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 Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 208090
Supplement #:	000
Drug Name:	Xtampza ER (oxycodone extended-release capsules)
Indication(s):	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment
Applicant:	Collegium Pharmaceutical, Inc.
Date(s):	Submitted: December 12, 2014 PDUFA date: October 12, 2014
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewers:	Katherine B. Meaker, MS
Concurring Reviewers:	Freda Cooner, Ph.D.
Medical Division:	Division of Anesthesia, Analgesia, and Addiction Products
Clinical Team:	Steven Galati, M.D. Ellen Fields, M.D.
Project Manager:	Ayanna Augustus

Keywords: Clinical Studies

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1 EXECUTIVE SUMMARY

Xtampza ER contains oxycodone in an extended release formulation and in a capsule form, and is intended to have abuse-deterrent properties. This is the initial New Drug Application submission for this product. The application includes a single Phase 3, randomized, double-blind, parallel arm placebo-controlled study (CP-OXYDET-08), referred to as Study 08 hereafter.

Study 08 used an enriched enrollment, randomized withdrawal design, with 12 weeks of double-blind treatment, in patients with chronic low back pain. The study enrolled both opioid-naïve and opioid-experienced patients.

The single primary efficacy endpoint was the change in average pain score from baseline to Week 12. The baseline pain score is calculated using the daily pain scores for the last week of the titration phase, prior to randomization. Change from baseline to Week 12 represents the return of pain during the double-blind treatment period. The protocol did not pre-specify any additional endpoints to be tested for statistical significance.

The results of Study 08 indicate that Xtampza ER is significantly better than placebo for the mean change from baseline in average pain score. In the Xtampza ER treatment arm the average pain score increased by an average of 0.3 units on the 11-point pain scale, while in the placebo arm the average pain score increased by an average of 1.9 units. Supportive evidence was provided by secondary endpoints (use of rescue medication; proportion of patients who reported various levels of reduction in pain from screening to Week 12) which were consistently in the direction favoring Xtampza ER.

My conclusion is that the results of Study 08 provide sufficient evidence of efficacy for pain management in patients with chronic low back pain in need of around-the-clock long-term opioid treatment as measured by the change in average pain score from baseline to Week 12.

2 INTRODUCTION

2.1 Overview

Xtampza ER is a new formulation containing oxycodone extended release in a capsule dosing form. It is designed to have abuse-deterrent properties. The applicant is pursuing approval for dose strengths of 10, 20, and 40 mgs, on a twice a day (every 12 hours) dosing interval.

The clinical development plan was discussed at the End of Phase 2 meeting on March 30, 2010. The applicant subsequently conducted a single Phase 3 study (Study 08) in patients with chronic low back pain persisting at least 6 months, who were qualified for around-the-clock opioid therapy. Both opioid-naive and opioid-experienced patients were eligible to enroll. Prior pain management treatment was discontinued during the screening phase to assess screening baseline pain for eligibility. Study 08 is a multicenter, enriched enrollment, randomized withdrawal, double-blind, parallel arm, placebo-controlled study.

2.2 Data Sources

The clinical study report and all efficacy datasets were submitted to the electronic document room: \\CDSESUB1\EVSPROD\NDA208090\0000. All the documentation needed to complete my review was provided.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data for the efficacy study was submitted in CDISC format with sufficient documentation for my review. The derived endpoints provided by the applicant were pre-specified in the protocol. The analyses provided in the clinical study reports followed the statistical analysis plans. The applicant conducted a variety of sensitivity analyses to investigate the impact of drop-outs and missing data on the results.

3.2 Evaluation of Efficacy: Study 08

3.2.1 Study Design and Endpoints

Objective: The objective of Study 08 was to evaluate the analgesic efficacy of Xtampza ER formulation of oxycodone compared with placebo for treatment of moderate-to-severe chronic pain.

Design: Study 08 is a multicenter, enriched enrollment, randomized withdrawal, double-blind, parallel arm, placebo-controlled study. The patient population is adults with chronic low back pain, lasting at least 6 months, who were qualified for around-the-clock opioid therapy. Both opioid-naïve and opioid-experienced patients could be enrolled.

This is an enriched enrollment randomized withdrawal (EERW) design, commonly used for chronic pain clinical studies. There are three phases: Screening (up to 4 weeks) during which eligibility is assessed; Titration (up to 6 weeks) when patients receive open-label study drug and are titrated up to a tolerable dose with adequate pain relief; and Double-blind Treatment Phase which begins with randomization and lasts for 12 weeks.

During the screening phase, patients discontinued prior analgesia therapy and recorded daily pain intensity. Daily pain was assessed using a 0-10 (11-point) pain intensity numeric rating scale (PI-NRS) where a score of 0 indicated no pain and a score 10 indicated the worst possible pain. This was collected using an electronic diary, at approximately the same time every day, preferably at bedtime. An average screening pain score of ≥ 5 but ≤ 9 was required, along with other criteria, to continue in the study. During the open-label titration phase, patients were titrated to a stable, tolerated dose of Xtampza ER, determined by an average pain score of ≤ 4 and a reduction of at least 2 points from screening pain score during the last week of the titration phase. Eligible patients were then randomized to double-blind treatment for 12 weeks. Patients assigned to placebo received a blinded down-taper lasting up to 20 days for potential opioid withdrawal symptoms. Patients assigned to Xtampza receive the same stable dose from the end of titration, but in a blinded form. There are two treatment arms (placebo; Xtampza ER) with a planned enrollment of 390 patients to be randomized at a 1:1 ratio (195 per treatment arm). It was conducted at 49 sites in the United States.

Endpoints: The primary efficacy endpoint was defined as the change from baseline to Week 12 in average daily pain. The baseline pain score was the average of the last 7 days of the titration phase prior to randomization.

Acetaminophen (APAP) 500 mg tablets were provided for rescue if needed for pain. Patients were instructed to take 1 or 2 tablets every 4 to 6 hours for pain, not to exceed 4 tablets in 24 hours. If APAP was taken for pain, the daily pain score was recorded immediately prior, and was used for that pain assessment for the daily average calculation that day. If more than one dose of rescue medication was taken on the same day, pain was recorded before each dose of rescue, and the worst of the pain scores recorded prior to rescue on that day was used for the daily pain score.

The efficacy analysis dataset included all randomized patients (ITT).

The applicant used the following plan for assessing sensitivity of the treatment effect to the statistical approach for missing pain scores:

> Sensitivity of the results of the primary endpoint analysis to both the method for handling missing data and the statistical assumptions of the analysis were assessed through the following additional analysis. As an alternate method for handling missing data, an

imputation based method (ANCOVA with LOCF/baseline observation carried forward [BOCF]) was used. For the imputation based sensitivity analysis, the following algorithm was used:

- For subjects who discontinued after randomization, after receiving at least one dose of study drug, and prior to the first post-randomization efficacy data point, the Screening Phase Baseline PI-NRS score was carried forward (ie, SOCF).
- For subjects who discontinued due to an AE, the Screening Phase Baseline PI-NRS score was carried forward (SOCF).
- For placebo subjects who discontinued due to opioid withdrawal symptoms, the Randomization Baseline PI-NRS score was carried forward (BOCF).
- For all other subjects, the last available PI-NRS score was carried forward (ie, LOCF).

The resulting imputed final score was analyzed using ANCOVA with Randomization Baseline as the covariate and treatment and opioid subtype as the factors in the model.

Sample size: The sample size estimate was based on an anticipated effect size of 0.45 (between group treatment difference divided by pooled standard deviation). A sample size of 100 per treatment arm would achieve at least 88% power for a two-sided test (α=0.05). The planned sample size was adjusted to 195 per treatment group to account for dropouts and non-compliance.

Eligible subjects were randomized within strata: Opioid-naïve or opioid-experienced.

Statistical Methodologies

Analysis of the primary efficacy endpoint - Change from Baseline to Week 12 in Average Daily Pain

The average daily pain score was calculated for the 7 days prior to randomization and for each week during the 12 week double-blind treatment phase. The change from baseline to Week 12 was calculated for each subject. The applicant's primary analysis used a two-piece linear mixed model which includes the reason for discontinuation as a factor in the model. This was discussed and agreed upon (Information Request letter dated August 30, 2012) by the statistical reviewer, Jonathan Norton. Below is the full description from Statistical Analysis Plan (SAP):

Primary Analysis of the Primary Endpoint

Based on previous chronic pain studies, a 2-piece linear mixed model for the responses from Randomization Baseline through Week 12 was used to model the mean trajectory over time. In this 2-piece linear mixed model, the response is linear from Randomization Baseline to some post-baseline time and plateaus thereafter. The change point of the 2-piece linear mixed model is a fixed effect that may vary across subgroups. The intercepts and slopes are random effects with means that vary across mixture components.

> The introduction of a change point as a parameter in the growth curve model changes the estimation problem from a linear model to a non-linear model. Estimation of the parameters in this model was to be done by any Mixed Model Repeated Measure (MMRM) software that accommodates non-linear models (eg, SAS PROC NLMIXED). Under the assumption of missing at random (MAR), these parameter estimates were to be maximum likelihood estimates. Standard errors (SE) for the marginal means (marginal mean is the weighted average across mixture components [components are defined by the reason for study discontinuation per SAP {Section 8.1.1}: completers, lack of efficacy, adverse event, and other] where the weights are probabilities of component membership) and changes from baseline were to be estimated using the delta method, which incorporates variability from the estimation of both the probabilities of subgroup membership for each treatment and the growth curve model parameters. Thus, the p-value was to be derived based on the estimate and SE for marginal mean differences between treatments.

Typically this chronic pain outcome is analyzed using an ANCOVA model with terms for treatment, randomization stratification factor (prior opioid use: Y/N), and baseline pain score as the covariate. Missing data is imputed prior to the ANCOVA model analysis, rather than being included in the model as a factor. I applied this ANCOVA approach to the data from each of the imputation methods the applicant had used in the sensitivity analyses.

In the protocol the applicant defined secondary endpoints and pre-specified associated analyses. There was no adjustment for multiplicity to control the overall Type I error rate for the study. The results of the secondary endpoints will not be appropriate for inclusion in the labeling.

Analysis of secondary efficacy endpoints - Total Amount of Rescue Medication:
Acetaminophen (APAP) was allowed as rescue medication for break through pain (BTP). The average number of doses per day, the average amount (mg) per day, the total number of doses, and the total amount used in the double-blind treatment phase were calculated based on rescue medication data collected in the e-diary. Only descriptive statistics, summarized by treatment group, were planned. There were no between-group comparisons conducted.

Analysis of secondary efficacy endpoint - Cumulative Responder Analysis:
During the screening phase, patients discontinued prior analgesic therapy for at least a week. The daily pain scores during last 7 days of the screening phase are used to calculate the Screening Baseline value for eligibility assessment. A subject's response to treatment was defined as the percentage reduction in average pain score from the Screening Baseline to Week 12 of the double-blind treatment phase. If the average pain at Week 12 was worse (greater) than pain at Screening, the patient was classified as a non-responder. All subjects who discontinued the study prior to Week 12 of the double-blind treatment phase were considered non-responders and were assigned a 0% reduction pain score. Results are presented on a cumulative distribution graph by treatment group. The proportions of subjects demonstrating at least a 30% improvement and at least a 50% improvement from Screening Baseline to Week 12 of the Double-blind Maintenance Phase were calculated for each treatment group. Differences in the proportions between treatment groups were tested using the chi-square test, but there were no adjustments for multiplicity pre-specified. The results of the between-group comparisons are not appropriate for inclusion in the labeling.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

Patients were randomized on a 1:1 basis to the two treatment arms. The disposition of patients is shown in Table 1. During the 12 week Double-blind treatment phase, 37% of Xtampza patients and 49% of placebo patients discontinued from the study. The only notable imbalance in the reasons for discontinuation across the groups was that a higher percentage of subjects discontinued due to Lack of Efficacy in the Placebo group. In an enriched enrollment randomized withdrawal design study, both these patterns are not unusual.

Table 1: Patient Disposition: Study 08

	Xtampza ER	**Placebo**
Randomized	193	196
Received Study Treatment (AS)	193 (100%)	196 (100%)
Discontinued During Double-blind Phase	71 (37%)	96 (49%)
Reason for Discontinuation:		
Adverse Event	14 (7%)	13 (7%)
Opioid Withdrawal Symptoms	3 (2%)	1 (1%)
Lack of Efficacy	8 (4%)	34 (17%)
Lost to Follow-up	3 (2%)	7 (4%)
Protocol Violations	33 (17%)	25 (13%)
Withdrew Consent	6 (3%)	13 (7%)
Other	4 (2%)	3 (2%)
Completed Double-blind Treatment Phase	122 (63%)	100 (51%)

Source: Clinical Study Report Table 14.1.1.3

The demographic and baseline characteristics were fairly balanced across the two groups, as shown in Table 2. There were no notable differences between the groups. Opioid status was included as a stratification factor in randomization.

