CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201655Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 201655 Resubmission	Submission Date(s): 6/13/2011
Brand Name	OPANA ER
Generic Name	Oxymorphone HCl ER tablets
Clinical Pharmacology Reviewer	Srikanth C. Nallani, Ph.D.
Team Leader	Yun Xu, Ph.D.
OCP Division	Division of Clinical Pharmacology II
OND Division	Anesthesia and Analgesia Products
Sponsor	Endo Pharmaceuticals
Submission Type; Code	Response to CR action
Formulation; Strength(s)	Extended release tablet;
Indication	Relief of moderate to severe pain in patients requiring continuous opioid therapy for an extended period of time
Proposed Dosage Regimen	Titrated to effect with a twice daily dosing.

Recommendation: The proposed reanalysis of plasma samples is acceptable and the study results are acceptable from a clinical pharmacology perspective. The new formulation OPANA ER (EN3288) is bioequivalent to the previous formulation OPANA ER under fasting condition according to the resubmission result.

Regulatory Background:

Endo Pharmaceuticals Inc. (Endo) and its partner, Grünenthal GmbH (Aachen, Germany) have developed OPANA ER(505(b)(1) application), a new extended-release (ER) formulation of oxymorphone HCl for the relief of moderate to severe pain in subjects requiring continuous, around-the clock opioid therapy for an extended period of time. On January 7, 2011 Action Letter from Agency noted the following, "An audit performed by the Agency of the bioequivalence study EN3288-103 identified deficiencies in the methods used at the analytical site. Because of these deficiencies, the bioequivalence study cannot be relied upon to establish bioequivalence of your proposed product to the reference product". Endo addressed the above-noted deficiency by using back-up samples from study EN3288-103 for sample reassay, and all samples had sufficient volume available for reassay. In the current submission, Endo submitted results of pivotal bioequivalence study (EN3288-103) results after reanalysis of all plasma samples with stability data to address various discrepancies noted by Division of Scientific Investigations' audit in (b) (4). All plasma samples were reanalyzed for oxymorphone and 6-hydroxy (OH)-oxymorphone concentrations; and Division of Scientific Investigations recommends that the re-analyis results acceptable for review.

Division of Scientific Investigations memo summary and recommendation documented in Darrts on September 19, 2011:

Following the audit of the analytical records of study EN3288-103 (study conducted after (b) (4) *at* (b) (4) *no Form FDA-483 was issued and there were no significant adverse findings.*

Following the above inspection, the Division of Bioequivalence and GLP Compliance concludes (b) (4) *concerns raised* (b) (4) *implemented for the current study* (b) (4) *and recommends that the analytical data of study EN3288-103 be accepted for Agency review. (See memo attached)*

Study EN3288-103: BE study of 40 mg tablets in healthy subjects under fasted state

Study Design and Methods

This study was an open-label, randomized, 2-sequence, 4-period, crossover, replicated dosing design. Subjects were randomly allocated to receive a single dose of EN3288 or OPANA ER during alternate treatment periods. Each treatment period was separated by at least a 7-day washout. In total, each subject received 2 single doses of EN3288 and 2 single doses of OPANA ER.

Subjects included in each study were healthy males or females, of any race, between 18 and 45 years of age, inclusive. Plasma samples were obtained at 0 (predose, within 1 hour prior to administration of oxymorphone), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 hours after administration of oxymorphone in each period. Pharmacokinetic parameters were analyzed by a repeated measure ANOVA. Bioequivalence was demonstrated by 90% CIs for oxymorphone AUC0-t, AUC0-inf, and Cmax that were between 0.80 and 1.25.

Subject Disposition and Demographics

Three (3) out of 37 subjects who entered the study were administered naltrexone but not randomized to oxymorphone treatments, 2 because of an AE and 1 because the study panel was filled. Thirty-four (34) subjects were randomized. Three (3) subjects were administered only 1 dose of oxymorphone (1 each because of withdrawal of consent, physician decision, AE), so no data were available for pharmacokinetic analysis. All 3 subjects had been administered OPANA ER. Pharmacokinetic data were available from 31 subjects. There are data from 2 doses of each oxymorphone formulation for 30 subjects and data from 1 dose of each oxymorphone formulation for 1 subject.

Category	EN3288-103
Number of Subjects	31
Age (years), mean±SD (range)	33.7±7.33 (20-44)
Gender, n (%)	
Male	13 (41.9%)
Female	18 (58.1%)
Ethnicity, n (%)	
Hispanic	27 (87.1%)
Non-Hispanic	4 (12.9%)
Race, n (%)	
White	24 (77.4%)
Black or African American	7 (22.6%)
Weight (kg), mean±SD (range)	73.05±9.913 (55.6-95.0)
Height (cm), mean±SD (range)	167±7.9 (151- 184)
BMI (kg/m^2), mean±SD (range)	26.26±2.204 (22.1-29.8)

Results: The summary of pharmacokinetic parameters of oxymorphone after each product administration in the study is provided in the table below (reanalysis results).

Parameter	EN3288 40 mg	OPANA ER 40 mg
AUC_{0-t} (ng•h/mL)	31.23±10.326 (33.1)	31.51± 10.945 (34.7)
AUC_{0-inf} (ng•h/mL)	32.65±10.920 (33.4)	32.99±11.580 (35.1)
C_{max} (ng/mL)	2.42±0.941 (38.9)	2.37±1.200 (50.6)
T_{max} (h)[a]	5.0 (0.5-12.0)	3.0 (0.5-12.0)
C_t (ng/mL)	0.090±0.0552 (61.5)	0.092±0.0609 (66.0)
λ_z (1/h)	0.0754±0.02232 (29.6)	0.0736±0.01776 (24.1)
$t_{1/2}$ (h)	9.9±2.65 (26.9)	10.0±2.55 (25.5)

The Geometric Least Square Meam ratios and their 90% CIs of AUC and Cmax of oxymorphone, from the original analysis and reanalysis of plasma samples from the single oral 40 mg doses administered to fasted subjects (EN3288-103), are provided in the table below. As indicated in the table below, the new formulation OPANA ER (EN3288) is bioequivalent to the previous formulation OPANA ER under fasting condition according to both original submission and resubmission results. The results from the two submissions are very similar.

