from baseline in BPI-SF and PGA, and the percentage of subjects who used rescue medication supported the primary efficacy analysis. About 43% of the subjects randomized to placebo and 35% of the subjects used acetaminophen as rescue medication during the double-blind period. The average daily use of rescue acetaminophen in the ALO-02 group was very similar to that of the placebo group after adjusting for average daily rescue use during the titration period and final total daily dose of study medication of the titration period (Appendix, Table 1).

Figure 1: **Average Pain Intensity Score Over Time**

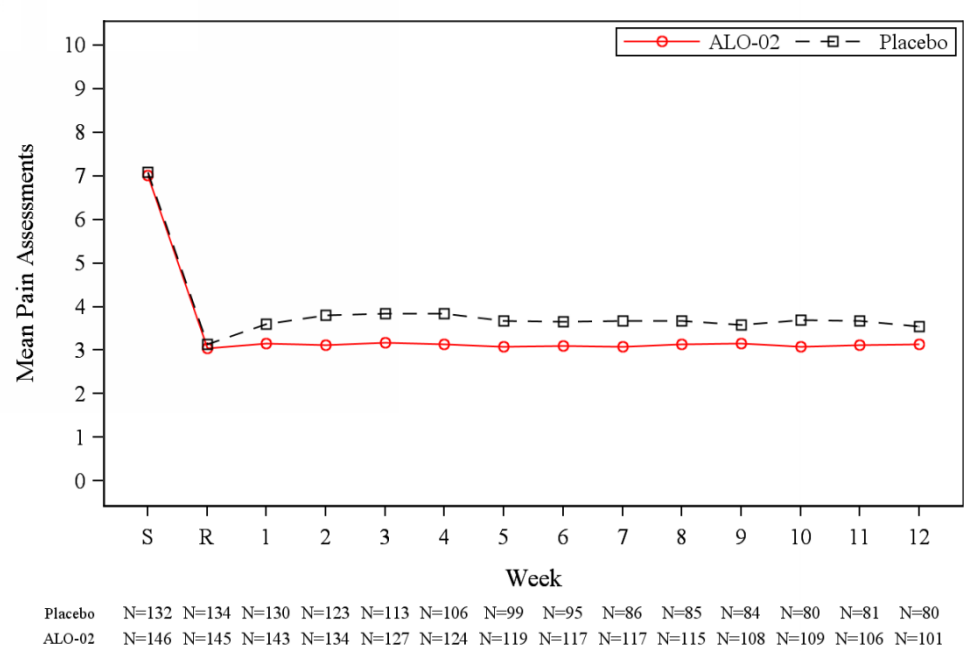
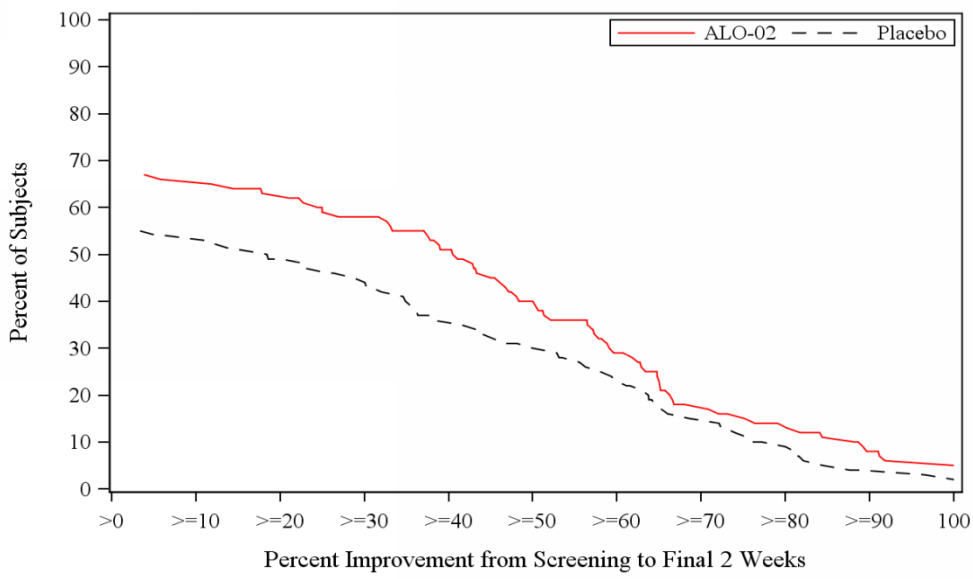


Figure 2: **Continuous Responder Curve**



3.3 Evaluation of Safety

The evaluation of the safety data was conducted by Dr. Elizabeth Kilgore. The reader is referred to Dr. Kilgore's review for detailed information regarding the adverse event profile.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The applicant presented subgroup summaries for the primary efficacy endpoint of Study B4531002 by age, gender, race, and prior opioid use in the Integrated Summery of Efficacy. The applicant's subgroup summaries were based on imputed datasets using the multiple imputation method employed in the primary analysis. Findings from the subgroup summaries of the primary efficacy endpoints were generally consistent with those observed in the overall population. Subgroup summaries based on the SOCF imputation method are presented in this section.