Table 2: Demographic and Baseline Characteristics: Study 08

	Xtampza ER N=193	**Placebo N=196**
Age (years)		
Mean (SD)	49 (13)	50 (13)
Median	50	52
Min, Max	18, 75	19, 75
Gender n (%)		
Male	90 (47%)	93 (47%)
Female	103 (53%)	103 (53%)
Race n (%)		
Caucasian	143 (74%)	133 (68%)
Black or African American	39 (20%)	36 (18%)
Asian	8 (4%)	23 (12%)
Other	3 (2%)	4 (2%)
BMI (kg/m^2)		
Mean (SD)	31 (7)	31 (7)
Median	31	30
Min, Max	17, 57	19, 53
Opioid Status n (%)		
Opioid-naïve	96 (50%)	96 (49%)
Opioid-experienced	97 (50%)	100 (51%)

Source: Clinical Study Report Tables 11-1 and 14.1.1.1

3.2.3 Results and Conclusions

Primary efficacy endpoint - Change from Baseline to Week 12 in Average Daily Pain:
The applicant's analyses for the primary efficacy endpoint, the change from baseline (randomization) to Week 12 in average daily pain, are presented in Table 3. This model estimates a slope and intercept separately for each subgroup according to reason for discontinuation. The overall result is a weighted average of the four subgroups, with weights determined by number of subjects in each subgroup.

In all four subgroups, the mean pain is higher in the placebo arm than the Xtampza ER treatment arm. The largest difference in estimated means is in the Lack of Efficacy (LOE) subgroup (3.4 for Xtampza; 6.3 for placebo; diff=2.9). In both treatment groups, the subgroup that discontinued due to LOE had mean pain much higher than any of the other subgroups as well.

The overall model result shows a significant difference between the two treatment arms. The results indicate Xtampza ER is superior to placebo for pain management.

Table 3: Applicant's Primary Efficacy Analysis of Study 08:
Chg from Baseline to Week 12 in Avg. Pain

Completers or Discontinuation Reason Subgroups		**Xtampza ER N=193**	**Placebo N=196**	**Difference (Xtampza ER – placebo)**
Completers	n (%) Estimated Mean [a] Std Error	122 (64) 0.2 0.15	100 (51) 0.7 0.18	
Lack of Efficacy	n (%) Estimated Mean Std Error	8 (4) 3.4 0.96	34 (17) 6.3 0.54	
Adverse Event	n (%) Estimated Mean Std Error	16 (8) 0.1 0.57	14 (7) 1.4 0.72	
Other	n (%) Estimated Mean Std Error	46 (24) 0.1 0.34	48 (25) 1.2 0.36	
Marginal Mean [b]	n (%) Estimated Mean Std Error p-value	192 0.3 0.15	196 1.9 0.22	-1.6 0.27 <0.0001

[a] Estimated change from Randomization Baseline to Week 12 in average weekly pain score based on the

2-piece linear mixed model.

[b] The marginal mean is the weighted average across mixture components where the weights are probabilities of component membership. The SE was estimated using the delta method taking into account the variability in the estimation of the probability of group membership and the variability of the within component mean. The p-value was calculated using a z-test.
Source: Clinical Study Report Table 11-2.

The applicant performed a variety of sensitivity analyses, including Mixed model repeated measures (MMRM) and single imputation approaches such as LOCF/BOCF analyzed with an ANCOVA model. In all the sensitivity analyses, Xtampza ER is statistically significantly better than placebo for pain management.

Because the applicant's 2-piece linear mixed model is not the typical analysis for the change from baseline to Week 12 in average pain, I analyzed the primary endpoint using an ANCOVA model with terms for treatment, opioid use, and baseline pain as the covariate. The results are shown in Table 4.

The treatment difference for this model (-0.8) is half the treatment difference estimated by the applicant's model (Table 3). This suggests that the applicant's model was being influenced by the higher pain scores in the Lack of Efficacy subgroup, and by the imbalance between the two treatment arms in the number of subjects who discontinued due to LOE. It appears the results in the LOE subgroup inflated the estimated mean for the placebo treatment arm in the applicant's two-piece linear mixed model.

The overall result for my analyses does show a significant difference in favor of Xtampza over placebo (p-value<0.001). This analysis provides evidence for the efficacy of Xtampza ER versus placebo.

Table 4: Statistical Reviewer's Primary Efficacy Analysis of Study 08:
Chg from Baseline to Week 12 in Avg. Pain

	Xtampza ER N=193	**Placebo N=196**	**Difference (Xtampza ER – placebo)**
LS Mean [a] Std Error p-value	0.3 0.13	1.1 0.13	-0.8 0.27 <0.001

[a] Estimated change from Randomization Baseline to Week 12 in average weekly pain score based on the ANCOVA model with treatment, opioid use, and baseline pain.
Source: SAS datasets

Opioid rescue use during Double-blind Treatment Phase endpoints:

In the protocol, the applicant did not pre-specify formal statistical testing of any endpoints except the primary efficacy endpoint. Secondary endpoints were defined and analyses planned, but without control of the overall Type I error rate for multiplicity. Discussion of secondary endpoints serves as supportive evidence but is not adequate for inclusion in the labeling.

Patients in Study 08 were provided with rescue medication for BTP. The rescue was APAP 500 mg tablets, with instructions to take 1 or 2 tablets 4 to 6 hours apart, with a maximum of 4 tablets in any 24 hours. The use of rescue was summarized by number of doses, amount (mg) and number of days rescue was used (Table 4). These endpoints are highly correlated and convey similar information with respect to efficacy of the blinded study treatment. The results for all of the endpoints pertaining to use of rescue medication for BTP were in the direction favoring Xtampza ER over placebo

Table 4: Secondary Efficacy Analysis - APAP Rescue Use for BTP during Double-blind 12 Week Treatment Phase

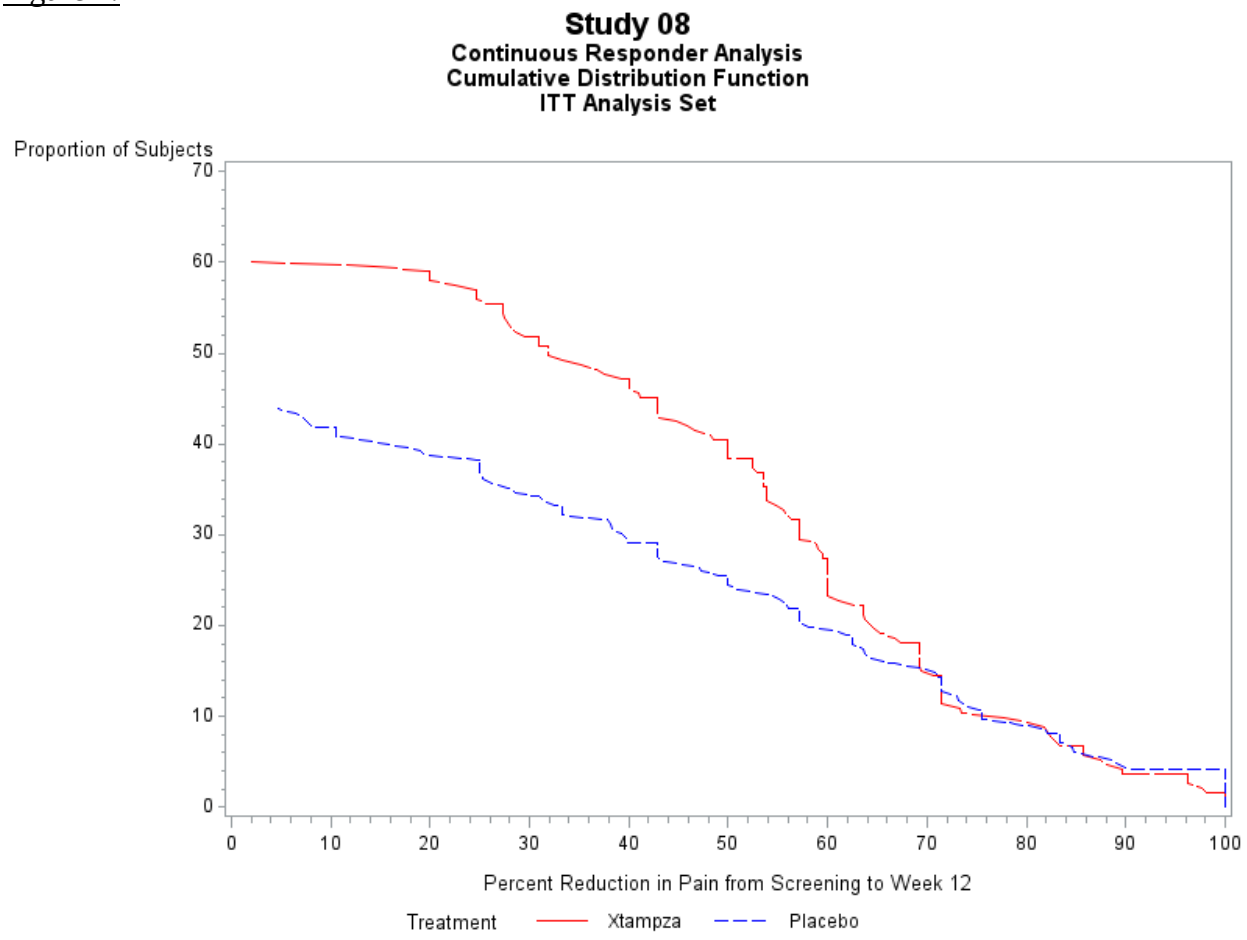
	Xtampza ER N=193	Placebo N=196
Number of Doses per Day Mean (SD)	0.15 (0.30)	0.23 (0.46)
Dosage (mg) per Day Mean (SD)	145 (289)	189 (318)
Total Number of Doses Mean (SD)	8.0 (16.4)	11.2 (31.6)
Total Amount Used (mg) Mean (SD)	7873 (16666)	9028 (20442)

Source: Clinical Study Report Table 14.2.5.2

Continuous Responder Analysis:

The Screening Baseline pain score was recorded while patients were not taking analgesic therapy for their chronic low back pain. Patients with a screening baseline pain score of at least 5 up to 9 on the 0-10 pain scale were eligible to enter the open-label titration. The percent improvement from screening to Week 12 was calculated, and then graphed as a cumulative distribution function showing proportion of subjects who achieved each level of percentage improvement (Figure 1). All patients who discontinue from the study during the double-blind treatment phase were classified as non-responders, as were patients with negative or zero improvement. The proportions of responders with at least a 30% and at least a 50% reduction in pain intensity at Week 12 of the double-blind treatment phase were also defined as secondary endpoints (Table 5). These provide consistent support of the efficacy of Xtampza versus placebo.

Figure 1:



Source: SAS datasets

Table 5: Secondary Efficacy Analysis - Percentage Improvement from Screening to Week 12

	Xtampza ER N=193	**Placebo N=196**
% of Patients Who Improved At least 30%	100 (52%)	68 (35%)
% of Patients Who Improved At least 50%	78 (40%)	50 (26%)

Source: SAS datasets

3.3 Evaluation of Safety

The evaluation of safety will be completed by Dr. Galati. He did not request any additional safety analyses for my review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

A comparison of the results across gender, age and race subgroups indicate no notable differences in the treatment effect. All study sites in Study 08 were in the United States.

Table 6 presents the group means for the subgroups. The study design is not appropriate to draw any comparative inferential conclusions based on subgroups. In Study 08 the results are consistently in the direction favorable to Xtampza ER versus placebo.

Table 6: Subgroup Analyses: Age, Gender, and Race – Reviewer's Results Study 08

Primary Endpoint: Change from Randomization Baseline to Week 12 in Daily Average Pain				
	Xtampza ER N=193		**Placebo N=196**	
	n	Mean (SD)	n	Mean (SD)
Age group				
< 65 years	160	0.3 (1.5)	164	1.2 (2.1)
≥ 65 years	25	0.1 (1.3)	26	0.5 (1.9)
Gender				
Female	99	0.2 (1.5)	101	1.0 (2.2)
Male	86	0.3 (1.5)	89	1.2 (1.9)
Race				
Caucasian	139	0.4 (1.4)	127	1.5 (1.8)
Non-Caucasian	46	0.3 (1.6)	63	0.3 (2.3)

Source: SAS datasets

4.2 Other Special/Subgroup Populations

This study enrolled both opioid-naïve and opioid-experienced patients. Table 7 shows the efficacy results by prior opioid use status. The results are consistent in support of Xtampza ER compared to placebo. There were no statistical comparative tests pre-specified or conducted.

Table 7: Subgroup Analyses: Prior Opioid Use – Reviewer's Results Study 08

Primary Endpoint: Change from Randomization Baseline to Week 12 in Daily Average Pain				
	Xtampza ER N=193		**Placebo N=196**	
	n	Mean (SD)	n	Mean (SD)
Prior Opioid Use				
Opioid-naïve	91	0.0 (1.6)	95	1.0 (2.3)
Opioid Experienced	94	0.4 (1.4)	95	1.2 (1.8)

Source: SAS datasets

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The rate of and reasons for dropouts in Study 08 were consistent with what is typical for the enriched enrollment randomized withdrawal (EERW) design for opioid pain treatment. The applicant's two-piece linear mixed model may overestimate the treatment effect in that it may have been influenced by the higher (imputed) pain scores in the Lack of Efficacy subgroup, and by the imbalance between the two treatment arms in the number of subjects who discontinued due to LOE. However, results from sensitivity analyses applying various imputation methods were all consistent, indicating the impact of dropouts and assumptions about missing data were not affecting the qualitative conclusions regarding the treatment effect.

5.2 Collective Evidence

At the End-of-Phase 2 meeting, held on March 30, 2010, it was agreed that a single successful well-controlled multicenter EERW designed study would be sufficient to support efficacy for Xtampza ER. Study 08 provides sufficient, consistent evidence in favor of Xtampza ER.