Bioequivalence Analysis of Oxymorphone Pharmacokinetic Parameters After Single Oral Doses Administered to Fasted Healthy Subjects:

Comparison of Original Submission and Resubmission

Parameter	Ratio of Least Squares Means (A/B)		90% Confidence Interval of the Ratio	
	Original Submission	Resubmission	Original Submission	Resubmission
AUC_{0-t}	0.9900	0.9942	0.9458 - 1.0363	0.9477 - 1.0430
AUC_{0-inf}	0.9874	0.9930	0.9443 - 1.0326	0.9477 - 1.0406
C_{max}	1.0383	1.0513	0.9720 - 1.0092	0.9838 - 1.1235

Summary of Assay Validation

The method (AP LC/MS/MS 374.100) for determining oxymorphone/6-OH-oxymorphone in human plasma has been validated with a detection range of 0.02500/0.02500 to 10.00/10.00 ng/mL using an atmospheric pressure ionization (API) 4000 liquid chromatography with tandem mass spectroscopy (LC/MS/MS) system.

The stability of oxymorphone and 6-OH-oxymorphone in stock solutions, after extraction, and in plasma was established. Stock solutions of oxymorphone, 6-OH-oxymorphone, and internal standard were stable at room temperature for 6 hours and were stable refrigerated at 4°C±6°C for 21 days.

Long Term Freezer Stability in HumanPlasma at -70°C ±20°C After 314 Days for

Oxymorphone

Run Date	LQC LTS 0.07500 ng/mL	HQC LTS 7.500 ng/mL
09-Dec-2009	0.07112	7.752
	0.06858	7.396
	0.06474	8.035
	0.07043	7.870
	0.06283	7.738
	0.06812	7.676
Intrarun Mean	0.06764	7.745
Intrarun SD	0.003242	0.2128
Intrarun %CV	4.8	2.7
Intrarun %Bias	-9.8	3.3
n	6	6

6-β-Hydroxyoxymorphone

Run Date	LQC LTS 0.07500 ng/mL	HQC LTS 7.500 ng/mL
09-Dec-2009	0.06795	6.693
	0.07585	7.206
	0.06817	7.490
	0.06955	7.365
	0.07096	7.296
	0.07273	7.786
Intrarun Mean	0.07087	7.306
Intrarun SD	0.003027	0.3616
Intrarun %CV	4.3	4.9
Intrarun %Bias	-5.5	-2.6
n	6	6

Plasma samples of oxymorphone and 6-OH-oxymorphone were stable for at least 6 freeze-thaw cycles and for at least 24 hours at room temperature. Extracted samples, reconstituted in preparation for injection, were stable at room temperature for 99 hours and were stable stored refrigerated (4°C±6°C) for 99 hours. Both analytes were stable in plasma stored at -70°C±20°C for at least 723 days.

Study ID	Precision (%CV)			Accuracy (%Bias)		
	LQC 0.075 ng/mL	MQC 0.75 ng/mL	HQC 7.50 ng/mL	LQC 0.075 ng/mL	MQC 0.75 ng/mL	HQC 7.50 ng/mL
EN3288-103	n = 66	n = 65	n = 66	n = 66	n= 65	n = 66
	9.6%	7.6%	6.3%	-5.5%	-4.7%	-1.8%
EN3288-103 Resubmission	n = 67	n = 66	n = 68	n = 67	n = 66	n = 68
	6.8%	5.0%	3.7%	-2.1%	1.0%	4.7%

Storage duration of plasma samples:

Study	First Sample Collected	First Sample Assayed	Last Sample Assayed	Duration of Sample Storage
EN3288-103	20090728	20090913	20091009	73 days
EN3288-103 Resubmission	20090728	20110222	20110312	592 days

Reanalysis of Study Samples

Study ID	Analyte	Number of Samples Reassayed	Reasons for Sample Reassays				
			Peak in Pre-Dose Sample	Low or High IS	Concentration >ULOQ	Low Volume in Auto Injector Vial	Other
EN3288-103	Oxymorphone	40	18	11	0	1	9[a]
	6-OH-oxymorphone	29	9	14	0	2	4[b]
EN3288-103 Resubmission	Oxymorphone	46	17	1	0	0	28[c]
	6-OH-oxymorphone	32	3	0	0	0	29[d]

(b) (4)

[redacted]

Very few samples had peak in pre-dose samples upon reanalysis and the concentration of drug upon integration of the noted peaks was very close to the detection limit.

At least 5% of the study samples were reanalyzed (incurred sample reanalysis) to demonstrate reproducibility. Assay reproducibility was established if at least two-thirds of the samples had repeat results within 20% of the original values. The results are

provided in Table 5 and show that more than two-thirds (67%) reanalyzed samples had results within 20% of reported assay result.

Reanalysis of Incurred Samples

Study ID	Number of Samples Assayed (2/3 the Number)	Number (Percent of Samples Assayed) Samples with Results within 20%	
		Oxymorphone	6-OH-oxymorphone
EN3288-103	150 (100)	123 (82%)	141 (94%)
EN3288-103 Resubmission	150 (100)	127 (85%)	136 (91%)

Conclusion: The proposed reanalysis of plasma samples is acceptable and the results of the study EN3288-103 establishing bioequivalence of previous OPANA ER product with new/reformulated OPANA ER are acceptable from a clinical pharmacology perspective.

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/s/

XIKUI CHEN
09/19/2011

SAM H HAIDAR
09/20/2011

ARINDAM DASGUPTA
09/20/2011

Addendum to Primary Clinical Pharmacology Review Dated 12/14/2010

NDA:	201-655
Date Received:	7/7/2010
Product Name:	(b) (4)
Active Ingredient:	Oxymorphone HCl extended-release tablets
Sponsor:	Endo Pharmaceuticals
Reviewer:	Srikanth C. Nallani, Ph.D.

