

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
201655Orig1s000

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: 201-655
Drug Name: Oxymorphone HCl-ER, (b) (4)
Study number: EN3288-109
Applicant: Endo Pharmaceuticals, Inc.
Date(s): Filing Mtg: 11/04/10
PDUFA date: 01/07/11
Completion date: 12/06/10
Review Priority: S
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Keywords: Crossover design; Drug abuse potential study; Self-reported endpoint; Multiple endpoints

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1. Executive Summary

Study EN3288-109 in NDA 201655 was a randomized, single-dose, double-blind, double-dummy, four-sequence, four-period, crossover study to evaluate the relative bioavailability and subjective effects of EN 3288 40 mg administered intact and after mastication compared with OPANA® ER 40 mg administered after mastication and with OPANA® 40 mg (4x10mg) administered intact in healthy nondependent recreational oral prescription opioid user experienced in mastication of extended-release opioid formulations.

There were four treatments in the study: EN 3288 40 mg – Intact, EN3288 40 mg - tablet ingested after mastication, OPANA® 40 mg IR (4x10 mg) – intact, and OPANA® ER 40 mg - tablet ingested after mastication. The comparisons of interest in this study were EN40 3288 40 after mastication versus other three treatments on the subjective abuse potential measures: Drug Liking VAS, Any Drug Effects, Good Drug Effects VAS, High VAS, Overall Drug Liking VAS, Take Drug Again VAS, ARCI MBG, Bad Effects VAS, Sick VAS and Difficulty Chewing VAS as well as Overall Chewing Experience VAS. The primary endpoint of interest in this review was Emax which was defined as the maximum response during 8 hours after dosing or the maximum of change from predose response during 8 hours after dosing if predose response is meaningful, for example, High VAS, and ARCI MBG.

A total of 41 subjects completed the study and were included in this reviewer's statistical analysis.

The reviewer's analysis showed that

- EN 3288 40 mg administered after mastication generated significantly larger drug liking, any effects, good effects, high, euphoria effect, and overall drug liking than EN3288 40 mg administered intact. There was no significant difference on Bad Effects VAS and Sick VAS in this comparison. Overall subjects wanted to administer EN 3288 40 mg after mastication more than to administer EN 3288 40 mg intact.
- EN 3288 40 mg administered after mastication produced significantly lower any effects, good effects and high than OPANA® 40 mg IR (4x10 mg) – intact and OPANA® ER 40 mg administered after mastication. However, such reduced effects were not seen for Drug Liking VAS, Overall Drug Liking VAS, Take Drug Again VAS, Bad Effects VAS and Sick VAS in these comparisons, and the least square means of the responses to EN 3288 40 mg administered after mastication on Good Effects VAS and High VAS are still considered large (72.78 ± 4.18 and 76.37 ± 4.12 , respectively) in the unidirectional visual analog scale.
- EN 3288 40 mg was significantly more difficult to chew than OPANA® ER 40 mg. However, there was no significant difference on overall chewing experience between EN 3288 40 mg and OPANA® ER 40 mg administered after mastication. Overall, subjects disliked the chewing experience for both drugs.

2. Review Report on Study EN3288-109

2.1 Overview

2.1.1 Objectives of the study

Primary objectives

The primary objective of this study was to evaluate the relative bioavailability (rate and extent of absorption) of EN3288 40 mg when administered intact and after mastication compared with OPANA ER 40 mg (administered after mastication) and OPANA 40 mg (4×10 mg) (administered intact) under fasted conditions in healthy, nondependent, recreational oral prescription opioid users experienced in mastication of opioid formulations.

Secondary objectives

The secondary objective of this study was to evaluate the subjective effects of EN3288 40 mg administered after mastication compared with EN3288 40 mg administered intact, OPANA ER 40 mg administered after mastication, and OPANA 40 mg (4×10 mg) administered intact in healthy, nondependent, recreational oral prescription opioid users experienced in mastication of opioid formulations. In addition, this study evaluated the tamper-resistant qualities of EN3288, and explored other potential methods of oral abuse of prescription opioids as described by the recreational oral prescription opioid users.

Reviewer's comment: This review report is only for the secondary objectives of the study.

2.1.2 Study design

This was a randomized, double-blind, double-dummy, 4-sequence, 4-period, single-dose, crossover study in healthy, nondependent, recreational oral prescription opioid users experienced in mastication of opioid formulations. Each subject participated in a screening visit, a qualification phase, and a treatment phase consisting of 4 treatment periods. The washout period between two treatments in the treatment phase was at least 72 hours.

There were four treatments in the study. These treatments were

- A: EN3288 40 mg – intact
- B: EN3288 40 mg – tablet ingested after mastication
- C: OPANA ER 40 mg – tablet ingested after mastication
- D: OPANA 40 mg IR (4x10 mg) – intact (reference product)

Four treatment sequences ABCD, BCDA, CDAB, DABC, were used in the study.

Reviewer's comments: The Sponsor reported that in the treatment phase, subjects were randomized to 1 to 4 treatment sequences based on a William's design (see page 30 on EN3288-109 report). However, the design stated in Sponsor's Table 5 (on page 30 of the study report) is not a William's design.

Data were collected for VAS “at this moment” measures and balanced measures, and ARCI MBG at hours -1, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24. For Overall Drug Liking VAS, for measures: Take Drug Again, and Price Value Assessment, data were collected at hours 8 and 24. Data for Pupillometry were collected at hours, -1, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24. Data for Difficult Chewing VAS and Overall Chewing Experience VAS were collected at hour 0.5.

2.1.3 Abuse Potential Measures

The Sponsor studied the following abuse potential measures:

Visual Analog Scale

Drug Liking (‘at this moment’), Good Effects, Bad Effects, Any Drug Effects, High, Overall Drug liking, Take Drug Again, Sick, Difficulty Chewing and Overall Chewing Experience.