5.3 Conclusions and Recommendations

The results of Study 08 indicate that Xtampza ER is significantly better than placebo for the mean change from baseline in average pain score. In the Xtampza ER treatment arm the average pain score increased by an average of 0.3 units on the 11-point pain scale, while in the placebo arm the average pain score increased by an average of 1.9 units. Supportive evidence was provided by secondary endpoints (use of rescue medication; proportion of patients who reported various levels of reduction in pain from screening to Week 12) which were consistently in the direction favoring Xtampza ER.

My conclusion is that the results of Study 08 provide sufficient evidence of efficacy for pain management in patients with chronic low back pain in need of around-the-clock long-term opioid treatment as measured by the change in average pain score from baseline to Week 12.

5.4 Labeling Recommendations

The sections of the proposed revised labeling which relate to the efficacy of Xtampza ER for the treatment of chronic low back pain are shown below. The study design and primary endpoint results are described in appropriate detail. The inclusion of the cumulative responder graph is acceptable to provide clinically relevant information.

The information provided in the proposed labeling is acceptable with the exception (b) (4) [redacted] We have requested that the applicant (b) (4) [redacted] submit a revised draft labeling.

Proposed clinical studies section:

14 CLINICAL STUDIES

(b) (4) [redacted]

(b) (4)

During the double-blind (b) (4) 122 patients (63%) completed the 12-week treatment with XTAMPZA ER and 100 (51%) completed with placebo. Overall, 11% of patients discontinued due to lack of efficacy (4% of XTAMPZA ER patients and 17% of placebo patients), and 7% discontinued due to adverse events (7% of XTAMPZA ER patients and 7% of placebo patients).

In this study, there was a significant difference in pain reduction, favoring XTAMPZA ER, between XTAMPZA ER (doses of 36-144 mg per day, equivalent to 40-160 mg of oxycodone HCl) and placebo, based on the primary endpoint of change in average pain intensity from randomization baseline to Week 12 of the double-blind (b) (4) phase.

The proportion of patients (responders) in each group who demonstrated improvement in their weekly average pain scores from screening baseline to Week 12, is shown in Figure xx. The figure is cumulative, so that patients whose change from screening is, for example, 30%, are also included at every level of improvement below 30%. Patients who did not complete the study were classified as non-responders. Treatment with XTAMPZA ER resulted in a higher proportion of responders, defined as patients with at least a 30% and 50% improvement as compared to placebo.

Figure xx: (b) (4)

(b) (4)

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/s/

KATHERINE B MEAKER
10/09/2015

RUTHANNA C DAVI
10/09/2015

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:	208090
Drug Name:	Oxycodone DETERx
Indication:	(b) (4)
Study number:	CP-OXYDET-24
Applicant:	Collegium Pharmaceutical, Inc.
Date(s):	Date of Document: November, 20, 2014 Consult received date: January 08, 2015 Completion date: 05/21/2015
Review Priority:	S
Biometrics Division:	DBVI
Statistical Reviewer:	Anna Sun, Ph.D., Mathematical Statistician, OB/DBVI
Concurring Reviewers:	Qianyu Dang, Ph.D., Lead Mathematical Statistician, OB/DBVI Yi Tsong, Ph.D., Division Director, OB/DBVI
Medical Division:	Control Substance Staff
The CSS Team:	James Tolliver, Ph.D., Pharmacologist, OCD/CSS
Project Manager:	Sandra Saltz, Project Manager, CSS

Keywords: *Crossover design, Drug abuse potential study, Self-reported endpoint, Multiple endpoints*

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1. Executive Summary

Study CP-OXYDET-24 was a randomized, double-blind, triple-dummy, active- and placebo-controlled, single-dose, 6-treatment, 6-period crossover comparison study designed to evaluate the oral abuse potential and PKs of intact Oxycodone DETERx HFHC, intact Oxycodone DETERx fasted, chewed Oxycodone DETERx HFHC, chewed Oxycodone DETERx fasted, and crushed IR oxycodone fasted.

The primary comparisons of interest were between chewed Oxycodone DETERx HFHC and crushed IR oxycodone fasted and between chewed Oxycodone DETERx fasted and crushed IR oxycodone fasted.

The study consisted of a Screening phase, Drug Discrimination Phase, Double-blind treatment phase and a Follow-up safety phase. There were six treatments in the study (intact Oxycodone DETERx HFHC, intact Oxycodone DETERx fasted, chewed Oxycodone DETERx HFHC, chewed Oxycodone DETERx fasted, crushed IR oxycodone fasted and placebo). 64 subjects entered the Treatment Phase and 38 completed the study.

The primary PD endpoints for this study were Drug Liking. The reviewer analyzed the primary endpoint Drug Liking, and the secondary endpoints: Drug High, Take Drug Again and ARCI/MBG. The results from the statistical reviewer's analyses establish that:

For Trt E (Crushed IR Oxycodone Fasted) Vs Trt C (Chewed Oxycodone DETERx HFHC):

- The Emax for Drug Liking VAS, Drug High VAS, Take Drug Again, and ARCI/MBG, were all significantly lower for chewed Oxycodone DETERx HFHC than crushed IR oxycodone fasted.

- The TEmax for Drug Liking VAS and Drug High VAS were significantly longer for chewed Oxycodone DETERx HFHC than crushed IR oxycodone fasted (P=0.0012 and 0.0023 respectively). No significant differences were observed for Take Drug Again and ARCI/MBG.

- Around 79% subjects showed some reduction in Drug Liking with Chewed Oxycodone DETERx HFHC (Trt C) compare to Crushed IR Oxycodone Fasted (Trt E), while 21% subjects had no reduction or negative reduction. In addition 47% and 29% of the subjects had at least 30% and 50% reduction in Drug Liking with Chewed Oxycodone DETERx HFHC (Trt C) compare to Crushed IR Oxycodone Fasted (Trt E).

For Trt E (Crushed IR Oxycodone Fasted) vs Trt D (Chewed Oxycodone DETERx Fasted):

- Except for Take Drug Again, the Emax for Drug Liking VAS, Drug High VAS and ARCI/MBG, were all significantly lower for chewed Oxycodone DETERx fasted than crushed IR oxycodone fasted. No significant difference was observed for Take Drug Again for the Emax of Drug Liking VAS.

- The TEmax for Drug Liking VAS was significantly longer for chewed Oxycodone DETERx fasted than crushed IR oxycodone fasted (P<0.0001). No significant differences were observed for Drug High, Take Drug Again and ARCI/MBG.

- About 66% of the subjects showed some reduction in Drug Liking with Chewed Oxycodone DETERx Fasted (Trt D) compare to Crushed IR Oxycodone Fasted (Trt E), while 34% of the subjects had no reduction or negative reduction in Drug Liking. At least a 30% and 50% reduction in Drug Liking with Chewed Oxycodone DETERx Fasted (Trt D) compare to Crushed IR Oxycodone Fasted were 31.6% and 23.7% of subjects respectively.

Additional comments:

1. In the sponsor's labeling file, Figure 1 shows the percentage reduction for Treatment E vs Treatment A and treatment E vs Treatment C. The reviewer asked sponsor to show the percentage reduction for the two primary comparisons instead, i.e. Treatment E vs Treatment D and treatment E vs Treatment C.

2. There is no food effect for Drug liking, drug high, take drug again and ARCI/MBG (P values are all >0.05). For manipulation effect, there is no manipulation effect between treatment A and treatment C for Drug liking, drug high, take drug again and ARCI/MBG (P values are all >0.05). There are some manipulation effect difference between treatment B and treatment D for Drug liking and drug high (P=0.0457 and 0.0194 respectively). No significant manipulation effect differences were found for take drug again and ARCI/MBG.

3. For the statistical analysis of ARCI/MBG, the baseline value is significant (P value <0.05), you should include baseline value as a covariate in the model fitting.

4. The new ADF guidance has published in April 2015, in the future, you should follow the new guidance.

2. Review Report on Study CP-OXYDET-24

2.1 Overview

Oxycodone DETERx formulation has been developed to provide clinicians and patients with a tamper-resistant version of the drug in the form of an ER oxycodone preparation. Oxycodone DETERx contains pharmaceutically-active microspheres delivered in a capsule for oral administration (capsules contain oxycodone in an amount equivalent to 10 mg, 15 mg, 20 mg, 30 mg, or 40 mg oxycodone hydrochloride [HCl]).

To date, there are no pharmacokinetic-pharmacodynamic oral human abuse potential data for Oxycodone DETERx. Because Oxycodone DETERx has a known food effect and will be labeled "…to take with food", Oxycodone DETERx 40 mg will be studied in the fed and fasted state.

An oral Oxycodone DETERx 40 mg treatment was studied to compare the oral (PO) administration of the Oxycodone DETERx formulation intact under fed and fasted conditions and the PO administration of the Oxycodone DETERx formulation chewed under fed and fasted conditions. The purpose of this study was to comparatively assess the oral human abuse potential and the plasma concentrations of oxycodone intact (fed and fasted) and chewed (fed and fasted) compared with the PO administration of immediate-release (IR) oxycodone crushed (fasted) and the PO administration of placebo in opioid-experienced, nondependent subjects.

2.1.1 Objectives of the study

The primary objective of this study was to evaluate the abuse potential and PK of Oxycodone DETERx 40 mg intact in the fed state, Oxycodone DETERx 40 mg intact in the fasted state, Oxycodone DETERx 40 mg chewed in the fed state, Oxycodone DETERx 40 mg chewed in the fasted state, and IR oxycodone 40 mg crushed in the fasted state.

2.1.2 Study design

This was a randomized, double-blind, triple-dummy, active- and placebo-controlled, single-dose, 6-treatment, 6-period crossover comparison study designed to evaluate the oral abuse potential and PKs of intact Oxycodone DETERx HFHC, intact Oxycodone DETERx fasted, chewed Oxycodone DETERx HFHC, chewed Oxycodone DETERx fasted, and crushed IR oxycodone fasted. All active doses of oxycodone were 40 mg. The primary comparisons of interest were between chewed Oxycodone DETERx HFHC and crushed IR oxycodone fasted and between chewed Oxycodone DETERx fasted and crushed IR oxycodone fasted.

Subjects who successfully completed the Screening Phase returned to the research clinic as inpatients to complete the Drug Discrimination Phase. The Drug Discrimination Phase comprised a Naloxone Challenge Test to confirm that subjects were not opioid tolerant and a Drug Discrimination Test to ensure that subjects could differentiate between the effects of a single 20 mg dose of crushed IR oxycodone dosed per os (PO) in solution and crushed placebo in solution.

Subjects who successfully completed the Naloxone Challenge Test remained as inpatients to complete the Drug Discrimination Test. In a two-way crossover, 1:1 ratio, double-blind, randomized design, subjects received a single, PO dose of the following treatments:

• IR Oxycodone 20 mg Dosed PO Crushed, in Solution

• Placebo Dosed PO Crushed, in Solution

Both doses were administered fasted. A minimum of 5 days separated the second treatment in the Drug Discrimination Test and the first treatment in the Double-blind Treatment Phase.

During the Double-blind Treatment Phase, subjects were randomized in a 1:1:1:1:1:1 ratio to receive a single dose of 6 treatments in a double-blind, triple-dummy design. Each treatment was separated by a minimum of 5 days.

Subjects received each of 6 treatments in random order:

Treatment	Chewed	Intact Capsules	IR Solution	Fed/Fasted
A	DETERx placebo	Oxycodone DETERx	Placebo	HFHC
B	DETERx placebo	Oxycodone DETERx	Placebo	Fasted
C	Oxycodone DETERx	DETERx placebo	Placebo	HFHC
D	Oxycodone DETERx	DETERx placebo	Placebo	Fasted
E	DETERx placebo	DETERx placebo	IR oxycodone	Fasted
F	DETERx placebo	DETERx placebo	Placebo	HFHC

HFHC=high-fat, high-calorie; IR=immediate-release

Pharmacodynamic Evaluations:

The parameters of interest that were collected in this study included the following:

• Drug Liking – bipolar VAS scale (Primary);

• Overall (Global) Drug Liking – bipolar VAS scale;

• Take Drug Again – bipolar VAS scale;

• DEQ (any drug effects, high, good effects, bad effects, sick, nausea, sleepy, and dizzy) – unipolar VAS scale;

• PVAQ;

• ARCI/MBG;

• Pupillometry

The following PD endpoints were calculated for each parameter of interest as appropriate:

• Emax during 24 hours after dosing

• TEmax

• Emin for bipolar scales only during 24 hours after dosing

• TEmin for bipolar scales only

• AUE0-1h

• AUE0-2h

• AUE0-4h

• AUE0-8h

• AUE0-24h

For Overall (Global) Drug Liking and the Take Drug Again Assessment, the Emax and Emean average of the 8 and 24 hour assessments.

2.1.3 Abuse potential measure and data collection times

The DEQ was assessed during each Treatment Period of the Double-blind Treatment Phase at the following times: 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 12.0 and 24.0 hours post dose. Predose assessments were limited to DEQ for nausea, feel sick, and ARCI/MBG. Data were

collected at 8.0 and 24.0 hours post dose for Take Drug Again Assessment and Overall (Global) Drug Liking. PVAQ was captured at 24 hours post dose.

Pupil diameter (pupillometry), an objective assessment, was measured during each Treatment Period of the Double-blind Treatment Phase at pre-dose and at 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, and 8.0 hours post dose.

2.1.4 Number of subjects

Planned: Thirty-six completed subjects were planned for this study. A sample size of 36 completed subjects was estimated to provide at least 90% power to detect treatment differences of $\geqslant$11.2 points in Emax for the bipolar Drug Liking visual analog scale (VAS), at the 1-sided significance level of 0.025, using a paired means test and correlation of 0.5, and assuming standard deviation differences of 20 points.