BACKGROUND:

Endo Pharmaceuticals submitted a 505(b)(1) NDA 201-655 (on 7/7/2010) for (b) (4) Tablets with pharmacokinetic data showing bioequivalence to their own currently marketed product OPANA ER Tablets. Approval of (b) (4) is based on successful demonstration of its bioequivalence (BE) to OPANA ER. Study EN3288-103 is the pivotal BE study comparing (b) (4) 40 mg compared to OPANA ER 40 mg in healthy subjects under fasting conditions. This study forms the primary support for the NDA submission as the highest formulation strength of (b) (4) was employed under fasting conditions in this study. Other bioequivalence studies were conducted with (b) (4) 40 mg under fed conditions and (b) (4) 5 mg under fasting conditions with corresponding strengths of OPANA ER. Biowaiver was sought for the intermediate strengths. Clinical pharmacology review for this NDA was signed off on (b) (4) with comments that the inspection results of pivotal BE study EN3288-103 from Division of Scientific Investigations were pending. In his review of inspection results dated (b) (4), Dr. John Kadavil of DSI indicated the following observations 1 and 2 and conclusions on BE study EN3288-103:

(b) (4)

Conclusion:

Following DSI's evaluation of the inspectional findings, DSI recommends the following:

• Study EN3288-103 should not be accepted for review at this time due to the (b) (4) (b) (4)

DSI is currently awaiting (b) (4) *response to the Form FDA-483 to determine what steps the firm will initiate to address the inspectional findings.*

Subsequently, after reviewing the written response submitted by (b) (4) on (b) (4) to the issues identified in Form FDA 483, Dr. Kadavil summarized his evaluation in an addendum dated (b) (4) as follows:

(b) (4)

In summary, DSI has no basis to reverse our recommendation.

RECOMMENDATION:

Based on the deficiencies identified in the DSI review, the BE study EN3288-103 data cannot be accepted. The following deficiencies and remedial actions to address the deficiencies from a clinical pharmacology perspective should be conveyed to Endo Pharmaceuticals:

Clinical Pharmacology

An audit performed by the Agency of the bioequivalence study EN3288-103 identified deficiencies in the methods used at the analytical site. Because of these deficiencies, the bioequivalence study cannot be relied upon to establish bioequivalence of your proposed drug product to the reference product.

This deficiency may be addressed by doing the following:

Provided adequate samples are available, reanalyze blood samples collected in bioequivalence study EN3288-103 and submit data establishing bioequivalence of (b) (4) 40 mg tablets with OPANA ER 40 mg tablets. Ensure that the inspectional findings identified in Agency's audit of study EN3288-103 are properly addressed in the reanalysis of blood samples.

OR

Conduct another pharmacokinetic study and establish bioequivalence of (b) (4) 40 mg tablets with OPANA ER 40 mg tablets under fasting condition using adequately validated analytical methodology.

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/s/

SRIKANTH C NALLANI
01/06/2011

SURESH DODDAPANENI
01/06/2011

CLINICAL PHARMACOLOGY REVIEW

NDA: 201655	Submission Date(s): 07/07/2010
Brand Name	(b) (4)
Generic Name	Oxymorphone HCl Extended Release Tablets
Clinical Pharmacology Reviewer	Srikanth C. Nallani, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	Division of Clinical Pharmacology II
OND Division	Anesthesia and Analgesia Products
Sponsor	Endo Pharmaceuticals Inc.
Relevant IND(s)	104,250
Submission Type; Code	Original NDA; New Formulation
Formulation; Strength(s)	5 , 7.5, 10, 15, 20, 30 and 40 mg
Indication	Relief of moderate to severe pain in patients requiring continuous opioid therapy for an extended period of time
Proposed Dosage Regimen	Titrated to effect with a twice daily dosing.

Table of Contents

1 Executive Summary

1.1 Recommendation

The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective provided that Division of Scientific Investigations finds data from pivotal BE study EN3288-103 a mutually satisfactory agreement can be reached between the applicant and the Agency regarding the language in the package insert.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

Endo Pharmaceuticals Inc. and its partner, Grünenthal GmbH (Aachen, Germany) have developed (b) (4) (505(b)(1) application), a new extended-release (ER) formulation of oxymorphone HCl for the relief of moderate to severe pain in subjects requiring continuous, around-the clock opioid therapy for an extended period of time.

(b) (4) or EN3288, a new formulation of oxymorphone hydrochloride was developed to resist accidental misuse and intentional abuse. (b) (4) tablet is characterized by a (b) (4) (b) (4) This product contains the same drug substance found in Endo Pharmaceuticals' immediate-release (IR) OPANA (NDA 21-611) and extended release OPANA ER (NDA 21-610) oral formulations of oxymorphone HCl, which were both approved by the FDA on June 22, 2006. This application seeks to market 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg and 40 mg strengths of (b) (4) tablets (same strengths as OPANA ER).

The applicant submitted pharmacokinetic studies seeking approval of (b) (4) by demonstrating bioequivalence to their own OPANA ER product. Pharmacokinetics and tamper resistance properties of (b) (4) were evaluated under conditions of normal use and accidental misuse (i.e., breaking and/or crushing for patient convenience) and certain methods of intended abuse (i.e., crushing for snorting and/or injection, alcohol interaction and chewing).

Six pharmacokinetic studies were conducted in healthy volunteers to support the efficacy, safety (b) (4) of (b) (4) tablets (See table below).

1.3.1 Studies establishing bioequivalence of (b) (4) to OPANA ER
Study # EN3288-103: BE study comparing (b) (4) 40 mg compared to OPANA ER 40 mg in healthy subjects under fasting state and naltrexone blockade.
Study # EN3288-104: BE study comparing (b) (4) 40 mg compared to OPANA ER 40 mg in healthy subjects **under fed state** and naltrexone blockade.
Study # EN3288-105: BE study comparing (b) (4) 5 mg compared to OPANA ER 5 mg in healthy subjects under fasting and naltrexone blockade.

1.3.2 PK studies conducted to evaluate dose dumping of [redacted] after improper use
Study # EN3288-107: Alcohol interaction study assessing relative bioavailability of [redacted] 40 mg taken with or without an alcoholic beverage and naltrexone blockade.
Study # EN3288-108: Relative bioavailability study comparing [redacted] 40 mg taken intact and after physical tampering (cutting, crushing and grinding) and naltrexone blockade.
Study # EN3288-109: Relative bioavailability and drug-liking study comparing [redacted] 40 mg taken intact and after chewing without naltrexone blockade.