ARCI (Addiction Research Center Inventory) short form

ARCI MBG (euphoria effect)

The sponsor also included Pupillometry and Price Value Assessment in the study.

The following summary parameters were calculated for all assessments except for pupillometry and VAS Overall Drug Liking and Take Drug Again: Emax (peak effect), tEmax (time of peak effect), AUE_{0-2h} (area under the effect curve to 2 hours), AUE_{0-8h}, AUE_{0-24h}.

For VAS Overall Drug Liking, Take Drug Again, and Price Value Assessment, the mean per treatment and peak response over all treatments were calculated. For the chewing experience VAS, the responses were summarized.

The following summary parameters were calculated for pupillometry: PCmin (apparent minimum postdose pupil diameter, PTmin (time to reach the apparent minimum diameter), PT25 (time to reach at least 25% reduction in pupil diameter from baseline, PAOC0-2h (the area over the curve to 2 hours, relative to the baseline), PAOC0-8h, PAOC0-24h.

2.1.4 Number of subjects

In the qualification phase, 51 subjects were exposed to 30 mg doses of OPANA immediate release formulation. Forty-three qualified subjects were randomized into the treatment phase, and 41 subjects completed all 4 treatment periods of the study. The pharmacodynamic population included 41 subjects.

2.1.5 Statistical Methodologies Used in the Sponsor’s Analyses

PD variables for each treatment period were derived from the pharmacodynamic assessments. In the calculation, actual sample times (hours, relative to the corresponding drug administration time) were used instead of planned time points. For each treatment period in the treatment phase, the time the subject swallowed the intact tablets was considered time zero. Each PD measure at each time during treatment phase was summarized by treatment (A, B, C, and D) using

appropriate statistics. The derived pharmacodynamic variables were summarized by treatment for qualification phase (if applicable) and treatment phase, respectively. All the assessments and the derived variables data were presented in the individual listings as well. A linear mixed effects model was fit to each endpoint with treatment, period, and sequence as fixed effects, baseline (predose) measurements as a covariate where applicable, and subject nested in sequence as a random effect. The endpoints were derived pharmacodynamic variables Emax, AUE0-t for VAS and ARCI, PCmin, PAOC0-t for Pupillometry, the scores of VAS Overall Drug Liking, Taken Drug Again, Chewing Experience and Price Value Assessment Questionnaires.

Reviewer's Comments: In the reviewer's analyses, Emax is defined as the maximum response during 8 hours after dosing of an abuse potential measure or the maximum of change from predose response during 8 hours after dosing if predose response is meaningful, for example, High VAS, and ARCI MBG. This reviewer found that the calculation of Emax from the sponsor was based on maximum response during 24 hours, and the Emax calculated was not adjusted by predose responses, even if the predose responses had been collected.

2.1.5 Sponsor's results and conclusion

The Sponsor reported the following results:

- The evaluation of pharmacodynamic assessment was valid as Emax for VAS Drug Liking (both 'At This Moment' and 'Overall') was significantly different between the OPANA 4×10 mg intact and EN3288 intact treatments.
- On measures of positive and balance effects, EN3288 masticated induced numerically lower Emax and AUE0-2h than OPANA ER masticated and OPANA 4×10 mg intact, however, the difference was statistically significant only on some of the "at the moment" assessments (VAS Good Effects, VAS High, and VAS Drug Liking [AUE0-2 only]). The difference was not significant on any of the "end of the day" measures.
- On measures of positive and balanced effects, administration of EN3288 intact was associated with significantly lower positive effects than administration of EN3288 masticated, OPANA ER masticated, and OPANA 4×10 mg intact.
- On measures of positive and balanced effects, the median time to reach Emax was within 2 hours postdose for all treatments.
- On the measure of negative effects, all treatments were associated with similar level of unpleasant responses and no consistent differentiation between treatments was noted.
- Administration of all treatments was associated with decreased pupil diameter, with EN3288 intact inducing the smallest maximum change from pre-dose in comparison to the remaining treatments.
- Chewing EN3288 was more difficult than chewing OPANA ER or placebo. The overall chewing experience for EN3288 and OPANA ER was disliked compared to placebo but there was no significant difference between these treatments.
- On individual interview questionnaires, oxycodone had the highest rate of abuse, with subjects clearly preferring that over morphine, codeine, oxymorphone, or other prescription opioids.
- The majority of subjects abuse oxycodone by swallowing (intact and after chewing) and chewing as major routes methods of abuse, however, the preferred route is swallowing whole.

The Sponsor concluded that

- Mastication did partially reduce the extended-release properties of EN3288 and OPANA ER. The relative ranking for decreasing C_{max} and increasing T_{max} is as follows: immediate release formulation (intact OPANA 4×10 mg) < OPANA ER 40 mg masticated < EN3288 40 mg masticated < EN3288 40 mg intact. Relative to EN3288, mastication of EN3288 increased oxymorphone C_{max} by 122% in comparison to administration of EN3288 intact.
- There were no new implications from the safety evaluation for the intended uses of extended-release EN3288 tablets. Overall, it can be concluded that the mastication of EN3288 is associated with subjective and objective drug effects similar to OPANA ER and OPANA. However, the new (b) (4) formulation was significantly more difficult to masticate. Further, based on the results of the interview questionnaire, subjects mostly abused oxycodone by swallowing whole and chewing in similar proportions. No new methods of tampering became apparent through the results of the interview sessions.
- At least 1 treatment-related TEAE occurred in 92% of subjects. The following TEAEs occurred in generally increasing numbers from treatment A to treatment D: pruritus, nausea, vomiting, headache, somnolence, and dizziness. There was 1 SAE reported for 1 subject while taking placebo during the qualification phase. All treatment-related TEAEs had been identified in OPANA ER labeling.