Analyzed: A total of 111 subjects entered the Drug Discrimination Phase and underwent the Naloxone Challenge Test; 110 subjects passed the test. Three subjects withdrew consent prior to the Drug Discrimination Test. Of the 107 subjects who participated in the Drug Discrimination Test, 24 failed the Drug Discrimination Test (i.e., they were unable to discriminate between opioid and placebo based on Drug Liking scores); 7 were considered Drug Discrimination failures as per the Sponsor; 3 experienced an adverse event (AE) that required withdrawal according to a protocol-mandated criterion (i.e., emesis within the first 6 hours after dosing during the Drug Discrimination Phase); 7 subjects withdrew consent, and 2 subjects were withdrawn due to protocol deviations. Of the 64 subjects who entered the Double-blind Treatment Phase, 38 completed the study.

2.1.5 Statistical methodologies used in the Sponsor's analyses

Hypothesis Testing

The hypothesis for the primary analysis for Drug Liking, Emax, was follows:

$$H_o: \mu_C - \mu_T \leq 0 \text{ vs } H_a: \mu_C - \mu_T > 0$$

where μ_C is the mean of the control treatment, crushed IR oxycodone fasted (Treatment E), and μ_T is the mean of the test treatment, chewed Oxycodone DETERx HFHC (Treatment C) or chewed Oxycodone DETERx fasted (Treatment D).

The hypothesis for the validation of the positive control was as follows:

$$H_o: \mu_C - \mu_p \leq 0 \text{ vs } H_a: \mu_C - \mu_p > 0$$

where μ_C is the mean of the control treatment, crushed IR oxycodone fasted (Treatment E), and

μ_P is the mean of the placebo treatment, placebo HFHC (Treatment F).

The primary outcome measure was Drug Liking; the primary endpoint was Drug Liking Emax during the 24 hours after dosing. The secondary outcome measures were: DEQ, feeling high, any drug effects, good effects, bad effects, feel sick, nausea, sleepy, and dizzy; Overall (Global) Drug Liking; ARCI/MBG; Take Drug Again Assessment; PVAQ; and pupillometry.

The primary analysis was based on the pairwise comparison between crushed IR oxycodone fasted (control - Treatment E) and chewed Oxycodone DETERx HFHC (Treatment C) and chewed Oxycodone DETERx fasted (Treatment D) for Drug Liking Emax. The Drug Liking Emax comparison between crushed IR oxycodone fasted (Treatment E) and placebo HFHC (Treatment F) was used for validation of the appropriateness of the positive control.

Secondary comparisons were done between chewed Oxycodone DETERx HFHC (Treatment C) and chewed Oxycodone DETERx fasted (Treatment D) compared with intact Oxycodone DETERx HFHC (Treatment A), as well as between chewed Oxycodone DETERx fasted (Treatment D) and intact Oxycodone DETERx fasted (Treatment B). Other relevant comparisons were done between intact Oxycodone DETERx HFHC (Treatment A) and crushed IR oxycodone fasted (Treatment E), between intact Oxycodone DETERx fasted (Treatment B) and crushed IR oxycodone fasted (Treatment E), between intact Oxycodone DETERx HFHC (Treatment A) and placebo HFHC (Treatment F), between intact Oxycodone DETERx fasted (Treatment B) and placebo HFHC (Treatment F), between chewed Oxycodone DETERx HFHC (Treatment C) and placebo HFHC (Treatment F), and between chewed Oxycodone DETERx fasted (Treatment D) and placebo HFHC (Treatment F).

The following treatment comparisons were made for each of the PD endpoints:

• Treatment E vs. Treatment C (Primary Comparison);

• Treatment E vs. Treatment D (Primary Comparison);

• Treatment E vs. Treatment F (Validity);

• Treatment C vs. Treatment A (Secondary Comparison);

• Treatment D vs. Treatment A (Secondary Comparison);

• Treatment D vs. Treatment B (Secondary Comparison);

• Treatment E vs. Treatment A;

• Treatment E vs. Treatment B;

• Treatment A vs. Treatment F;

• Treatment B vs. Treatment F;

• Treatment C vs. Treatment F;

• Treatment D vs. Treatment F.

Pharmacodynamic Statistical Methodology

For the Double-blind Treatment Phase, the PD endpoints or time point (for those measured once) were analyzed using a mixed-effect model with fixed effects for sequence, period, and treatment with subject nested within sequence as a random effect. Least squares means (LS means) and 95% confidence intervals (CIs) were calculated for each treatment. The LS means differences and

95% CIs were generated for each pairwise treatment comparison. Pairwise comparisons were not adjusted for multiplicity.

Assumptions of normality of residuals were investigated for each response measurement. If the normality assumption was rejected at the 1% level with the Shapiro-Wilk test then an analysis using ranked values was performed. The median differences for the pairwise comparisons were derived using Hodges-Lehman estimates. The 95% CIs were provided.

The comparison of Treatment E versus Treatment F for Drug Liking Emax must have been statistically significant in order to validate the appropriateness of the positive control and to proceed with further testing.

Descriptive statistics for the PD parameters of interest are presented at each time point collected. For PD parameters collected pre dose, the changes from pre dose to each subsequent time point were calculated and descriptive statistics are provided.

PD parameters of interest collected over time are presented in graphs. Additionally, a correlation plot of the mean of the PD parameters vs. the mean of the PK parameters is presented for PD Drug Liking Emax versus PK of Cmax/Tmax (abuse quotient), Cmax, and Tmax using logarithmic regression models to display a linear line through the treatments.

Secondary Responder Analysis

Percent Reduction

For the parameter of Emax based on Drug Liking, percent reduction was calculated for each subject as:

$$\%\,reduction = \left\{ \begin{array}{l} \dfrac{c_i - t_i}{c_i - 50} \times \left(1 - \dfrac{p_i - 50}{50}\right) \times 100\%,\ i = 1, 2, \ldots n,\ \ if\ p_i > 55; \\ \dfrac{c_i - t_i}{c_i - 50} \times 100\%,\ \ \ i = 1, 2, \ldots n,\ if\ p_i \le 55. \end{array} \right\}$$

where ci, ti, and pi are the Drug Liking Emax values for the control, crushed IR oxycodone fasted (Treatment E), test, chewed Oxycodone DETERx HFHC (Treatment C) or chewed Oxycodone DETERx fasted (Treatment D), and the placebo HFHC (Treatment F), respectively; from the ith subject; and n is the sample size. The % reduction was calculated if data for the active control, test product, and placebo were available. In cases where one of those values was not available percent reduction was set to missing. In cases where the control was equal to 50, the percent reduction was set to the largest negative percent observed in the study for that comparison; if no negative percent existed (or it was less than -101%) then the percent reduction was set to -101%. The number and percent of subjects with % reductions falling within 10% increments are presented (i.e., 0% to 10% reduction, 10% to 20% reduction, etc.) for % reduction for Treatment C and % reduction for Treatment D.

Responder Analysis

The % reduction in Drug Liking Emax was used to analyze the data using a responder analysis for Treatment C and Treatment D. A responder was defined as a subject who had at least a pre-

specified level of reduction, where levels from 0 to 100% in 10% increments are presented in a sensitivity analysis. The number and percent of subjects determined as responders and non-responders are presented. The binominal test of proportions was utilized to test the null hypothesis that 50% or fewer subjects were responders.

2.1.6 Sponsor's Pharmacodynamic Conclusions

An abuse potential assessment is typically conducted by comparing an investigational drug to a drug of known abuse and placebo. The primary endpoint of interest for this study was the 0 to 100 mm bipolar VAS score for Drug Liking; larger values indicate greater liking. The primary parameter was Emax.

Study validity was evaluated with the comparison of Drug Liking Emax for crushed IR oxycodone fasted to placebo HFHC. LS mean ± SEM Emax for Drug Liking was significantly higher for crushed IR oxycodone fasted than placebo HFHC (81.56 ± 1.915 vs 54.70 ± 1.915 mm, $p < 0.0001$), which confirms validity of the study. The difference of LS means between the crushed IR oxycodone fasted and placebo HFHC was also significantly higher for all AUE parameters ($p < 0.0001$), further supporting study validity.

Primary Comparisons for the Primary Endpoint
The LS Mean Emax for Drug Liking was significantly lower for chewed Oxycodone DETERx HFHC than crushed IR oxycodone fasted ($p < 0.0001$). Specifically, Drug Liking Emax for chewed Oxycodone DETERx HFHC was approximately 87% of Emax for crushed IR oxycodone fasted. The primary PD analysis comparing chewed Oxycodone DETERx HFHC and crushed IR oxycodone fasted was corroborated by the supporting analysis of the AUE parameters through 8 hours with significantly less liking of chewed Oxycodone DETERx HFHC and crushed IR oxycodone fasted ($p \leqslant 0.0293$). TEmax was significantly longer for chewed Oxycodone DETERx HFHC than crushed IR oxycodone fasted (LS mean ± SEM: 3.31 ± 0.421 vs 1.36 ± 0.421 hours; median difference ± SEM: -2.00 ± 0.505 hours, $p < 0.0001$) indicating that central exposure took longer to achieve with chewed Oxycodone DETERx HFHC than crushed IR oxycodone fasted.

The LS Mean Emax for Drug Liking was significantly lower for chewed Oxycodone DETERx fasted than crushed IR oxycodone fasted ($p = 0.0007$). Specifically, Drug Liking Emax for chewed Oxycodone DETERx fasted was approximately 91% of Emax for crushed IR oxycodone fasted. The primary PD analysis comparing chewed Oxycodone DETERx fasted and crushed IR oxycodone fasted was corroborated by the supporting analysis of the AUE parameters at the earlier time points with significantly less liking of chewed Oxycodone DETERx fasted than crushed IR oxycodone fasted ($p \leqslant 0.0077$) for the AUE parameters through 4 hours. TEmax was significantly longer for chewed Oxycodone DETERx fasted than crushed IR oxycodone fasted (LS mean ± SEM: 3.77 ± 0.421 vs 1.36 ± 0.421 hours, $p < 0.0001$) indicating that central exposure took longer to achieve with chewed Oxycodone DETERx fasted than crushed IR oxycodone fasted.

Secondary Comparisons for the Primary Endpoint
Neither Emax for Drug Liking nor any of the other PD parameters were significantly different for chewed Oxycodone DETERx HFHC and intact Oxycodone DETERx HFHC ($p \geqslant 0.1134$). TEmax was not significantly different for chewed Oxycodone DETERx HFHC and intact Oxycodone DETERx HFHC ($p = 0.6083$), indicating that chewing did not compromise the extended-release property of Oxycodone DETERx. Emax for Drug Liking and the AUE

parameters through 4 hours were significantly higher for chewed Oxycodone DETERx fasted than for intact Oxycodone DETERx HFHC ($p \leqslant 0.0307$). TEmax was significantly shorter for chewed Oxycodone DETERx fasted than intact Oxycodone DETERx HFHC (median difference ± SEM: -1.00 ± 0.510 hours, $p = 0.0224$), indicating that central exposure was achieved more rapidly with chewed Oxycodone DETERx fasted than intact Oxycodone DETERx HFHC. Emax for Drug Liking and the AUE parameters through 4 hours were also significantly higher for chewed Oxycodone DETERx fasted than intact Oxycodone DETERx fasted ($p \leqslant 0.0457$), although the difference in TEmax for these treatments was not significantly different (LS mean ± SEM: 3.77 ± 0.421 vs 2.77 ± 0.421 hours; median difference ± SEM: 0.00 ± 0.383 hours, $p = 0.5819$), indicating more drug liking for the chewed formulation despite similarities in TEmax.

Other Relevant Comparisons for the Primary Endpoint
Emax for Drug Liking and the AUE parameters through 8 hours were significantly lower for both intact Oxycodone DETERx HFHC and intact Oxycodone DETERx fasted when compared with crushed IR oxycodone fasted ($p \leqslant 0.0493$), indicating less drug liking for intact Oxycodone DETERx relative to the dose of equivalent crushed IR oxycodone fasted. TEmax was significantly longer for both intact Oxycodone DETERx HFHC and intact Oxycodone DETERx fasted when compared with crushed IR oxycodone fasted ($p < 0.0001$), indicating central exposure took longer with intact DETERx under both fed and fasted conditions relative to crushed IR oxycodone fasted.

2.2 Data Location

The analysis datasets are located at

\\CDSESUB1\evsprod\NDA208090\0014\m5\datasets\cp-oxydet-21\analysis\adam\datasets

2.3 Reviewer's Assessment

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

2.3.1 Descriptive Statistics

The descriptive statistics for the E_{max} and TE_{max} endpoint for primary variable Drug Liking, secondary variables Drug High VAS, Take Drug Again VAS and ARCI/MBG are provided in Table 1 and Table 2. E_{max} is calculated as the maximum effect in the first 24 hours in the review's analysis. Table 1 summarizes the mean, standard deviation, minimum, the first quartile (Q1), median, the third quartile (Q3), and maximum of E_{max} for the six treatments in the study. Similarly table 2 summarizes results for TE_{max}.