Additional in vitro studies were performed by the applicant to address if different methods of tampering with controlled release products known to drug addicts would defeat the extended release properties of [redacted] These in vitro studies are reviewed by biopharmaceutics reviewer Dr. Sandra Suarez of Office of New Drug Quality Assurance and control substance staff reviewer Dr. James Tolliver.

1.3.1 Studies establishing bioequivalence of [redacted] to OPANA ER

Bioequivalence of [redacted] to OPANA ER was established with the highest (40 mg) strength [redacted] and OPANA ER under fasting condition (Study # EN3288-103) under fed condition (Study # EN3288-104). With regard to intermediate strengths (7.5 – 30 mg) of [redacted] results of bioequivalence of the lowest (5 mg) tablet strength of [redacted] compared to OPANA ER under fasting condition (Study # EN3288-105) along with similarity of intermediate tablet strength in vitro dissolution profiles was provided to support biowaiver. Biopharmaceutics review by Dr. Sandra Suarez will address the adequacy of the dissolution data and biowaiver request of the intermediate strengths .

The above described bioequivalence studies were generally open-label, randomized, single-dose, 2-sequence, 4-period, replicate, crossover studies in healthy subjects receiving naltrexone to block opioid effects of oxymorphone. In BE studies, bioequivalence is concluded if the 90% CI of the geometric mean ratio ([redacted] or EN3288 over OPANA ER) for oxymorphone AUC_{0-t} and C_{max} fall within the limits of 0.8 to 1.25.

The results of the ANOVA comparison of geometric mean results of oxymorphone AUC and Cmax for the three BE studies are provided in the table below. As indicated in the table, the analysis confirms that the 5 mg and 40 mg [redacted] tablets are bioequivalent to 5 mg and 40 mg OPANA ER, respectively under fasting condition. Additionally, 40 mg [redacted] tablet is also bioequivalent to OPANA ER under fed condition.

Summary table indicating BE analysis of (b) (4) compared to OPANA ER

Parameter	Geometric Least Squares Means		Ratio of Means	90% Confidence Interval
	EN3288	OPANA ER		
EN3288-103: Single 40 mg Oral Doses to Fasted Healthy Subjects*				
Cmax (ng/mL)	(b) (4)			
AUC0-t (ng•h/mL)				
EN3288-104: Single 40 mg Oral Doses to Healthy Subjects with a High-Fat Meal				
Cmax (ng/mL)	5.24	5.55	0.94	0.88-1.02
AUC0-t (ng•h/mL)	47.10	48.43	0.97	0.93-1.02
EN3288-105: Single 5 mg Oral Doses to Fasted Healthy Subjects				
Cmax (ng/mL)	0.352	0.360	0.98	0.93-1.03
AUC0-t (ng•h/mL)	5.04	4.82	1.05	1.01-1.09

*Pending Division of Scientific Investigations inspection report

Previously, during the review of OPANA ER in NDA 21-610, Clinical Pharmacology reviewer Dr. David Lee noted that the mean oxymorphone C_{max} in the fed state (4.25 ng/mL) was about 52% higher than the C_{max} in fasted state (2.79 ng/mL). Since (b) (4) and OPANA ER are bioequivalent under fasting and fed conditions, it can be assumed that (b) (4) has the same degree of food effect as OPANA ER. Current dosing recommendations for OPANA ER indicate that the tablet should be dosed at least one hour prior to or two hours after eating. No change in dosing recommendation is needed taking into consideration the safety and efficacy of OPANA ER and bioequivalence of (b) (4) to OPANA ER under fasting and fed condition.

1.3.2 PK studies conducted to evaluate safety of (b) (4) taken intact or after improper use

Extended release profile of (b) (4) is characterized by lower plasma levels and delayed time to peak plasma levels when compared to equal dose of immediate release product in the same dosing interval. Peak plasma levels of 40 mg (b) (4) taken intact under fasting condition are ~ $1/4^{th}$ (~ 2 ng/mL) of that noted with 4 X 10 mg dose of OPANA IR (~8 ng/mL). Time to peak plasma levels is ~ 5 hours with (b) (4) compared to ~ 0.5 hour with immediate release product. Hence, extended release profile of (b) (4) under normal use or improper use is discussed with particular attention to peak plasma levels in the clinical pharmacology summary. Over all systemic profile is discussed later in the QBR section of the review and individual study reviews.

Alcohol Interaction Study: PK study # EN3288-107 was conducted to evaluate alcohol-drug interaction effect of consuming 20% alcohol or 40% alcohol on PK of (b) (4) Results indicate that, similar to OPANA ER, administration of (b) (4) with alcohol contained beverages (20% or 40%) will result in significant increase in peak plasma

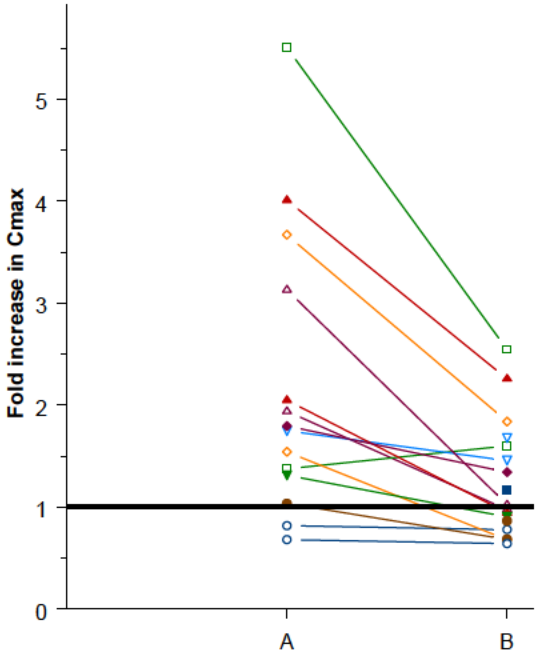
levels. The study was not powered to establish bioequivalence, but rather provide relative bioavailability adequate to allow clinical interpretation. Eighteen (18) subjects were to be randomized to ensure that 12 subjects had evaluable pharmacokinetic data from 12 of the ethanol treatment arms and the water treatment arm.