2.2 Data Location

The analysis dataset is located the sponsor's electronic submission Section 5.3.1.2.25.3.1. However, the sponsor did not include original data recorded at scheduled time points. An analysis dataset request was sent to the Sponsor on November 9, 2010, and the requested dataset was posted on November 12, 2010 at the location:

<\\CDSESUB1\EVSPROD\NDA201655\201655.enx>

2.3 Reviewer's Analysis

2.3.1 Descriptive statistics

Tables 1-3 summarizes the mean, standard error, minimum, the first quartile (Q₁), median, the third quartile (Q₃), and maximum for the abuse potential measures considered in this reviewer's analysis.

This reviewer categorized abuse potential measures of interest into three categories:

1. "At this moment" measures: Drug Liking VAS Any Effects VAS, Good Effects VAS, High VAS, ARCI MBG, Bad Effects VAS, and Sick VAS;
2. Overall measures: Take Drug Again VAS and Overall Drug Liking VAS;
3. Chewing Experience Measures: Difficult Chewing VAS and Overall Chewing Experience VAS.

Table 1: Summary Statistics for Emax on “At This Moment” Measures (N=41)

Abuse Potential Measure	TRT	Mean	StdErr	Min	Q1	Med	Q3	Max
Drug Liking VAS	EN40_I	62.08	3.27	0	50.85	58.6	74.8	100
	EN40_M	79.70	3.19	0	69.9	85.7	93.6	100
	O40I_I	82.46	2.43	49.9	72.55	86.5	97.75	100
	O40E_M	82.04	2.63	49.4	72.15	84.4	100	100
Good Drug Effects VAS	EN40_I	45.75	5.48	0	7.9	51.3	75.55	100
	EN40_M	72.98	4.64	0	57.5	83	99	100
	O40I_I	84.44	2.97	26	75.05	89.4	100	100
	O40E_M	83.45	3.01	22.1	76.3	87	100	100
High VAS	EN40_I	43.75	5.55	0	9.4	43.9	75.65	100
	EN40_M	76.49	4.45	0	62.45	87.5	100	100
	O40I_I	88.53	2.97	24.4	85	100	100	100
	O40E_M	85.97	3.25	7.8	75.6	100	100	100
ARCI MBG	EN40_I	5.05	0.83	0	0	3	9	16
	EN40_M	7.98	0.73	0	4	9	11	16
	O40I_I	8.29	0.78	0	4	9	12	16
	O40E_M	8.59	0.77	0	4.5	9	13	16
Bad Effects VAS	EN40_I	15.51	4.04	0	0	1.3	19.85	100
	EN40_M	22.88	4.12	0	0	8.5	44.85	82.3
	O40I_I	25.64	4.67	0	0	9.1	55.6	93.5
	O40E_M	24.30	4.86	0	0	6.2	52.75	89.2
Sick VAS	EN40_I	10.81	2.90	0	0	0	16.65	75.1
	EN40_M	19.28	4.24	-4.1	0	11	25.9	100
	O40I_I	20.55	4.92	-51.1	0	6.7	34	100
	O40E_M	13.75	3.87	0	0	0	16.65	100

Table 2: Summary Statistics for Emax on Overall Measures (N=41)

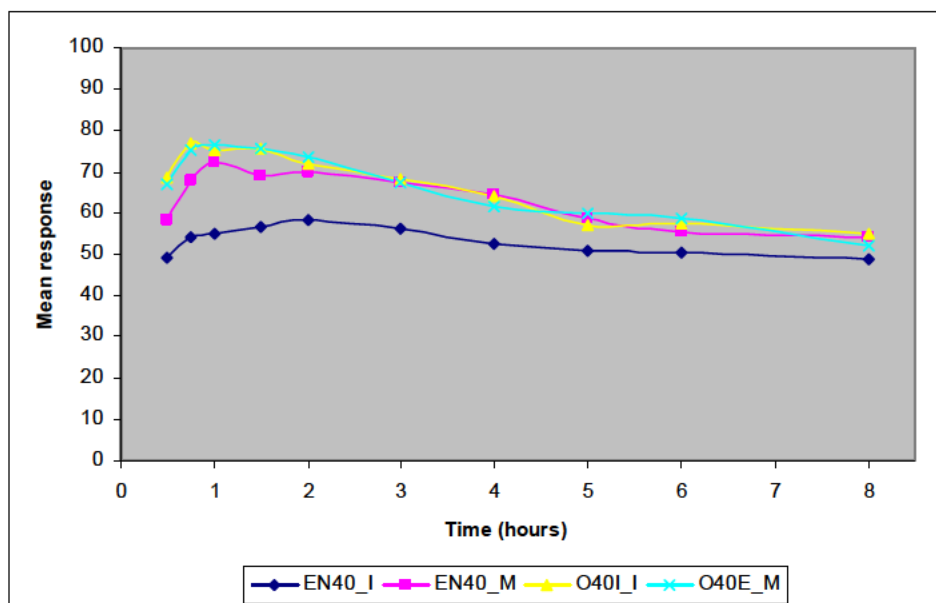
Abuse Potential Measure	TRT	Mean	StdErr	Min	Q1	Med	Q3	Max
Overall Drug Liking VAS	EN40_I	54.98	3.56	0	49.9	51	65.65	100
	EN40_M	69.05	3.71	0	50.3	75.1	85.45	100
	O40I_I	70.90	3.39	16.2	53.35	71.1	89.7	100
	O40E_M	71.53	3.69	15.2	50	78	89.55	100
Take Drug Again VAS	EN40_I	55.55	3.62	0	50	55.6	71.5	100
	EN40_M	69.22	3.91	0	50.5	74.1	88.65	100
	O40I_I	72.56	3.40	13.9	51.9	73.2	92.25	100
	O40E_M	71.36	4.18	10.7	50.4	75	98.25	100