Table 1. E_{max} Descriptive Statistics for Drug Liking, Drug High, Take Drug Again, ARCI/MBG, PD population (N=38)

Parameter	Treatment	Mean	Std Dev	Min	Q1	Median	Q3	Max
Drug Liking VAS	A: Intact Oxycodone Deterx 40mg Hfhc	68.61	13.14	50.00	55.00	70.00	78.00	93.00
	B: Intact Oxycodone Deterx 40mg Fasted	68.79	13.01	50.00	55.00	72.00	78.00	89.00
	C: Chewed Oxycodone Deterx 40mg Hfhc	70.76	11.45	50.00	63.00	70.00	79.00	90.00

	D: Chewed Oxycodone Deterx 40mg Fasted	73.45	13.90	50.00	62.00	76.00	82.00	95.00
	E: Crushed Ir Oxycodone 40mg In Solution Fasted	81.76	11.46	50.00	74.00	82.50	91.00	99.00
	F: Placebo	54.87	8.42	50.00	50.00	51.00	55.00	84.00
Drug High VAS	A: Intact Oxycodone Deterx 40mg Hfhc	36.00	26.94	1.00	10.00	34.50	54.00	94.00
	B: Intact Oxycodone Deterx 40mg Fasted	33.58	26.20	0.00	4.00	34.50	56.00	82.00
	C: Chewed Oxycodone Deterx 40mg Hfhc	37.42	24.44	1.00	19.00	33.00	55.00	89.00
	D: Chewed Oxycodone Deterx 40mg Fasted	44.68	29.04	0.00	21.00	51.50	66.00	95.00
	E: Crushed Ir Oxycodone 40mg In Solution Fasted	68.92	24.97	3.00	62.00	72.00	89.00	99.00
	F: Placebo	10.26	19.16	0.00	1.00	2.00	5.00	79.00
Take Drug Again VAS	A: Intact Oxycodone Deterx 40mg Hfhc	70.58	18.12	26.00	50.00	74.00	85.00	99.00
	B: Intact Oxycodone Deterx 40mg Fasted	70.18	15.96	50.00	52.00	68.50	83.00	98.00
	C: Chewed Oxycodone Deterx 40mg Hfhc	69.26	18.90	3.00	57.00	69.00	84.00	98.00
	D: Chewed Oxycodone Deterx 40mg Fasted	73.74	14.92	50.00	63.00	74.00	87.00	98.00
	E: Crushed Ir Oxycodone 40mg In Solution Fasted	75.45	16.79	37.00	64.00	75.50	90.00	100.00
	F: Placebo	52.66	13.35	3.00	50.00	50.00	50.00	95.00
ARCI/MBG	A: Intact Oxycodone Deterx 40mg Hfhc	4.13	4.80	0.00	0.00	2.00	8.00	14.00
	B: Intact Oxycodone Deterx 40mg Fasted	4.26	5.03	0.00	0.00	3.00	7.00	16.00
	C: Chewed Oxycodone Deterx 40mg Hfhc	4.03	4.33	0.00	0.00	2.50	7.00	14.00
	D: Chewed Oxycodone Deterx 40mg Fasted	5.05	4.94	0.00	0.00	3.50	8.00	14.00
	E: Crushed Ir Oxycodone 40mg In Solution Fasted	6.95	5.60	0.00	1.00	7.00	12.00	16.00
	F: Placebo	1.37	2.62	0.00	0.00	0.00	2.00	14.00

For Drug Liking VAS, as can be seen in table 1, for placebo the mean is 54.87, median is 51, third quartile is 55 and maximum value is 84, moreover, from figure 4, the heat-map of drug liking VAS shows that 7 of 38 (18%) of the subjects has placebo >60. The placebo response of this study is very high. Meanwhile for those subjects who had high placebo response, most of them had a neutral response for one of the other treatments. One reason is that those subjects may think the treatment that they had the neutral response was placebo. Treatment C has mean 70.76 and median 70, treatment D has mean 73.45 and median 76, treatment E has mean 81.76 and median 82.5, treatment E has the highest mean and median among the six treatments.

For Drug High VAS, from table 1, mean Emax of Drug High for placebo, the mean is 10.26, median is 2 and from figure 5, the heat-map of drug high, 7 out of 38 (18%) subjects had placebo response >15. In the same way as drug liking VAS, most of the subjects who had high placebo response, they had a very low score for one of the other treatments. Treatment C has mean 37.42 and median 33, treatment D has mean 44.68 and median 51.5, treatment E has mean 68.92 and median 72, treatment E has the highest mean and median among the six treatments.

For Take Drug Again VAS, table 1 shows that place has mean 52.66, and median equal to 50, from table 1 and figure 6, the heat-map for Take Drug Again, all the other five treatments have very close mean and median value. For ARCI/MBG, place has mean 1.37, with median equal 0. Treatment E has the highest mean value among these treatments which is 6.95, with median 7.00. Treatment C has mean value 4.03, median 2.5, and treatment D has mean value 5.05 with median equals to 3.5.

Table 2. TE_{max} Descriptive Statistics for Drug Liking, Drug High, Take Drug Again, ARCI/MBG, PD population (N=38)

Parameter	Treatment	Mean	Std Dev	Min	Q1	Median	Q3	Max
Drug Liking VAS	A: Intact Oxycodone Deterx 40mg Hfhc	3.66	2.20	0.25	2.00	4.00	5.00	8.00
	B: Intact Oxycodone Deterx 40mg Fasted	2.68	1.51	0.25	2.00	3.00	4.00	6.00
	C: Chewed Oxycodone Deterx 40mg Hfhc	3.28	1.75	0.25	2.00	3.00	4.00	6.00
	D: Chewed Oxycodone Deterx 40mg Fasted	3.63	5.16	0.25	1.50	2.00	3.00	24.00
	E: Crushed Ir Oxycodone 40mg In Solution Fasted	1.22	0.79	0.25	0.50	1.00	1.50	4.00
	F: Placebo	1.52	1.70	0.25	0.25	1.25	2.00	8.00
Drug High VAS	A: Intact Oxycodone Deterx 40mg Hfhc	4.36	2.33	0.25	3.00	5.00	6.00	8.00
	B: Intact Oxycodone Deterx 40mg Fasted	3.18	1.56	0.25	2.00	3.00	4.00	6.00
	C: Chewed Oxycodone Deterx 40mg Hfhc	3.76	1.87	0.50	2.00	4.00	5.00	8.00
	D: Chewed Oxycodone Deterx 40mg Fasted	2.72	1.79	0.25	1.50	2.00	4.00	8.00
	E: Crushed Ir Oxycodone 40mg In Solution Fasted	1.83	3.73	0.50	1.00	1.00	1.50	24.00
	F: Placebo	2.51	4.39	0.25	0.25	1.00	2.00	24.00
Take Drug Again VAS	A: Intact Oxycodone Deterx 40mg Hfhc	12.63	7.35	8.00	8.00	8.00	24.00	24.00
	B: Intact Oxycodone Deterx 40mg Fasted	13.47	7.69	8.00	8.00	8.00	24.00	24.00
	C: Chewed Oxycodone Deterx 40mg Hfhc	13.47	7.69	8.00	8.00	8.00	24.00	24.00
	D: Chewed Oxycodone Deterx 40mg Fasted	13.47	7.69	8.00	8.00	8.00	24.00	24.00
	E: Crushed Ir Oxycodone 40mg In Solution Fasted	16.00	8.11	8.00	8.00	16.00	24.00	24.00
	F: Placebo	13.47	7.69	8.00	8.00	8.00	24.00	24.00
ARCI/MBG	A: Intact Oxycodone Deterx 40mg Hfhc	2.12	2.27	0.00	0.00	1.25	4.00	8.00
	B: Intact Oxycodone Deterx 40mg Fasted	1.46	1.92	0.00	0.00	1.00	2.00	8.00
	C: Chewed Oxycodone Deterx 40mg Hfhc	2.39	4.07	0.00	0.00	1.50	3.00	24.00
	D: Chewed Oxycodone Deterx 40mg Fasted	1.32	1.61	0.00	0.00	1.00	2.00	6.00
	E: Crushed Ir Oxycodone 40mg In Solution Fasted	1.57	4.03	0.00	0.25	0.50	1.00	24.00
	F: Placebo	1.89	5.42	0.00	0.00	0.00	1.00	24.00

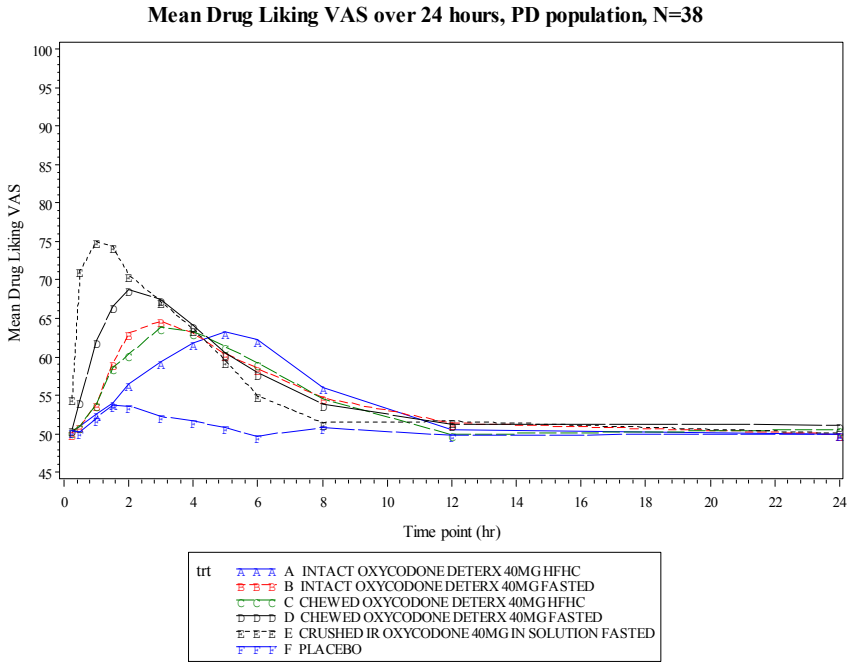
TEmax is a secondary PD parameter, the larger the TEmax value, the longer for a subject to reach the Emax. So shorter time to reach peak TEmax indicates the treatment has potential abuse-deterrence. From table 2, For Drug Liking VAS, TEmax for placebo is 1.52, the TEmax of treatment E is 1.22, while TEmax for treatment C and treatment D are 3.28 and 3.63 respectively, treatment E reached Emax faster than the other treatments.
For Drug high, take drug again and ARCI/MBG, no significant differences were found for TEmax.

Figure 1 shows the mean drug liking VAS over time, Mean scores of treatment F (placebo) remains ~54 slightly above the neutral value throughout the time course of assignment.

- For the comparison between treatment E and Treatment D: Started from 0.5 hour post-dose, means score of treatment E resulted a sharp increase and reached a mean peak score (~75) at 1hours post-dose, then decrease afterwards. Treatment D also associated with an increase and reached to a peak score (~68) at 2 hours post-dose then decrease over time. After 4.5 hours post-dose there is no big difference between treatment E and treatment D.

- For the comparison between treatment E and treatment C, started from 0.5 hour post-dose, mean score of treatment C slowly increase and reach the mean peak at 2.5 hours post-dose ~64), then gradually decline over time. Treatment E had significant higher mean value than treatment C in the first 2 hours, and started from 4 hours post-dose, there is no big difference between treatment E and treatment C.

Figure 1. Mean Drug Liking Scores over time (PD Population, N=38)



Similar patterns were found for Drug High VAS and ARCI/MBG. Treatment E had a rapid increase and reached to the highest peak value in a short period of time then decreased over time, in contrast treatment C had relative slower increase, and had the lowest peak value comparing

with treatment E and treatment D. However, after 4 hours post-dose, there is no visual mean difference among these three treatments.

Figure 2. Mean Scores over time for Drug High VAS

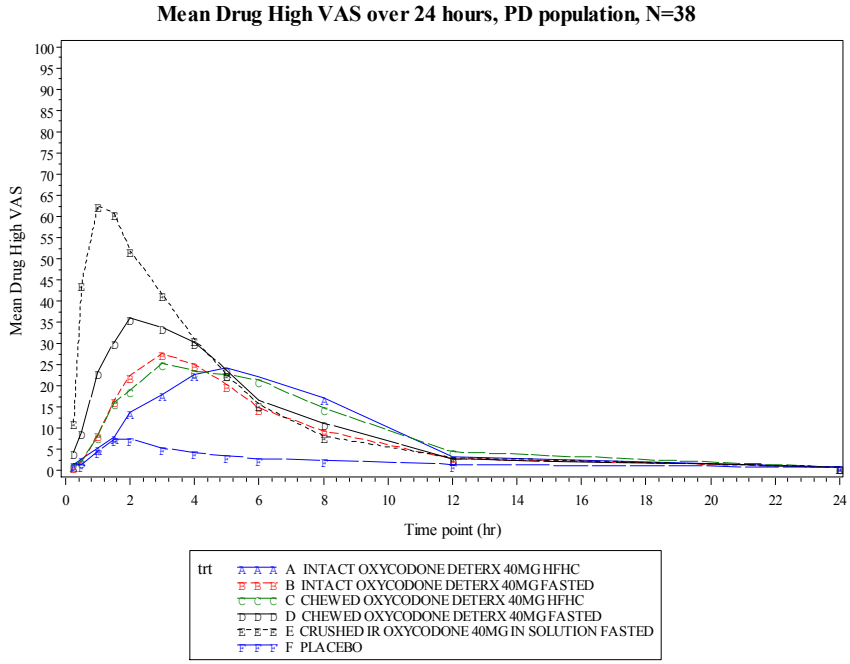
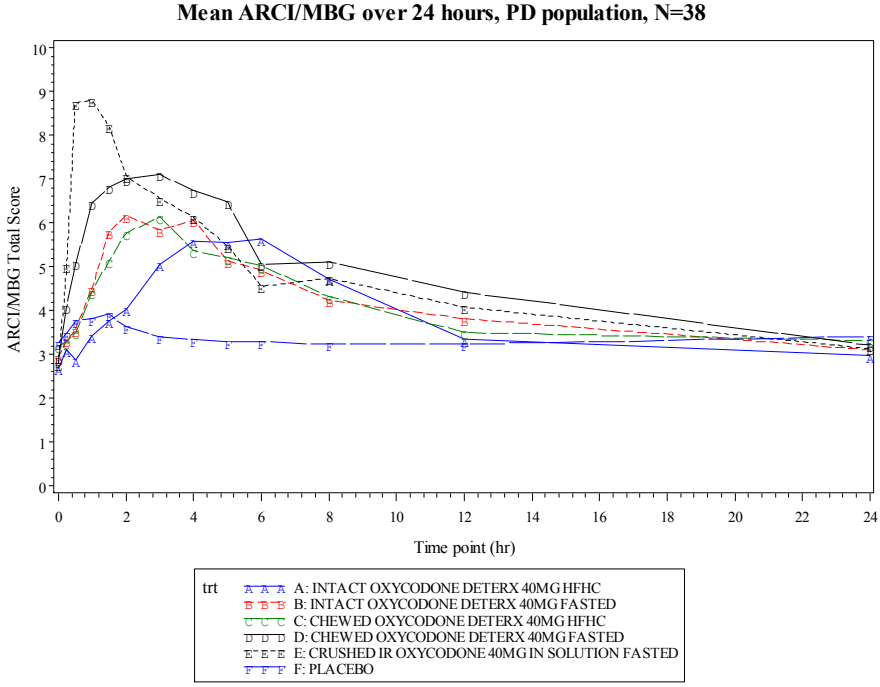