Table: Oxymorphone pharmacokinetic parameters after each treatment (with or without alcohol) administration are provided in the table below.

Parameter[a]	EN3288 40 mg Administered with 240 mL 40% Ethanol (N=14)	EN3288 40 mg Administered with 240 mL 20% Ethanol (N=17)	EN3288 40 mg Administered with 240 mL Water (N=17)
AUC_{0-t} (ng•h/mL)	35.57±14.136 (39.7)	28.38±8.800 (31.0)	29.96 ±9.218 (30.8)
AUC_{0-inf}(ng•h/mL)[b]	35.61±13.891 (39.0)	29.99±8.969 (29.9)	31.63±9.913 (31.3)
C_{max} (ng/mL)	3.94±2.307 (58.5)	2.34±1.118 (47.7)	1.99±0.757 (38.1)
T_{max} (h)[c]	2.0 (0.5-6.0)	5.0 (0.5-12.0)	5.0 (0.8-12.0)
C_t (ng/mL)	0.083±0.0372 (44.8)	0.072±0.0418 (57.9)	0.094±0.0624 (66.4)
λ_z (1/h)[b]	0.0801±0.01980 (24.7)	0.0743±0.01532 (20.6)	0.0708±0.02075 (29.3)
$t_{1/2}$ (h)[b]	9.2±2.28 (24.9)	9.8±2.61 (26.6)	10.7±3.48 (32.5)

On average, oxymorphone Cmax increased with the amount of ethanol consumed and was 1.14-fold and 1.80-fold higher with 20% and 40% ethanol, respectively. Noteworthy is the fact that in certain individuals maximum fold change in Cmax upto 2.5-fold or 5.5-fold were noted in 20% or 40% alcohol treatment groups compared to [redacted] alone (see figure below).

Figure: Fold increase in Cmax following administration of [redacted] with 40% alcohol (A) or 20% alcohol (B) compared to water (C, not shown) in individual subjects.



A: Cmax with Treatment A / Cmax with Treatment C
B: Cmax with Treatment B / Cmax with Treatment C

Treatment A: 40 mg, [redacted] + 240 mL 40% ethanol

Treatment B: 40 mg, [redacted] + 240 mL 20% ethanol

Treatment C: 40 mg, [redacted] + 240 mL Water (**reference**)

Previously, OPANA ER also exhibited highly variable but significant alcohol-drug interaction. Following concomitant administration of 240 mL of 40% ethanol the Cmax increased on average by 70% and up to 270% in individual subjects. Following the concomitant administration of 240 mL of 20% ethanol, the Cmax increased on average by 31% and up to 260% in individual subjects. As noted with OPANA ER previously, a slight increase (15% increase) in AUC is noted when [redacted] (b) (4) is taken with alcohol (20 or 40%, data not shown). Hence, [redacted] (b) (4) and OPANA ER are similar in their susceptibility to alcohol-related drug interaction. It should be noted that this interaction is not due to the failure of the extended release characteristics of the formulation but is probably due to the alcohol effect on the absorption of oxymorphone itself. For both OPANA ER and [redacted] (b) (4) in vitro dissolution studies have demonstrated that these products do not release oxymorphone more rapidly in dissolution media containing alcohol.

Accidental misuse study: Pharmacokinetic study # EN3288-108 was conducted to evaluate dose dumping of [redacted] (b) (4) under conditions of accidental or intentional misuse by breaking and/or crushing with different methods. This study was an open-label, randomized, 6-sequence, 6-period, crossover design. Subjects were randomized to receive the following treatments:

A EN3288 40 mg – intact tablet
B EN3288 40 mg – tablet tampered with a commercial pill crusher
C EN3288 40 mg – tablet cut [redacted] (b) (4)
D EN3288 40 mg – tablet tampered [redacted] (b) (4)
E OPANA ER 40 mg – tablet tampered with a commercial pill crusher
F OPANA 40 mg (4×10 mg) – intact tablets

The applicant compared bioavailability (Cmax and AUC) of [redacted] (b) (4) following physical manipulation (Treatments B, C and D) with Treatment A (intact [redacted] (b) (4) tablet) or Treatment F (40 mg immediate release tablets). The plasma concentration measurements (timing and assay range), sample size (29 subjects) were designed to accurately characterize the measures of systemic exposure to oxymorphone that provided evidence of bioequivalence.

The first step in misusing or abusing opioid drug products involves methods that would destroy the extended-release characteristics of drug product, followed later by oral consumption or nasal administration (snorting; not evaluated) or IV injection (not evaluated). Hence, pharmacokinetic analyses are conducted to understand the change in extended-release characteristics of drug products by comparing Cmax and AUC noted when the product is consumed under different conditions. Bioequivalence was concluded if the 90% CI of the geometric mean ratio of a treatment compared to appropriate reference for oxymorphone AUC_{0-t} and C_{max} fall within the limits of 0.8 to 1.25.

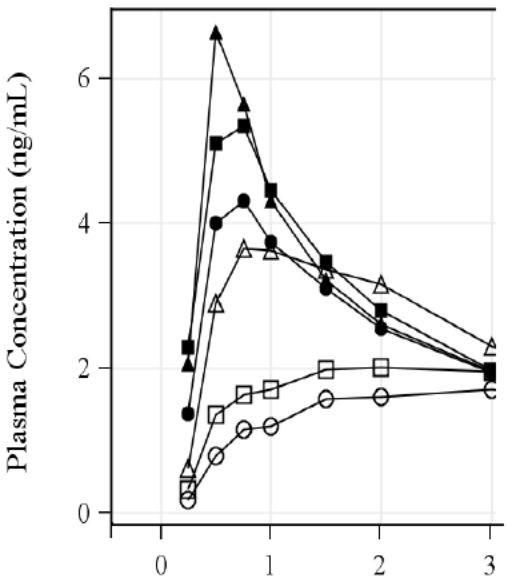


Figure: Mean plasma oxymorphone profiles over an initial 3 hour period with treatments as follows:

- ○ Treatment A: EN3288 40 mg - intact tablet
- □ Treatment B: EN3288 40 mg - (commercial pill crusher)
- △ Treatment C: EN3288 40 mg - (tablet cut [(b) (4)]
- ● Treatment D: EN3288 40 mg - [(b) (4)]
- ■ Treatment E: OPANA® ER 40 mg - (commercial pill crusher)
- ▲ Treatment F: OPANA 40 mg (4 × 10 mg) - intact tablets (reference product)

Classically, immediate release (IR) tablets produce peak plasma levels that are higher than extended-release drug products containing the same dose upon single dose administration. Use of such high Cmax values noted with OPANA IR tablets (See figure above) as reference would indicate a decrease in peak plasma levels to 0.4 – 0.7-fold when [(b) (4)] is consumed intact or under any condition of physical manipulation (See table below).