Table 3: Summary Statistics for Emax on Chewing Experience (N=41)

Abuse Potential Measure	TRT	Mean	StdErr	Min	Q1	Med	Q3	Max
Difficult Chewing VAS	EN40_I	10.62	3.04	0	0	0	14.2	74.3
	EN40_M	95.54	1.23	70.3	93.25	100	100	100
	O40I_I	9.00	3.20	0	0	0	9.35	100
	O40E_M	16.10	4.00	0	0	1.5	22.45	83.8
Overall Chewing Experience VAS	EN40_I	49.41	2.82	0	48.7	50	50.4	94.2
	EN40_M	19.81	4.08	0	0	12.6	28.4	100
	O40I_I	54.42	3.20	20.4	49.65	50.3	60.6	100
	O40E_M	26.89	3.97	0	0	20	49.5	89.1

Figures 1-4 are mean time course profiles for Drug Liking VAS, Good Drug VAS, High VAS, and ARCI MBG. These figures show that the mean time course profiles of EN40_I separated from those from EN40_M, O40E_M and O40I_I, and the mean time course profiles from O40I_I and O40E_M are very close to each other. The profile from EN40_M is lower than those of both O40I_I and O40E_M in early hours, especially for Good Effects VAS and High VAS.

Figure 1: Mean Time Course Profiles for Drug Liking VAS (N=41)



Note: Drug Liking VAS is on a bipolar scale.

Figure 2: Mean Time Course Profiles for Good Effects VAS (N=41)

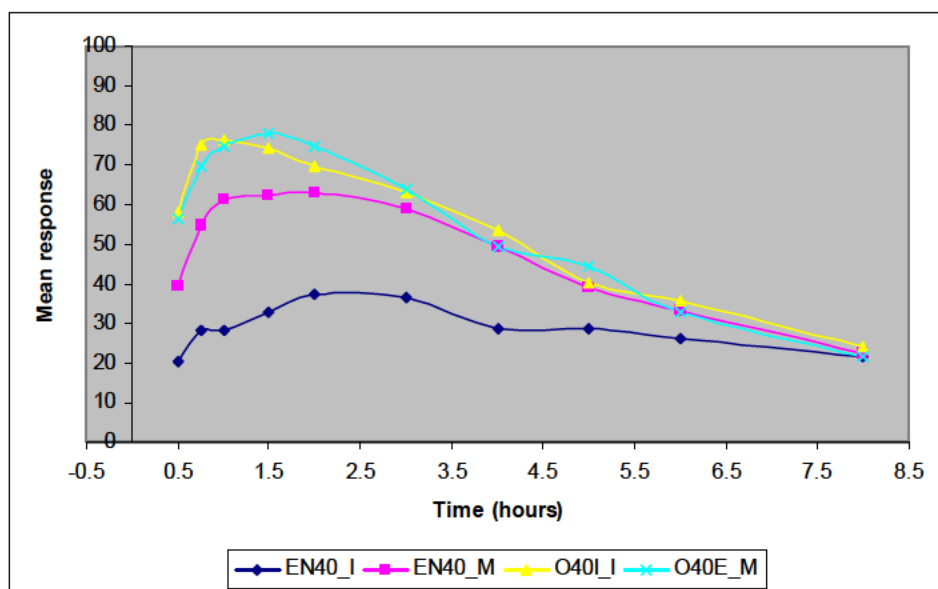


Figure 3: Mean Time Course Profiles for High VAS (N=41)

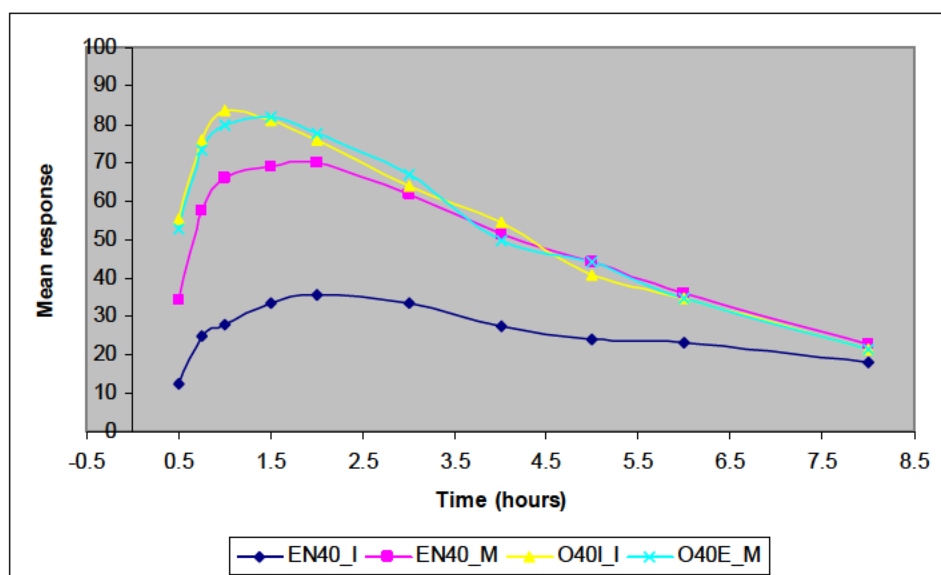
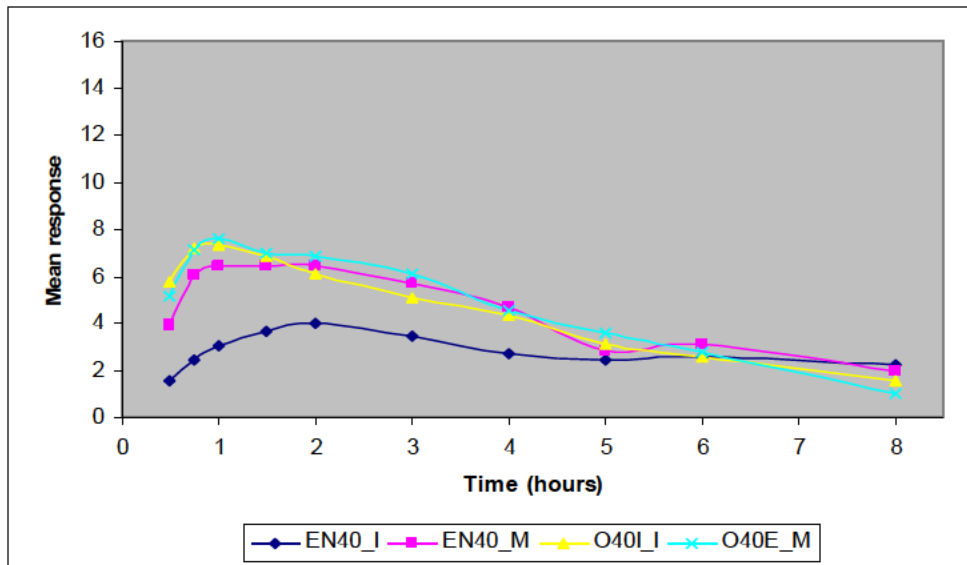