Figure 3. Mean Scores over time for ARCI/MBG



Individual E_{max} scores are displayed by subject for all treatments in Figure 4, Figure 5 and Figure 6, each row represent one patient with six treatments, the darker color means the more like. We can compare the E_{max} score for each patient at different treatment. Figure 4 and Figure 5 show general more like for treatment E comparing with treatment D and treatment C. But there is no big difference for take drug again for these three treatments.

Figure 4. Heatmap for Emax of Drug Liking VAS by treatment

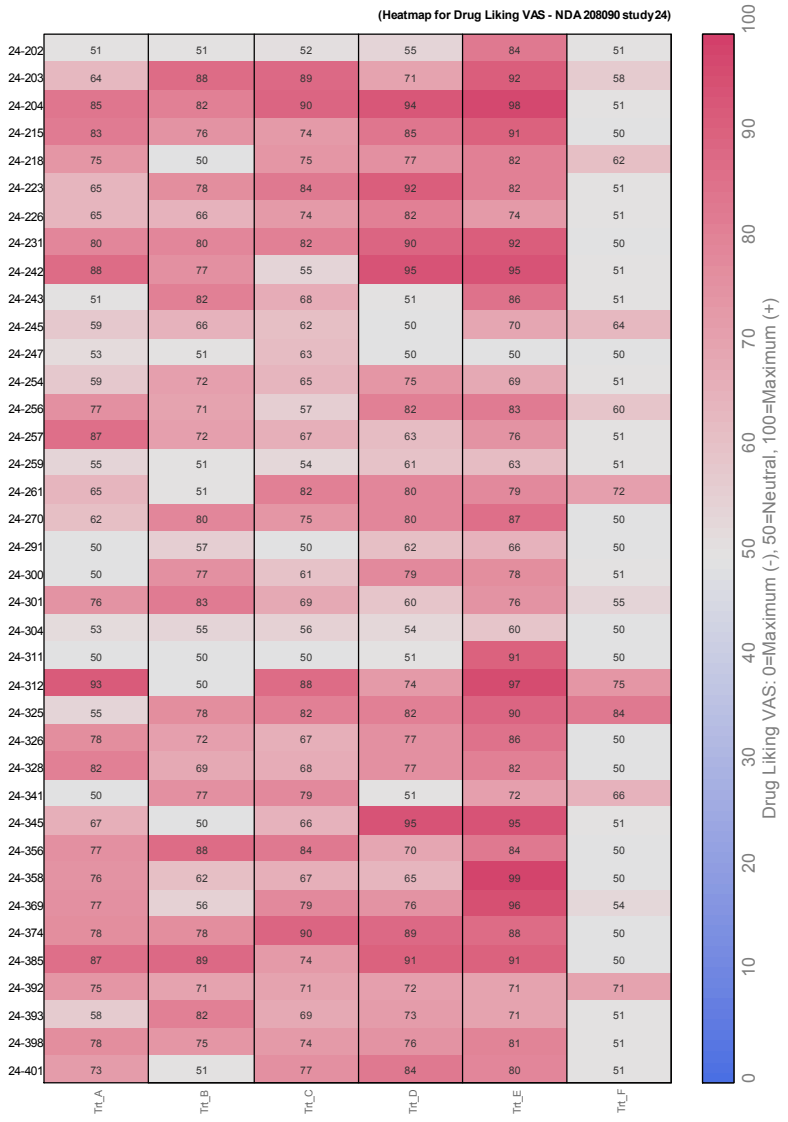


Figure 5. Heatmap for Emax of Drug High VAS by treatment

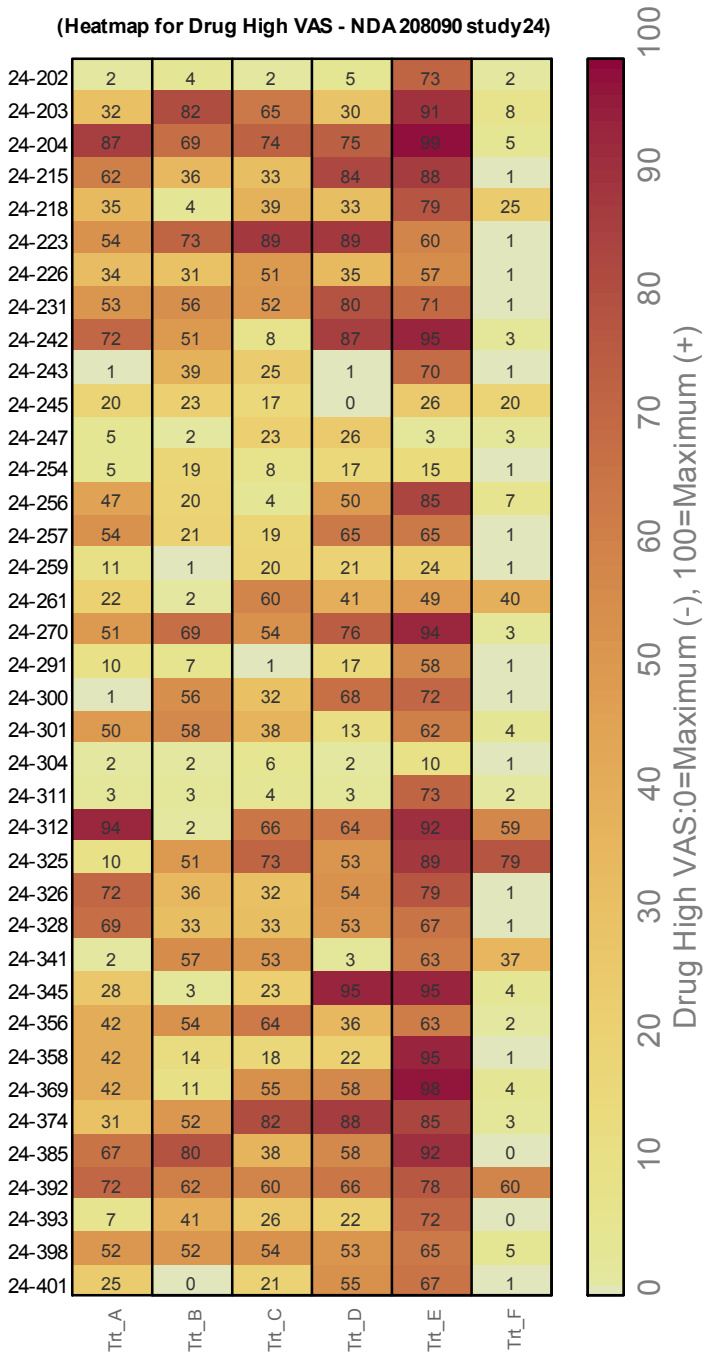
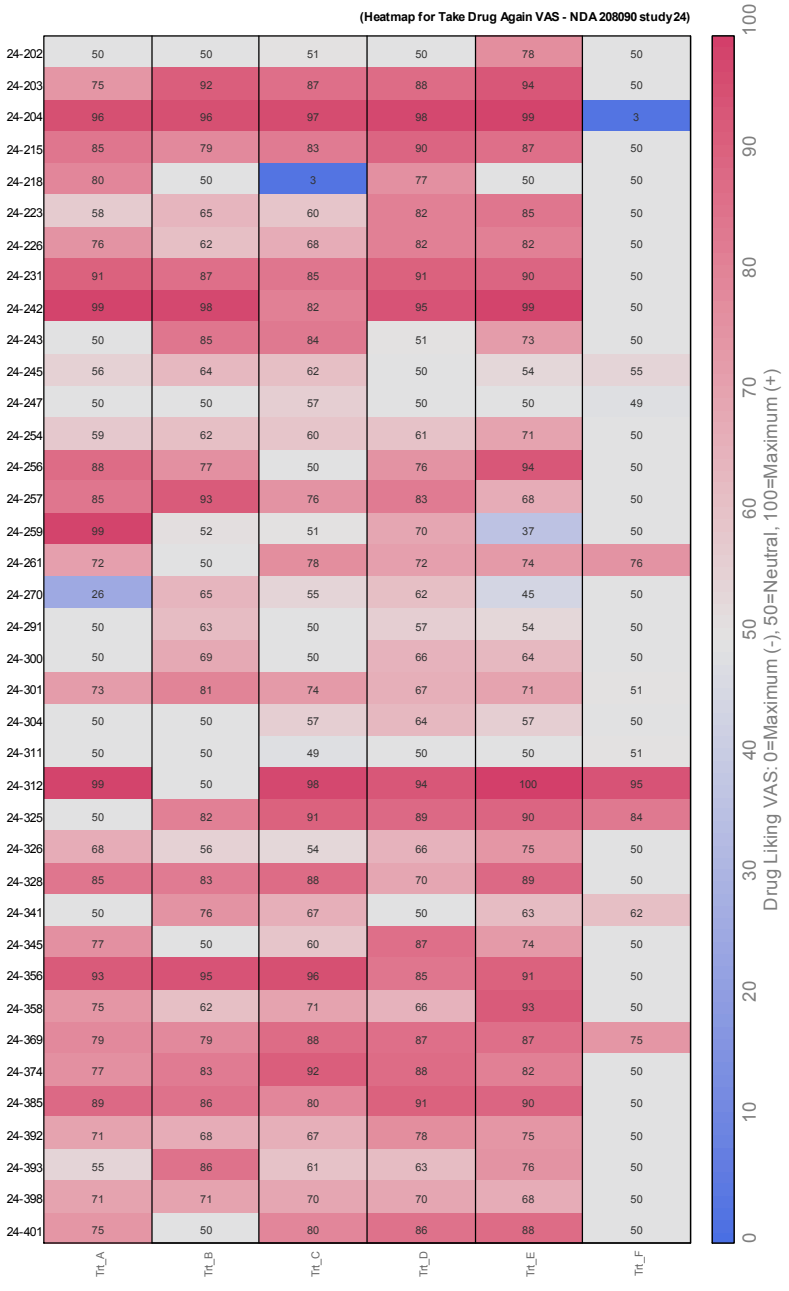


Figure 6. Heatmap for Emax of Take Drug Again VAS by treatment



2.3.2 Statistical Analysis

Analysis of Primary Endpoints for Primary Comparisons

The reviewer analyzed the hypotheses of the primary objective using the mixed-effect model, for the analysis of drug liking, drug high and take drug again, the reviewer used the model: treatment, period and sequence as fixed effects and subject nested within sequence as a random effect. For ARCI/MBG, since pre-dose is significant in the model testing, so the reviewer added pre-dose together with treatment, period and sequence as fixed effects and subject nested within sequence as a random effect.

Table 3 to table 6 are the analysis results for Emax of Drug Liking VAS, Drug High VAS, Take Drug Again and ARCI/MBG respectively. Table 7 is the summary statistical analysis of the mean difference in Emax for the primary comparisons.

From table 3 to table 7, we can see that for the comparisons between:

Trt E (Crushed IR Oxycodone Fasted) Vs Trt C (Chewed Oxycodone DETERx HFHC):

The Emax for Drug Liking VAS, Drug High VAS, Take Drug Again, and ARCI/MBG, were all significantly lower for chewed Oxycodone DETERx HFHC than crushed IR oxycodone fasted. The LS mean ± SEM (95% CI) Emax for Drug Liking for chewed Oxycodone DETERx HFHC was 70.73 ± 1.915 mm (66.95,74.51) compared with 81.56 ± 1.915 mm (77.78, 85.34) for crushed IR oxycodone fasted (P<0.0001). The LS mean ± SEM (95% CI) Emax for Drug high for chewed Oxycodone DETERx HFHC was 37.70 ± 4.080 mm (29.65,47.75) compared with 68.32 ± 4.080 mm (60.27, 76.38) for crushed IR oxycodone fasted (P<0.0001). The LS mean ± SEM (95% CI) Emax for Take Drug Again for chewed Oxycodone DETERx HFHC was 68.85 ± 2.66 mm (63.59, 71.10) compared with 74.73 ± 2.663 mm (69.47, 79.98) for crushed IR oxycodone fasted (P=0.0484).The LS mean ± SEM (95% CI) Emax for ARCI/MBG for chewed Oxycodone DETERx HFHC was 4.25 ± 0.740 mm (2.89, 5.82) compared with 7.25 ± 0.747 mm (5.77, 8.72) for crushed IR oxycodone fasted (P=0.0002).