Table: Change in Cmax, with respect to OPANA IR 40 mg, when [(b) (4)] 40 mg is consumed intact or following physical manipulation

Treatment	N	Geometric Least Squares Mean	Ratio of Least Squares Mean		Lower 90% CI	Upper 90% CI
A	29	3.4	A/F	0.42	0.37	0.48
B	29	3.3	B/F	0.41	0.36	0.47
C	29	5.1	C/F	0.63	0.55	0.72
D	29	5.3	D/F	0.65	0.57	0.75
E	29	6.5	E/F	0.79	0.69	0.91
F	29	8.1				

Since the goal of this PK study is to understand whether the extended-release product can withstand physical tampering, PK results from an intact extended-release product should be used as reference. Use of IR tablets as a reference is masking the effects of physical manipulation which are obviously defeating the control release properties of [(b) (4)] (see table below). Hence, from a clinical pharmacology perspective, bioavailability comparisons are appropriate using Treatment A or the intact extended-release tablet as reference. Using intact [(b) (4)] (Treatment A) as reference, peak plasma levels of oxymorphone failed bioequivalence and were significantly higher when [(b) (4)] was consumed following grinding and cutting [(b) (4)] indicating loss of extended-release characteristics. However, data indicates that [(b) (4)] resists physical crushing

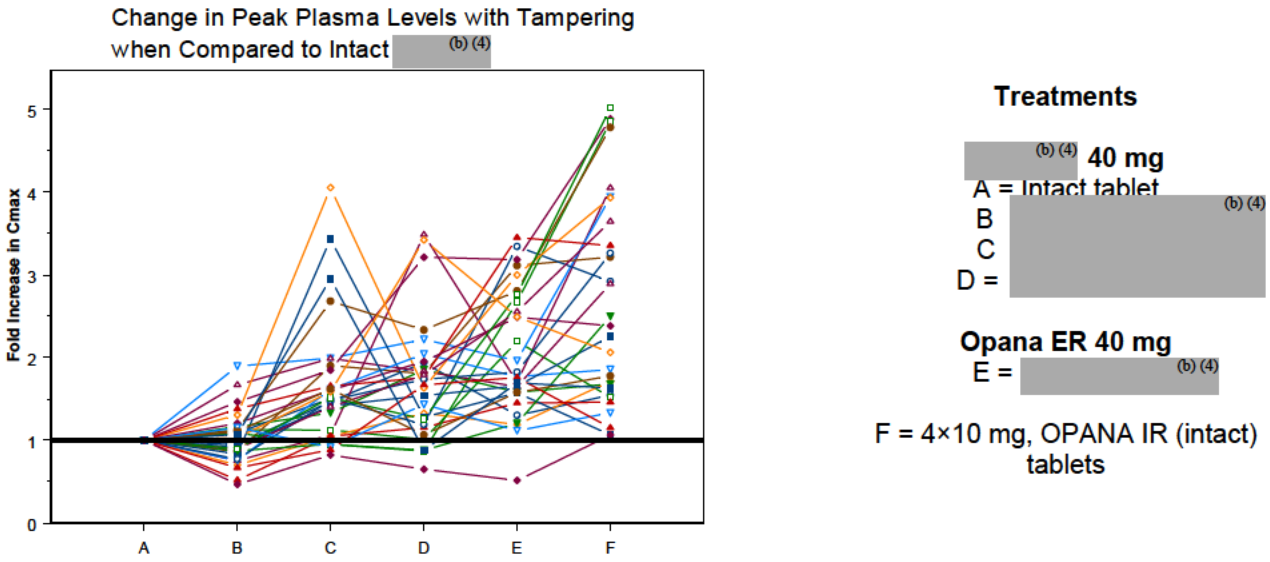
forces noted using a pill crusher as demonstrated by bioequivalence to intact [redacted] with respect to Cmax (see table below) and AUC (not shown).

Table: Change in Cmax when [redacted] 40 mg is consumed following physical manipulation, with respect to intact [redacted] 40mg.

Treatment	N	Geometric Least Squares Mean	Ratio of Least Squares Mean		Lower 90% CI	Upper 90% CI
A	29	3.4	B/A	0.98	0.86	1.12
B	29	3.3	C/A	1.51	1.32	1.73
C	29	5.1	D/A	1.56	1.37	1.78
D	29	5.3				
E	29	6.5				
F	29	8.1				

A [redacted] 40 mg – intact tablet
B [redacted] 40 mg – tablet tampered with a commercial pill crusher
C [redacted] 40 mg – tablet cut [redacted]
D [redacted] 40 mg – tablet tampered [redacted]
E OPANA ER 40 mg – tablet tampered with a commercial pill crusher
F OPANA 40 mg (4×10 mg) – intact tablets

When considering individual data, fold increase in Cmax as high as 4-fold were noted with cutting (Treatment C) and grinding (Treatment D) (See figure below). Fold change in Cmax for each individual were calculated by dividing Cmax noted for each treatment with Cmax noted with reference treatment A ([redacted] 40 mg intact). As indicated previously, bioequivalence was noted for Treatment B indicating no significant change compared to Treatment A.
With regard to AUC, bioequivalence was demonstrated between different methods of physical manipulation irrespective of the reference used (data not shown).