Figure 4: Mean Time Course Profiles for ARCI MBG (N=41)



Figures 5 and 6 present Boxplots for individual responses at hours 0.75, 1.0, 1.5 and 2.0 for Good Drug Effects VAS and High VAS respectively.

Figure 5: Boxplots for Good Effects VAS (N=41)

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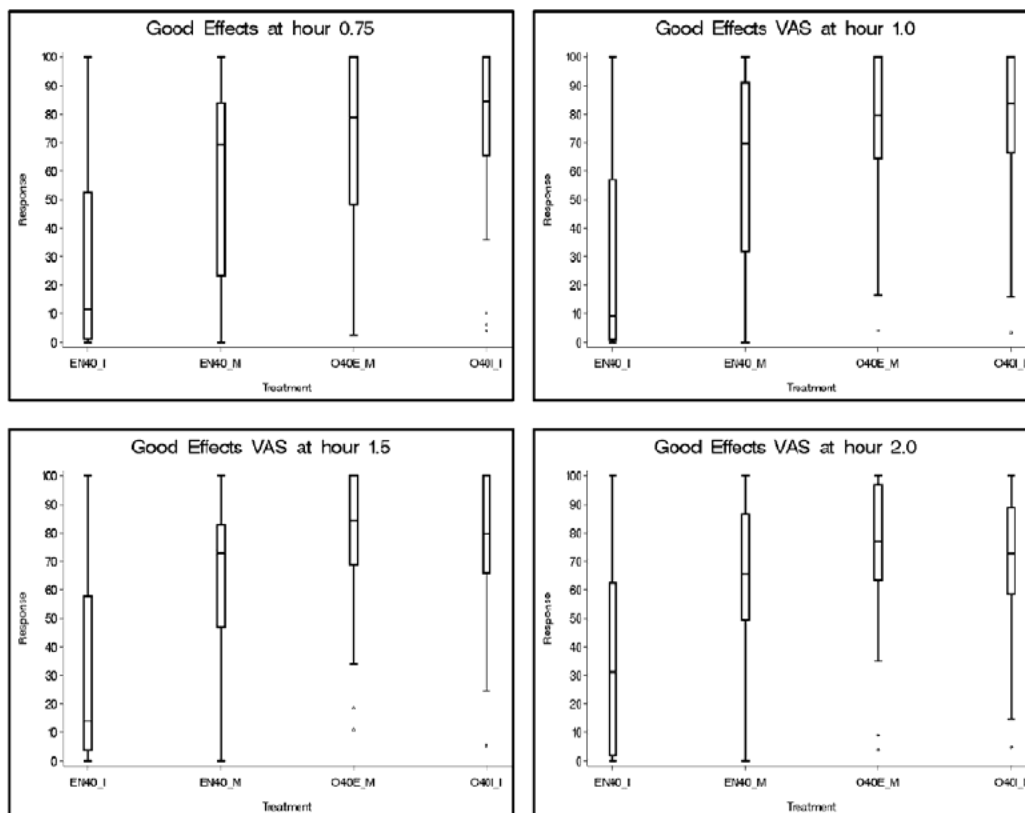
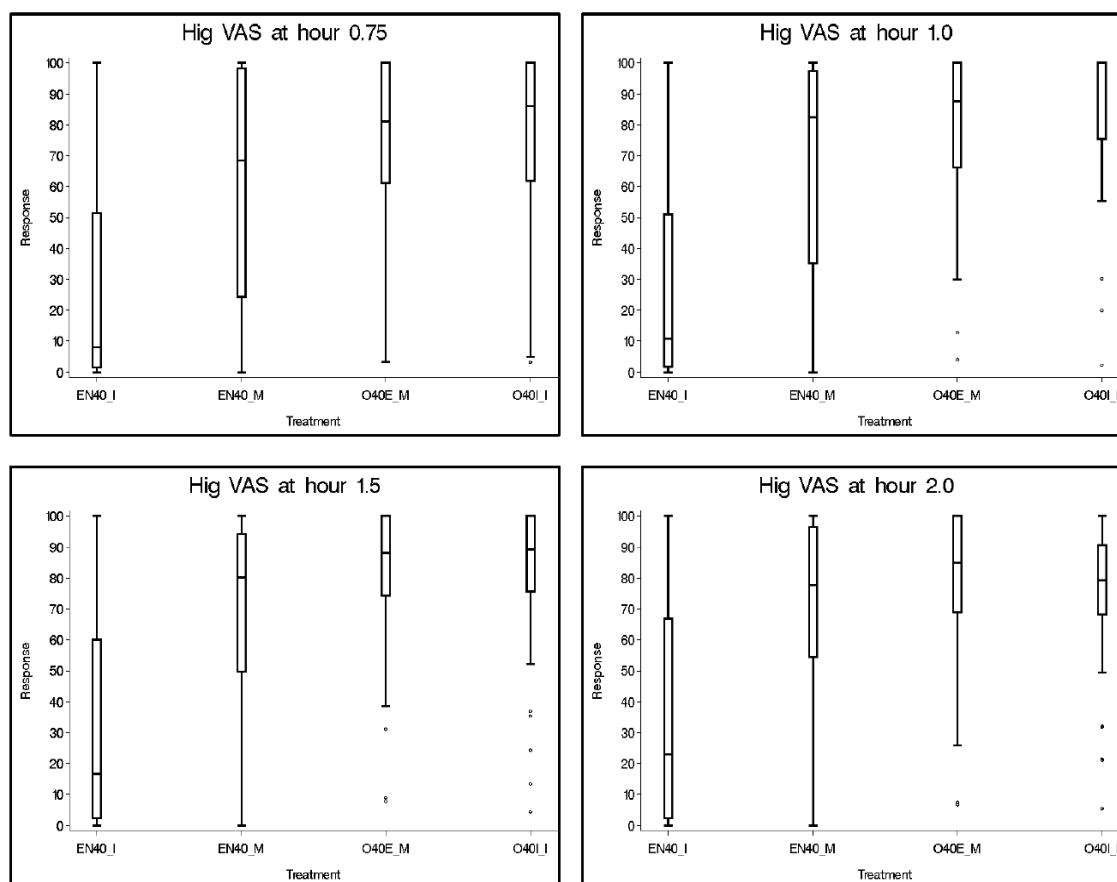