Trt E (Crushed IR Oxycodone Fasted) vs Trt D (Chewed Oxycodone DETERx Fasted):

Except for Take Drug Again, the Emax for Drug Liking VAS, Drug High VAS and ARCI/MBG, were all significantly lower for chewed Oxycodone DETERx fasted than crushed IR oxycodone fasted. The LS mean ± SEM (95% CI) Emax for Drug Liking for chewed Oxycodone DETERx fasted was 73.83 ± 1.915 mm (70.05, 77.61) compared with 81.56 ± 1.915 mm (77.78, 85.34) for crushed IR oxycodone fasted (P=0.0007). The LS mean ± SEM (95% CI) Emax for Drug High for chewed Oxycodone DETERx fasted was 45.56 ± 4.080 mm (37.51, 53.61) compared with compared with 68.32 ± 4.080 mm (60.27, 76.38) for crushed IR oxycodone fasted (P<0.0001). The LS mean ± SEM (95% CI) Emax for Take Drug Again for chewed Oxycodone DETERx fasted was 73.63 ± 2.66 mm (68.38, 78.89) compared with 74.73 ± 2.663 mm (69.47, 79.98) for crushed IR oxycodone fasted (P=0.7105).The LS mean ± SEM (95% CI) Emax for ARCI/MBG for chewed Oxycodone DETERx fasted was 5.22 ± 0.740 mm (3.76, 6.68) compared with 7.25 ± 0.747 mm (5.77, 8.72) for crushed IR oxycodone fasted (P=0.0081).

Table 3. Statistical Analysis of the Mean Difference in Emax for Drug Liking for the primary comparisons (PD Population, N=38)

	LS Mean	StdE	Pr > |t|	Lower	Upper
Treatments					
C: CHEWED OXYCODONE DETERX 40MG HFHC	70.7275	1.9151	<.0001	66.9486	74.5065
D: CHEWED OXYCODONE DETERX 40MG FASTED	73.8299	1.9151	<.0001	70.0509	77.6089
E: CRUSHED IR OXYCODONE 40MG IN SOLUTION FASTED	81.5629	1.9151	<.0001	77.7839	85.3419
Contrasts (difference)					
1. Treatment E vs. Treatment C	10.8354	2.2465	<.0001	6.4026	15.2682
2. Treatment E vs. Treatment D	7.7331	2.2346	0.0007	3.3236	12.1425

Table 4. Statistical Analysis of the Mean Difference in Emax for Drug High for the primary comparisons (PD Population, N=38)

	LS Mean	StdE	Pr > |t|	Lower	Upper
Treatments					
C: CHEWED OXYCODONE DETERX 40MG HFHC	37.6983	4.0802	<.0001	29.6471	45.7495
D: CHEWED OXYCODONE DETERX 40MG FASTED	45.5583	4.0802	<.0001	37.5071	53.6095
E: CRUSHED IR OXYCODONE 40MG IN SOLUTION FASTED	68.3243	4.0802	<.0001	60.2731	76.3755
Contrasts (difference)					
1. Treatment E vs. Treatment C	30.6260	4.4937	<.0001	21.7588	39.4932
2. Treatment E vs. Treatment D	22.7660	4.4700	<.0001	13.9456	31.5864

Table 5. Statistical Analysis of the Mean Difference in Emax for Take Drug Again for the primary comparisons (PD Population, N=38)

	LS Mean	StdE	Pr > |t|	Lower	Upper
Treatments					
C: CHEWED OXYCODONE DETERX 40MG HFHC	68.8486	2.6630	<.0001	63.5938	74.1034
D: CHEWED OXYCODONE DETERX 40MG FASTED	73.6325	2.6630	<.0001	68.3777	78.8872
E: CRUSHED IR OXYCODONE 40MG IN SOLUTION FASTED	74.7259	2.6630	<.0001	69.4711	79.9807
Contrasts (difference)					
1. Treatment E vs. Treatment C	5.8773	2.9567	0.0484	0.04292	11.7116
2. Treatment E vs. Treatment D	1.0934	2.9411	0.7105	-4.7101	6.8970

Table 6. Statistical Analysis of the Mean Difference in Emax for ARCI/MBG for the primary comparisons (PD Population, N=38)

	LS Mean	StdE	Pr > |t|	Lower	Upper
Treatments					
C: CHEWED OXYCODONE DETERX 40MG HFHC	4.3546	0.7406	<.0001	2.8930	5.8162
D: CHEWED OXYCODONE DETERX 40MG FASTED	5.2170	0.7397	<.0001	3.7572	6.6768
E: CRUSHED IR OXYCODONE 40MG IN SOLUTION FASTED	7.2490	0.7471	<.0001	5.7747	8.7233
Contrasts (difference)					
1. Treatment E vs. Treatment C	2.8944	0.7644	0.0002	1.3858	4.4030
2. Treatment E vs. Treatment D	2.0320	0.7587	0.0081	0.5348	3.5293

Table 7. Summary Statistical Analysis of the Mean Difference in Emax for Drug Liking, Drug High, Take Drug Again and ARCI/MBG for the primary comparisons (PD Population, N=38)

Parameter	Comparisons	Chewed Oxycodone DETERx HFHC(Trt C) vs Crushed IR Oxycodone Fasted (Trt E)	Chewed Oxycodone DETERx Fasted(Trt D) vs Crushed IR Oxycodone Fasted (Trt E)
Emax for Drug Liking VAS	Mean difference from Trt E	10.84	7.73
	95% CI of the difference	6.40, 15.27	3.32, 12.14
	P-value	<0.0001	0.0007
Emax for Drug High VAS	Mean difference from Trt E	30.63	22.77
	95% CI of the difference	21.76,39,49	13.95, 31.59
	P-value	<0.0001	<0.0001
Emax for Take Drug Again VAS	Mean difference from Trt E	5.88	1.09
	95% CI of the difference	0.04, 11.71	4.71, 6.70
	P-value	0.048	0.71
Emax for ARCI/MBG	Mean difference from Trt E	2.89	2.03
	95% CI of the difference	1.39, 4.40	0.53, 3.53
	P-value	0.0002	0.0081

Table 8. Summary Statistical Analysis of the Mean Difference in TEmax for Drug Liking, Drug High, Take Drug Again and ARCI/MBG for the primary comparisons (PD Population, N=38)

Parameter	Comparisons	Chewed Oxycodone DETERx HFHC(Trt C) vs Crushed IR Oxycodone Fasted (Trt E)	Chewed Oxycodone DETERx Fasted(Trt D) vs Crushed IR Oxycodone Fasted (Trt E)
TEmax for Drug Liking	Mean difference from Trt E	-1.96	-2.41
	95% CI of the difference	-3.12, -0.79	-3.58, -1.25
	P-value	0.0012	<0.0001
TEmax for Drug High	Mean difference from Trt E	-2.04	-0.92
	95% CI of the difference	-3.33, -0.74	-2.21, 0.37
	P-value	0.0023	0.16
Emax for Take Drug Again VAS	Mean difference from Trt E	2.18	2.52
	95% CI of the difference	-1.26, 5.61	-0.89, 5.94
	P-value	0.213	0.147
TEmax for ARCI/MBG	Mean difference from Trt E	-0.50	0.47
	95% CI of the difference	-1.87, 0.87	-0.89, 1.84
	P-value	0.47	0.4929

From table 8, we can see that for the comparisons between:

Trt E (Crushed IR Oxycodone Fasted) Vs Trt C (Chewed Oxycodone DETERx HFHC): The TEmax for Drug Liking VAS and Drug High VAS were significantly longer for chewed Oxycodone DETERx HFHC than crushed IR oxycodone fasted (P=0.0012 and 0.0023 respectively). No significant differences were observed for Take Drug Again and ARCI/MBG.

Trt E (Crushed IR Oxycodone Fasted) vs Trt D (Chewed Oxycodone DETERx Fasted): The TEmax for Drug Liking VAS was significantly longer for chewed Oxycodone DETERx fasted than crushed IR oxycodone fasted. No significant differences were observed for Drug High, Take Drug Again and ARCI/MBG.

Percentage Reduction Analysis

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

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

where ci, ti, and pi, are the Drug Liking Emax values for the control, crushed IR oxycodone fasted (Treatment E), test, chewed Oxycodone DETERx HFHC (Treatment C) or chewed

Oxycodone DETERx fasted (Treatment D), and the placebo HFHC (Treatment F), respectively; from the ith subject; and n is the sample size.

Chewed Oxycodone DETERx HFHC (Trt C) vs Crushed IR Oxycodone Fasted (Trt E):

From Table 9 and Figure 7, 30 out of the 38 subjects who completed the study (~79%) had some reduction in Drug Liking with Chewed Oxycodone DETERx HFHC (Trt C) compare to Crushed IR Oxycodone Fasted (Trt E), while 21% subjects had no reduction or negative reduction. 18 subjects (~47%) had at least 30% reduction in Drug Liking with Chewed Oxycodone DETERx HFHC (Trt C) and 11 subjects (~29%) had at least 50% reduction.

Chewed Oxycodone DETERx Fasted (Trt D) vs Crushed IR Oxycodone Fasted (Trt E):

Table 10 and Figure 8, 25 out of 38 of subjects (66%) showed some reduction in Drug Liking with Chewed Oxycodone DETERx Fasted(Trt D) compare to Crushed IR Oxycodone Fasted (Trt E), while 34% of the subjects had no reduction or negative reduction in Drug Liking. At least a 30% and 50% reduction in Drug Liking with Chewed Oxycodone DETERx Fasted (Trt D) compare to Crushed IR Oxycodone Fasted were 31.6% and 23.7% of subjects respectively.

Table 9. **%reduction, Drug Liking VAS, Chewed Oxycodone DETERx HFHC (Trt C) vs Crushed IR Oxycodone Fasted (Trt E) (PD population, N=38)**

Percentage of Reduction (%)	Frequency	Percentage of subjects (%)
>0	30	78.95
≥10	26	68.42
≥20	23	60.53
≥30	18	47.37
≥40	15	39.47
≥50	11	28.95
≥60	9	23.68
≥70	4	10.53
≥80	4	10.53
≥90	3	7.89
≥100	2	5.26

Figure 7. %reduction, Drug Liking VAS, Chewed Oxycodone DETERx HFHC (Trt C) vs Crushed IR Oxycodone Fasted (Trt E)

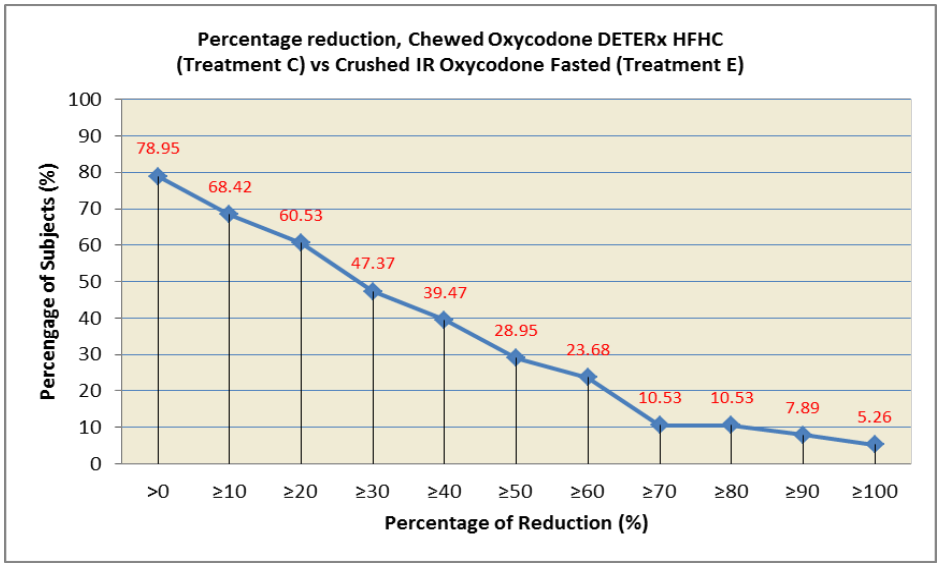


Table 10: %reduction, Drug Liking VAS, Chewed Oxycodone DETERx Fasted (Trt D) vs Crushed IR Oxycodone Fasted (Trt E)

Percentage of Reduction (%)	Frequency	Percentage of subjects (%)
>0	25	65.79
≥10	21	55.26
≥20	15	39.47
≥30	12	31.58
≥40	12	31.58
≥50	9	23.68
≥60	8	21.05
≥70	4	10.53
≥80	3	7.89
≥90	2	5.26
≥100	0	0

Figure 8. %reduction, Drug Liking VAS, Chewed Oxycodone DETERx Fasted (Trt D) vs Crushed IR Oxycodone Fasted (Trt E)