4.1 Gender, Age and Race

For age, subjects were categorized as < 65 or ≥65 years old. For race, subjects were categorized as White or non-White. The findings from the subgroup summaries of the pain scores at the final two weeks are consistent with those observed in the overall population. Generally, subjects treated with ALO-02 reported numerically less pain than subjects treated with placebo in all the subpopulations.

Table 5: Reviewer's Subgroup Summaries I

Subgroups	Statistics	Placebo (N=134)	ALO-02 (N=146)
Sex			
Female	n (%)	75 (56%)	81 (55%)
	Mean (SD)	4.6 (2.6)	3.8 (2.2)
Male	n (%)	59 (44%)	65 (45%)
	Mean (SD)	5.5 (2.3)	4.6 (2.6)
Age			
<65	n (%)	119 (89%)	130 (89%)
	Mean (SD)	5 (2.6)	4.3 (2.5)
≥65	n (%)	15 (11%)	16 (11%)
	Mean (SD)	4.8 (2.2)	3.1 (1.6)
Race			
White	n (%)	103 (77%)	102 (70%)
	Mean (SD)	5.3 (2.4)	4.3 (2.3)
Non-white	n (%)	31 (23%)	44 (30%)
	Mean (SD)	3.8 (2.5)	3.8 (2.6)

SD: Standard deviation

4.2 Other Special/Subgroup Populations

Subgroup summaries by prior opioid use are presented below. Regardless of prior opioid experience, subjects treated by ALO-02 reported less pain at the final two weeks.

Table 6: Reviewer's Subgroup Summaries II

Subgroups	Statistics	Placebo (N=134)	ALO-02 (N=146)
Opioid experienced subjects	n (%)	58 (43%)	61 (42%)
	Mean (SD)	5.3 (2.3)	4.3 (2.5)
Opioid naïve subjects	n (%)	76 (57%)	85 (58%)
	Mean (SD)	4.7 (2.7)	4.0 (2.4)

SD: Standard deviation

5. SUMMARY AND CONCLUSIONS

Statistical Issues

No major statistical issues were identified for this study. The applicant's primary efficacy analysis was based on a hybrid single and multiple imputations procedure for handling dropouts and missing values. The proposed imputation method is rather ad-hoc in its nature. On one hand, it penalized dropouts due to AEs or lack of efficacy by assigning high pain scores to these subjects. On the other hand, for subjects who discontinued due to other reasons, the method estimated what would have been observed should these subjects continue the study drug by using a multiple imputation procedure. So it seems to estimate one kind of estimand for some subjects and another kind of estimand for the other subjects, which appears not desirable. In addition, it also relies on accurate adjudication of the dropout reason. Nevertheless, the imputation approach was not overly concerning as it assigns high pain scores to apparent bad clinical outcomes and the conclusion from the primary analysis was supported by various sensitivity analyses in general.

5.2 Collective Evidence

The collective evidence from Study B4531002 was in support of the efficacy of ALO-02 in comparison to placebo. There was a statistically significant difference in pain response between the treatment groups. This conclusion was supported by the results from various sensitivity analyses. The secondary efficacy endpoints were also numerically in favor of ALO-02 in general.

5.3 Conclusions and Recommendations

Study B4531002 demonstrated that ALO-02 was better than placebo in management of chronic pain. The review team will need to consider the totality of evidence including findings from safety analyses and abuse deterrent studies to decide whether the benefit-risk profile justifies the approval of this combination product.

5.4 Labeling Recommendations

The clinical study section of the labeling submitted by the applicant is attached below. The applicant should round the percentages to integer. Furthermore, the p-values should be removed. In addition, the applicant should include a figure for the continuous responder curves of the two treatments.

14 CLINICAL STUDIES

The analgesic efficacy of TROXYCA ER has been evaluated in one randomized, double-blind, placebo-controlled clinical trial in patients with moderate to severe chronic low back pain. (b) (4)

(b) (4)

APPENDIX

Table 1: Amount of Rescue Acetaminophen Administered During the Double-Blind Period

	Statistics	Placebo (N=134)	ALO-02 (N=146)
Subjects used rescue	Non-rescued, n (%)	76 (57%)	95 (65%)
	Rescued, n (%)	58 (43%)	51 (35%)
Model adjusted daily use [a]	LS Mean (mg/day)	208	204
	SE	36	35
	Difference in LS Means	-4	
	SE	51	
	95% CI	(-103, 96)	
	p-value	0.9	

Source: Clinical Study Report, Table 14.2.3.4; SE: standard error; CI: confidence interval
[a] Analysis of covariance with treatment and prior pain analgesic as factors and the average daily rescue use during the titration period and final total daily dose of study medication of the titration period as covariates.

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/s/

FENG LI
09/11/2015

FREDA COONER
09/11/2015
I concur.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 207-621 **Applicant: Pfizer Inc.** **Stamp Date: December 19, 2014**

Drug Name: ALO-02 (oxycodone hydrochloride and naltrexone hydrochloride) **NDA/BLA Type: NDA**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.	X			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			X	See clinical review.
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

Comment to sponsor: Submit the SAS programs for generating the analysis datasets, efficacy Tables and Figures for Study B4531002.

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

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/s/

FENG LI
02/18/2015

FREDA COONER
02/19/2015