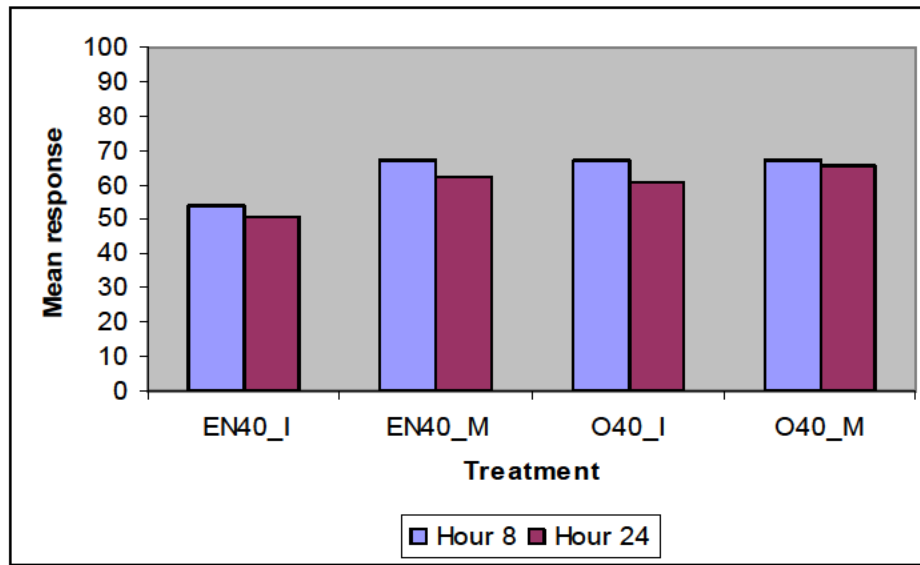
Figure 6: Boxplots for High VAS (N=41)

Note: the middle line in a boxplot represents median of the distribution.

Even though the peak mean response to EN40_M is lower than that of O40I_I and O40E_M on Good Effects VAS and High VAS (see Figures 2 and 3), approximately 50% of study subjects had a score greater than 72 on Good Effects VAS at hour 1.5 and a score greater than 82 on High VAS at hour 1.0. These scores are still considered large good effects and high in the unidirectional visual analogy scale.

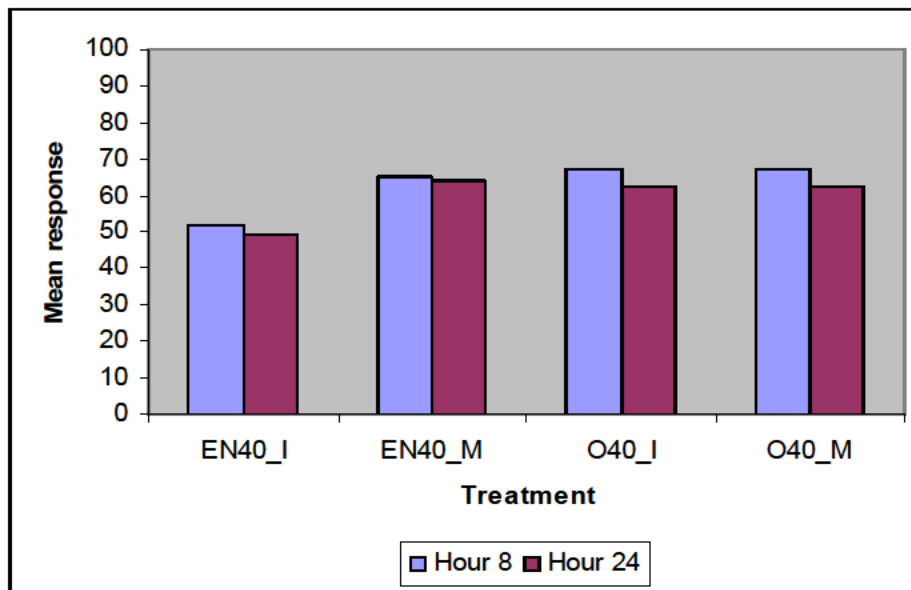
Figures 7 and 8 present mean responses for overall measures: Overall Drug Liking and Take Drug Again at hours 8 and 24. From these two graphs, one may see that the mean responses at hour 24 are lower than at hour 8 for all treatments. Mean responses to EN40_I is lower than those to the other treatments. There is no much difference in mean response to EN40_M, O40I_I and O40E_M for these two measures.