Study of intentional abuse by chewing: Pharmacokinetic study # EN3288-109 was conducted to evaluate the effect of mastication on bioavailability of (b) (4) 40 mg. This was a randomized, double-blind, double-dummy, 4-period, 4-sequence, single-dose, crossover study in healthy, nondependent, recreational oral prescription opioid users experienced in mastication of ER opioid formulations. Unlike the previous bioavailability studies, subjects did not receive naltrexone to block opioid effects. The treatment arms in this PK study were as follows:
A EN3288 40 mg – intact tablet
B EN3288 40 mg – tablet ingested after mastication
C OPANA ER 40 mg – tablet ingested after mastication
D OPANA 10 mg (4×10 mg) – intact tablets

No specific instructions with regard to rate of chewing or duration of chewing were given to the subjects. The subjects were instructed to "completely and carefully" chew the tablet for as long as possible. This instruction was given verbally to each individual subject just prior to administration of each treatment. A mouth and hand check was performed after ingestion of the tablets. The time the tablet allocated for chewing was given and the time that the subject indicated chewing was completed was recorded on source documentation.

In addition to pharmacokinetic assessments, a number of pharmacodynamic measures as it relates to drug effects were assessed over a 24 hour period. While pharmacokinetic analysis is discussed below, pharmacodynamic assessments are discussed in detail by Controlled-Substance Staff reviewer Dr. James Tolliver in his review.

The applicant compared bioavailability (Cmax and AUC) of (b) (4) following mastication (Treatment B) with Treatment A (intact (b) (4) 40 mg tablet) or Treatment D (40 mg immediate release tablets). Bioequivalence was concluded if the 90% CI of the geometric mean ratio of a treatment compared to appropriate reference for oxymorphone AUC_{0-t} and C_{max} fell within the limits of 0.8 to 1.25.

Using intact OPANA IR tablets (Treatment D) as reference, which has the highest Cmax compared to all treatment groups (See figure below), peak plasma levels following chewing ranged between 0.5 – 0.7-fold (See table below).

Treatment	**N**	**Geometric Least Squares Mean**	**Ratio of Least Squares Mean**		**Lower 90% CI**	**Upper 90% CI**
A	31	2.05	A/D	0.27	0.23	0.3
B	31	4.55	B/D	0.59	0.52	0.67
C	31	5.15	C/D	0.67	0.58	0.76
D	31	7.72				

A EN3288 40 mg – intact tablet
B EN3288 40 mg – tablet ingested after mastication
C OPANA ER 40 mg – tablet ingested after mastication
D OPANA 10 mg (4×10 mg) – intact tablets

Intact or chewed [redacted] treatments were bioequivalent in terms of oxymorphone AUC (data not shown).

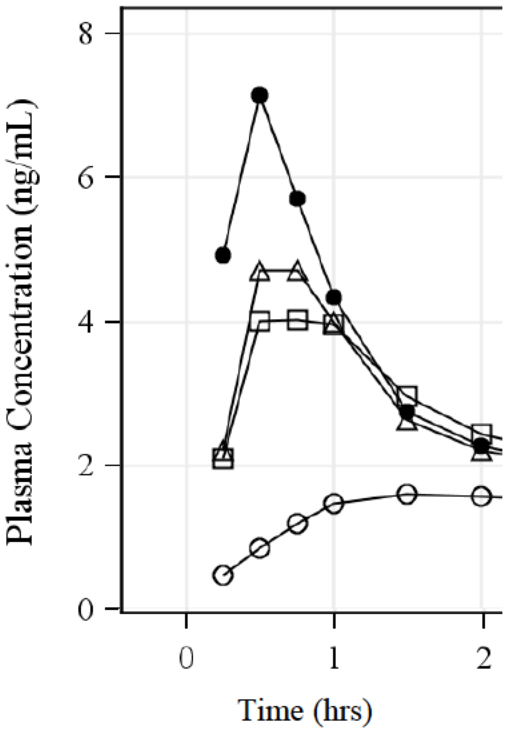


Figure: Mean plasma oxymorphone profiles over an initial 2 hour period with treatments as follows:

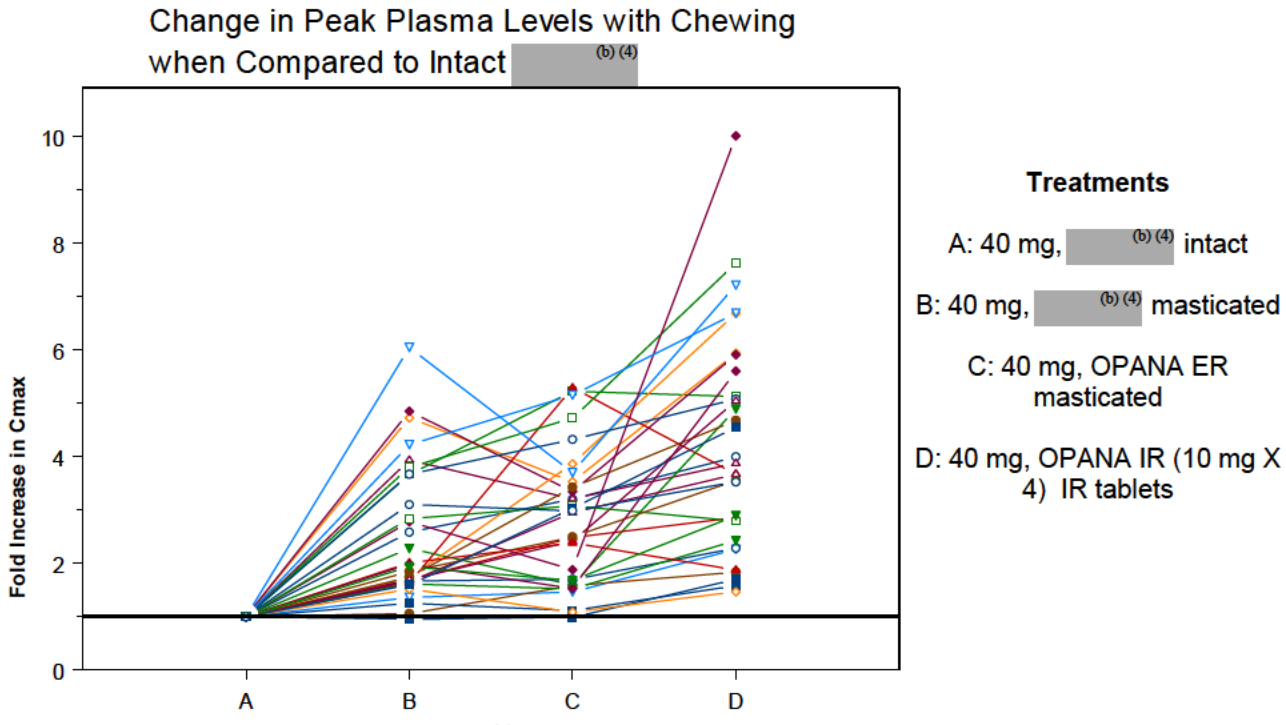
- Treatment A: EN3288 40 mg - intact tablet
- Treatment B: EN3288 40 mg - tablet ingested after mastication
- Treatment C: OPANA ER 40 mg – tablet ingested after mastication
- Treatment D: OPANA 40 mg (4 × 10 mg) – intact tablets (reference product)