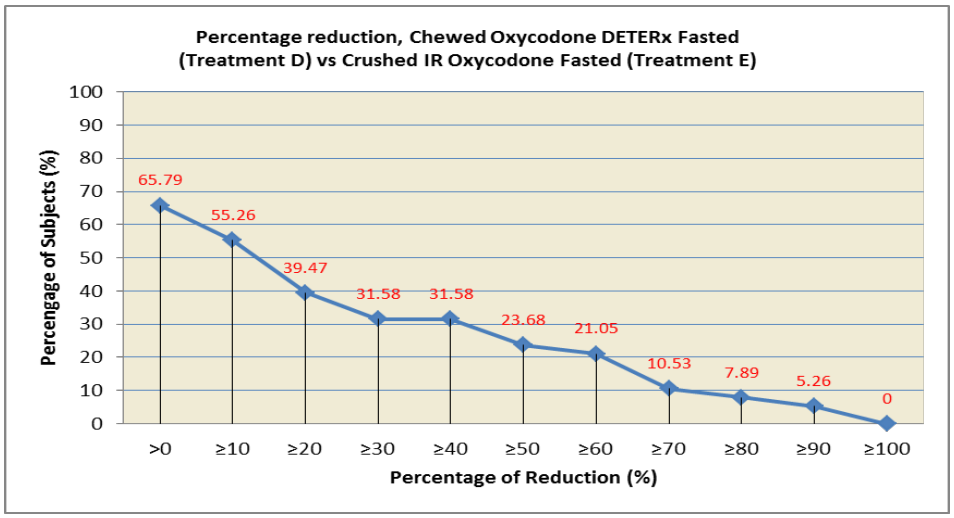


Figure 9. %reduction, Drug Liking VAS (PD population, N=38)

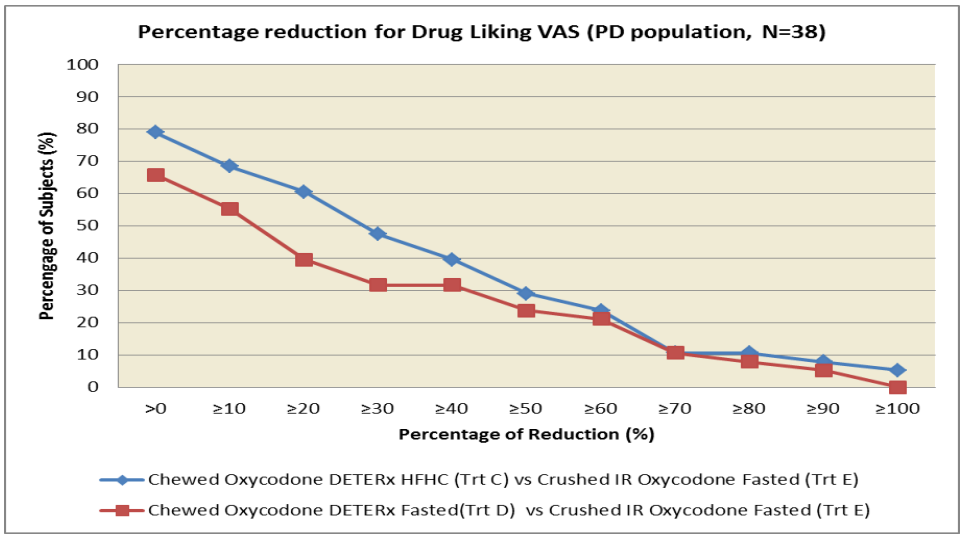


Figure 9 shows the combined percent reduction for the two primary comparisons. In the sponsor's labeling file, Figure 1 shows the percentage reduction for Treatment E vs Treatment A and treatment E vs Treatment C. The reviewer asked sponsor to show the percentage reduction for the two primary comparisons, i.e. Figure 9 in the reviewer's report, Treatment E vs Treatment D and treatment E vs Treatment C.

2.3.3 Food effect and manipulation effect comparisons

By CSS request, the reviewer also did food effect and manipulation effect comparisons.

To determine if there is a food effect, we are interested in the following comparisons:

Trt A vs Trt B

Trt C vs Trt D

To determine if the effect of manipulation (chewing) compared to intact (non-manipulated), we are interested in the following comparisons:

Trt A vs Trt C

Trt B vs Trt D

The following tables show the comparison results for the food effect and manipulation effect comparisons.

Table 11. Statistical Analysis of the Mean Difference in Emax for Drug Liking for the food effect and manipulation effect comparisons (PD Population, N=38)

	LS Mean	StdE	Pr > |t|	Lower	Upper
Treatments					
A: INTACT OXYCODONE DETERX 40MG HFHC	68.9368	1.9151	<.0001	65.1578	72.7158
B: INTACT OXYCODONE DETERX 40MG FASTED	69.3090	1.9151	<.0001	65.5300	73.0880
C: CHEWED OXYCODONE DETERX 40MG HFHC	70.7275	1.9151	<.0001	66.9486	74.5065
D: CHEWED OXYCODONE DETERX 40MG FASTED	73.8299	1.9151	<.0001	70.0509	77.6089
food effect (difference)					
1. Treatment A vs. Treatment B	-0.3722	2.2346	0.8679	-4.7816	4.0372
2. Treatment C vs. Treatment D	-3.1023	2.2346	0.1668	-7.5117	1.3071
manipulation effect (difference)					
1. Treatment A vs. Treatment C	-1.7907	2.2465	0.4264	-6.2235	2.6421
2. Treatment B vs. Treatment D	-4.5208	2.2465	0.0457	-8.9537	-0.08803

Table 12. Statistical Analysis of the Mean Difference in Emax for Drug High for the food effect and manipulation effect comparisons (PD Population, N=38)

	LS Mean	StdE	Pr > |t|	Lower	Upper
Treatments					
A: INTACT OXYCODONE DETERX 40MG HFHC	37.3172	4.0802	<.0001	29.2660	45.3684
B: INTACT OXYCODONE DETERX 40MG FASTED	34.9554	4.0802	<.0001	26.9042	43.0066
C: CHEWED OXYCODONE DETERX 40MG HFHC	37.6983	4.0802	<.0001	29.6471	45.7495
D: CHEWED OXYCODONE DETERX 40MG	45.5583	4.0802	<.0001	37.5071	53.6095

FASTED					
food effect (difference)					
1. Treatment A vs. Treatment B	2.3618	4.4700	0.5979	-6.4586	11.1822
2. Treatment C vs. Treatment D	-7.8600	4.4700	0.0804	-16.6804	0.9604
manipulation effect (difference)					
1. Treatment A vs. Treatment C	-0.3811	4.4937	0.9325	-9.2483	8.4861
2. Treatment B vs. Treatment D	-10.6029	4.4937	0.0194	-19.4701	-1.7357

Table 13. Statistical Analysis of the Mean Difference in Emax for Take Drug Again for the food effect and manipulation effect comparisons (PD Population, N=38)

	LS Mean	**StdE**	**Pr > |t|**	**Lower**	**Upper**
Treatments					
A: INTACT OXYCODONE DETERX 40MG HFHC	70.4588	2.6630	<.0001	65.2040	75.7136
B: INTACT OXYCODONE DETERX 40MG FASTED	70.3956	2.6630	<.0001	65.1408	75.6504
C: CHEWED OXYCODONE DETERX 40MG HFHC	68.8486	2.6630	<.0001	63.5938	74.1034
D: CHEWED OXYCODONE DETERX 40MG FASTED	73.6325	2.6630	<.0001	68.3777	78.8872
food effect (difference)					
1. Treatment A vs. Treatment B	0.06326	2.9411	0.9829	-5.7403	5.8668
2. Treatment C vs. Treatment D	-4.7838	2.9411	0.1056	-10.5874	1.0197
manipulation effect (difference)					
1. Treatment A vs. Treatment C	1.6102	2.9567	0.5867	-4.2241	7.4445
2. Treatment B vs. Treatment D	-3.2369	2.9567	0.2751	-9.0712	2.5975

Table 14. Statistical Analysis of the Mean Difference in Emax for ARCI/MBG for the food effect and manipulation effect comparisons (PD Population, N=38)

	LS Mean	**StdE**	**Pr > |t|**	**Lower**	**Upper**
Treatments					
A: INTACT OXYCODONE DETERX 40MG HFHC	4.3430	0.7406	<.0001	2.8815	5.8045
B: INTACT OXYCODONE DETERX 40MG FASTED	4.5963	0.7397	<.0001	3.1365	6.0560

C: CHEWED OXYCODONE DETERX 40MG HFHC	4.3546	0.7406	<.0001	2.8930	5.8162
D: CHEWED OXYCODONE DETERX 40MG FASTED	5.2170	0.7397	<.0001	3.7572	6.6768
food effect (difference)					
1. Treatment A vs. Treatment B	-0.2533	0.7541	0.7374	-1.7414	1.2348
2. Treatment C vs. Treatment D	-0.8624	0.7540	0.2543	-2.3504	0.6256
manipulation effect (difference)					
1. Treatment A vs. Treatment C	-0.01161	0.7606	0.9878	-1.5127	1.4894
2. Treatment B vs. Treatment D	-0.6207	0.7569	0.4133	-2.1145	0.8730

Table 11 to table 14 show that for food effect comparison there is no food effect for Drug liking, drug high, take drug again and ARCI/MBG (P values are all >0.05). For manipulation effect, there is no manipulation effect between treatment A and treatment C for Drug liking, drug high, take drug again and ARCI/MBG (P values are all >0.05). There are some manipulation effect difference between treatment B and treatment D for Drug liking and drug high (P=0.0457 and 0.0194 respectively). No significant manipulation effect differences were found for take drug again and ARCI/MBG.

3. Conclusions

The primary objective of this study was to evaluate the abuse potential and PK of Oxycodone DETERx 40 mg intact in the fed state, Oxycodone DETERx 40 mg intact in the fasted state, Oxycodone DETERx 40 mg chewed in the fed state, Oxycodone DETERx 40 mg chewed in the fasted state, and IR oxycodone 40 mg crushed in the fasted state.

The study was validated by the comparison of Drug Liking Emax for crushed IR oxycodone fasted to placebo HFHC. The results from the statistical reviewer's analyses establish that:

For Trt E (Crushed IR Oxycodone Fasted) Vs Trt C (Chewed Oxycodone DETERx HFHC):

- The Emax for Drug Liking VAS, Drug High VAS, Take Drug Again, and ARCI/MBG, were all significantly lower for chewed Oxycodone DETERx HFHC than crushed IR oxycodone fasted.
- The TEmax for Drug Liking VAS and Drug High VAS were significantly longer for chewed Oxycodone DETERx HFHC than crushed IR oxycodone fasted (P=0.0012 and 0.0023 respectively). No significant differences were observed for Take Drug Again and ARCI/MBG.
- Around 79% subjects showed some reduction in Drug Liking with Chewed Oxycodone DETERx HFHC (Trt C) compare to Crushed IR Oxycodone Fasted (Trt E), while 21% subjects had no reduction or negative reduction. In addition 47% and 29% of the subjects had

at least 30% and 50% reduction in Drug Liking with Chewed Oxycodone DETERx HFHC (Trt C) compare to Crushed IR Oxycodone Fasted (Trt E).

For Trt E (Crushed IR Oxycodone Fasted) vs Trt D (Chewed Oxycodone DETERx Fasted):

- Except for Take Drug Again, the Emax for Drug Liking VAS, Drug High VAS and ARCI/MBG, were all significantly lower for chewed Oxycodone DETERx fasted than crushed IR oxycodone fasted. No significant difference was observed for Take Drug Again for the Emax of Drug Liking VAS.

- The TEmax for Drug Liking VAS was significantly longer for chewed Oxycodone DETERx fasted than crushed IR oxycodone fasted (P<0.0001). No significant differences were observed for Drug High, Take Drug Again and ARCI/MBG.

- About 66% of the subjects showed some reduction in Drug Liking with Chewed Oxycodone DETERx Fasted (Trt D) compare to Crushed IR Oxycodone Fasted (Trt E), while 34% of the subjects had no reduction or negative reduction in Drug Liking. At least a 30% and 50% reduction in Drug Liking with Chewed Oxycodone DETERx Fasted (Trt D) compare to Crushed IR Oxycodone Fasted were 31.6% and 23.7% of subjects respectively.

Additional comments:

5. In the sponsor's labeling file, Figure 1 shows the percentage reduction for Treatment E vs Treatment A and treatment E vs Treatment C. The reviewer asked sponsor to show the percentage reduction for the two primary comparisons instead, i.e. Treatment E vs Treatment D and treatment E vs Treatment C.

6. There is no food effect for Drug liking, drug high, take drug again and ARCI/MBG (P values are all >0.05). For manipulation effect, there is no manipulation effect between treatment A and treatment C for Drug liking, drug high, take drug again and ARCI/MBG (P values are all >0.05). There are some manipulation effect difference between treatment B and treatment D for Drug liking and drug high (P=0.0457 and 0.0194 respectively). No significant manipulation effect differences were found for take drug again and ARCI/MBG.

7. For the statistical analysis of ARCI/MBG, the baseline value is significant (P value <0.05), you should include baseline value as a covariate in the model fitting.

8. The new ADF guidance has published in April 2015, in the future, you should follow the new guidance.

4. References

1) Guidance for Industry: Assessment of Abuse Potential for Drugs (January 2010) http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf

2) Guidance for Industry: Abuse Deterrent Opioids – Evaluation and Labeling (January 2013)

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf

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

4) Abuse-Deterrent Opioids — Evaluation and Labeling Guidance for Industry

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf

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/s/

ANNA SUN
06/01/2015

QIANYU DANG
06/01/2015

YI TSONG
06/02/2015