Figure 7: Mean Responses for Overall Drug Liking VAS (N=41)



Note: Overall Drug Liking VAS is on a bipolar scale.

Figure 8: Mean Responses for Take Drug Again VAS (N=41)



Figures 9 and 10 are boxplots for Emax of individual responses to Difficulty Chewing VAS and Overall Chewing Experience.

Figure 9: Boxplots of Responses at hour 0.5 to Difficulty Chewing VAS by Treatment (N=41)

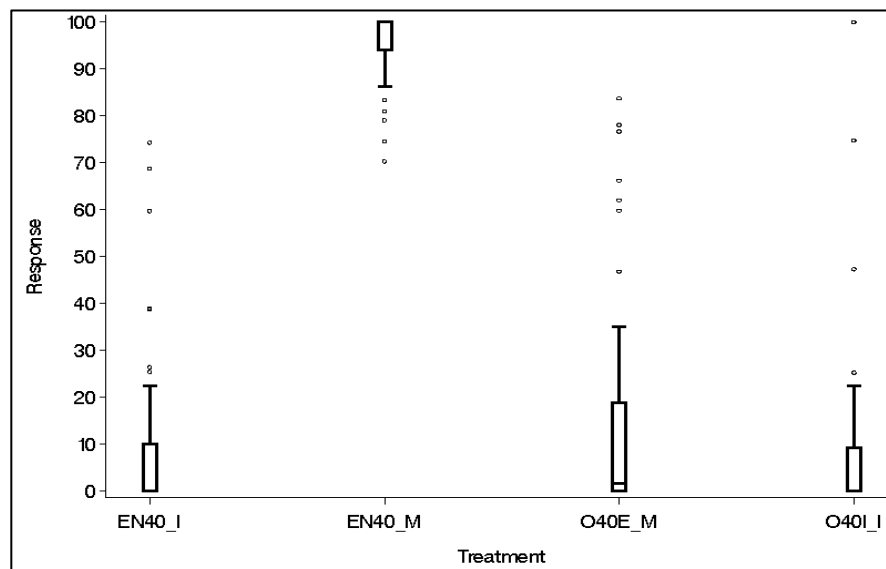
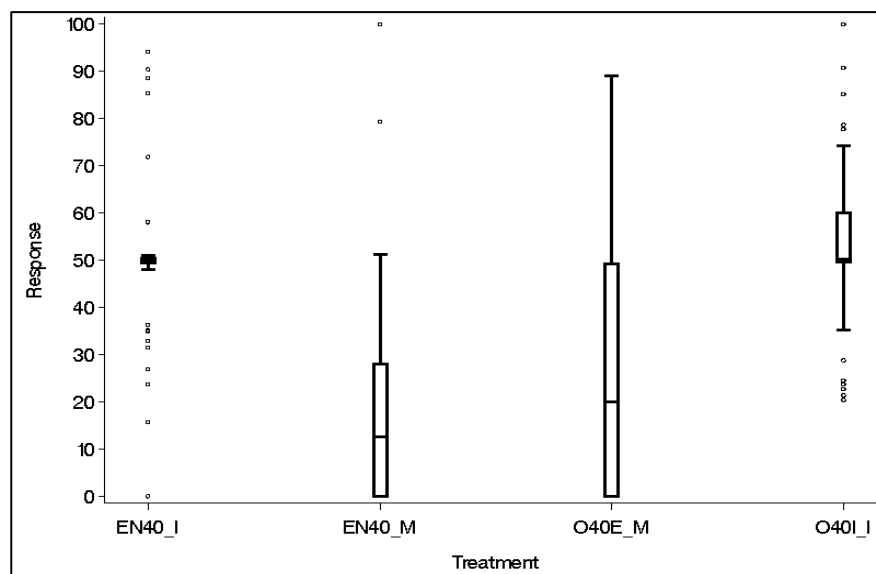


Figure 10: Boxplots of Responses at hour 0.5 to Overall Chewing Experience VAS by Treatment (N=41)



Note: 0: strong disliking; 50: neutral; 100: strong liking.

This study was designed using double dummy strategy. The responses to EN40_I and O40I_I on Difficulty Chewing VAS and Overall Chewing Experience were, in fact, from chewing placebos. Difficult Chewing VAS was on a unidirectional scale, while Overall Chewing Experience VAS was on a bipolar scale. Chewing EN40 was more difficulty than chewing O40 ER or placebo. The overall chewing experience for both EN40_M and O40E_M was disliked compared to placebo.

2.3.2 Statistical testing

2.3.2.1 Study model and statistical methodologies

The statistical model used in the reviewer's primary analysis includes sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect. The model assumption of the normality of error terms was checked using Shapiro-Wilk W-test on the residuals. If the normal assumption was not satisfied, the rank data (ranking treatment responses within subject) were used to obtain the p-value of the test for difference in medians between two treatments.

2.3.2.2 Results

Table 4 lists the least square mean, and its standard error for each treatment and for each abuse potential measure.

Table 4: Summary on Least Square Means and Standard Errors (N=41)

Abuse Potential Measure	EN40 I		EN40 M		O40E M		O40I I	
	LSmean	StdErr	LSmean	StdErr	LSmean	StdErr	LSmean	StdErr
Drug Liking VAS	62.11	2.93	79.63	2.93	81.94	2.93	82.43	2.93
Any Effects VAS	49.70	3.89	77.56	3.89	87.52	3.89	89.35	3.89
Good Effects VAS	45.71	4.17	72.78	4.17	83.33	4.17	84.37	4.17
High VAS	43.80	4.10	76.37	4.10	85.89	4.10	88.55	4.10
ARCI MBG	5.05	0.79	7.97	0.79	8.59	0.79	8.29	0.79
Overall Drug Liking VAS	55.16	3.65	69.06	3.65	71.64	3.65	70.92	3.65
Take Drug Again VAS	55.80	3.79	69.40	3.79	71.61	3.79	72.70	3.79
Bad Effects VAS	15.38	4.38	22.87	4.38	24.27	4.38	25.59	4.38
Sick VAS	10.65	4.08	19.12	4.08	13.66	4.08	20.41	4.08
Difficult Chewing VAS	10.55	2.81	95.52	2.81	16.18	2.81	9.02	2.81
Overall Chewing Experience VAS	49.35	3.54	19.87	3.54	26.80	3.54	54.31	3.54

Table 5 lists the difference in the least square means, standard error of the difference, and p-value from testing result in the significance of the comparisons EN40_I versus EN40_I, EN40_M versus O40E_M, and EN40_M versus O40I_I.

Table 5: Statistical Analysis Results for Three Comparisons ($\alpha=0.05$, N=41)

Comparison	EN40 M vs. EN40 I			EN40 M vs. O40E M			EN40 M vs. O40I I		
Abuse Potential Variable	LSmean diff	StdErr	P-value	LSmean diff	StdErr	P-value	LSmean diff	StdErr	P-value
Drug Liking VAS	17.52	2.61	S+	-2.31	2.61	NS-	-2.80	2.61	NS-
Any Effects VAS	27.86	4.11	S+	-9.96	4.11	S-	-11.79	4.11	S-
Good Effects VAS	27.07	4.32	S+	-10.55	4.32	S-	-11.59	4.32	S-
High VAS	32.57	4.24	S+	-9.52	4.24	S-	-12.18	4.24	S-
ARCI MBG	2.92	0.54	S+	-0.62	0.54	NS-	-0.32	0.54	NS-
Overall Drug Liking VAS	13.90	3.33	S+	-2.58	3.33	NS-	-1.86	3.33	NS-
Take Drug Again VAS	13.60	3.64	S+	-2.21	3.64	NS-	-3.30	3.64	NS-
Bad Effects VAS	7.49	4.64	NS+	-1.40	4.64	NS-	-2.72	4.64	NS-
Sick VAS	8.47	4.64	NS+	5.46	4.64	NS+	-1.30	4.64	NS-
Difficult Chewing VAS	84.97	3.98	S+	79.34	3.98	S+	86.51	3.98	S+
Overall Chewing Experience VAS	-29.48	4.42	S-	-6.93	4.42	NS-	-34.44	4.42	S-

Note: S denotes Significant at $\alpha=0.05$, NS denotes not significant at $\alpha=0.05$. “+” (or “-”) sign denotes the least square mean in treatment 1 is larger (or smaller) than that in treatment 2.

Table 5 shows that

- EN40_M had significantly larger mean response than EN40_I on Drug Liking VAS, Any Effects VAS, Good Effects VAS, High VAS, ARCI MBG and Overall Drug Liking VAS. There was no significant difference in means on Bad Effects VAS and Sick VAS in this comparison. Overall, subjects wanted to take EN40_M more than to take EN40_I (significant at $\alpha=0.05$).
- EN40_M had significantly lower mean response than O40I_I and O40E_M on Any Effects VAS, Good Effects VAS, and High VAS. However, such reduced effects did not show on Drug Liking VAS, Overall Drug Liking VAS, Take Drug Again VAS, Bad Effects VAS and Sick VAS in these comparisons, and the least square means on Good Effects VAS and High VAS are still considered large in the unidirectional scale (72.78 ± 4.18 for Good Drug Effects VAS and 76.37 ± 4.12 for High VAS).
- EN40_M had significantly larger mean response than O40E_M on Difficulty Chewing VAS. However, there was no significant difference on Overall Chewing Experience VAS between EN40_M and O40E_M. Overall subjects disliked Chewing Experience for both drugs.

3. Conclusion

After evaluating Study EN3288-109, the reviewer concludes that

- EN 3288 40 mg administered after mastication generated significantly larger drug liking, any effects, good effects, high, euphoria effect, and overall drug liking than EN40 mg administered intact. Overall, subjects wanted to administer EN 3288 40 mg after mastication more than to administer EN 3288 40 mg intact.

- EN 3288 40 mg administered after mastication produced significantly lower any effects, good effects and high than to OPANA® 40 mg IR (4x10 mg) – intact and OPANA® ER 40 mg administered after mastication. However, such reduced effects were not seen for Drug Liking VAS, Overall Drug Liking VAS, Take Drug Again VAS, Bad Effects VAS and Sick VAS, and the least square means of the responses to EN 3288 40 mg administered after mastication on Good Effects VAS and High VAS are still considered large (72.78 ± 4.18 and 76.37 ± 4.12 , respectively) in the unidirectional visual analog scale.
- EN 3288 40 mg was significantly more difficult to chew than OPANA® ER 40 mg. However, there was no significant difference on Overall Chewing Experience between EN 3288 40 mg and OPANA® ER 40 mg. Overall, subjects disliked the chewing experience for both drugs.

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/s/

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12/06/2010

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