However, comparison with intact extended-release tablet indicates a 2.2-fold increase in Cmax when [redacted] is consumed after chewing.

	Treatment	N	Geometric Least Squares Mean	Ratio of Least Squares Mean		Lower 90% CI	Upper 90% CI
Cmax (ng/mL)	A	31	2.05				
	B	31	4.55	B/A	2.22	1.94	2.54
	C	31	5.15	C/A	2.51	2.19	2.87
	D	31	7.72				

A EN3288 40 mg – intact tablet
B EN3288 40 mg – tablet ingested after mastication
C OPANA ER 40 mg – tablet ingested after mastication
D OPANA 10 mg (4×10 mg) – intact tablets

When considering individual data, fold increase in Cmax as high as 6-fold were noted when [redacted] was consumed after chewing (Treatment B) (See figure below). Fold change in Cmax for each individual were calculated by dividing Cmax noted for each treatment with Cmax noted with reference treatment A ([redacted] 40 mg intact).



Overall Conclusions:

1. (b) (4) 40 mg is bioequivalent to OPANA ER under fasted and fed conditions. At the time of writing this review, inspection report from DSI of study EN3288-103 is pending.
2. (b) (4) 5 mg is bioequivalent to OPANA ER under fasted condition.
3. Similar to OPANA ER, alcohol-related interaction results in high peak plasma levels.
4. Although (b) (4) seems to resist crushing by pill crusher, it is susceptible to defeat of extended-release characteristics by other methods of physical manipulation. Cutting and grinding (b) (4) resulted in a significant increase in peak plasma levels compared to intact product.
5. As demonstrated by significant increase in peak plasma levels compared to intact product, extended-release characteristics of (b) (4) were defeated when chewed and consumed.

2 QBR

2.1 General Attributes

Endo Pharmaceuticals submitted a 505(b)(1) type new drug application for the use of (b) (4) a new extended-release formulation of oxymorphone HCl for the relief of moderate to severe pain in subjects requiring continuous, around-the lock opioid therapy for an extended period of time. (b) (4) also referred to as EN3288, contains the same drug substance found in Endo Pharmaceuticals' immediate-release (IR) OPANA (NDA 21-611) and extended release (ER) OPANA ER (NDA 21-610) oral formulations of oxymorphone HCl, which were both approved by the FDA on June 22, 2006. This application seeks to market 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg and 40 mg strengths of (b) (4) tablets.

(b) (4) was developed to resist accidental misuse and intentional abuse of oxymorphone extended-release tablets. (b) (4) tablet is characterized by a (b) (4) (b) (4) The proposed indication, route of administration, dosing regimen remain identical to previously approved OPANA ER (NDA 21-610).

Oxymorphone HCl, a semi-synthetic opioid, exhibits its safety profile and efficacy in pain management due to its agonist activity at the mu-opioid receptor.

2.2 General Clinical Pharmacology

The applicant submitted pharmacokinetic studies with 5 mg and 40 mg strengths to establish bioequivalence of (b) (4) to OPANA ER, which was previously approved for the same indication. The applicant is requesting waiver for bioavailability studies of intermediate strengths based on compositional proportionality and in vitro dissolution studies. The in vitro dissolution studies for the purpose of bridging the intermediate strengths and alcohol drug interaction studies are reviewed by biopharmaceutics reviewer Dr. Sandra Suarez of Office of New Drug Quality Assurance.

Additionally, pharmacokinetics and safety of (b) (4) were evaluated under conditions of normal use and accidental misuse (i.e., breaking and/or crushing for patient convenience) and certain methods of intended abuse (i.e., crushing for snorting and/or injection). Additional in vitro studies were performed by the applicant to address if different common methods of tampering with controlled release products known to drug addicts would defeat the extended release properties of (b) (4) These in vitro studies were reviewed by control substance staff reviewer Dr. James Tolliver.

Six pharmacokinetic studies were conducted in healthy volunteers to establish bioequivalenc to OPANA ER and support (b) (4) (b) (4) tablets (See table below).

Studies establishing bioequivalence of (b) (4) to OPANA ER
Study # EN3288-103: BE study comparing (b) (4) 40 mg compared to OPANA ER 40 mg in healthy subjects under fasting state and naltrexone blockade.
Study # EN3288-104: BE study comparing (b) (4) 40 mg compared to OPANA ER 40 mg in

healthy subjects **under fed state** and naltrexone blockade.
Study # EN3288-105: BE study comparing [redacted] (b) (4) 5 mg compared to OPANA ER 5 mg in healthy subjects under fasting and naltrexone blockade.
PK studies conducted to evaluate dose dumping potential of [redacted] (b) (4) taken intact or after improper use
Study # EN3288-107: Alcohol interaction study assessing relative bioavailability of [redacted] (b) (4) 40 mg taken with or without an alcoholic beverage and naltrexone blockade.
Study # EN3288-108: Relative bioavailability study comparing [redacted] (b) (4) 40 mg taken intact and after physical tampering (cutting, crushing and grinding) and naltrexone blockade.
Study # EN3288-109: Relative bioavailability and drug-liking study comparing [redacted] (b) (4) 40 mg taken intact and after chewing without naltrexone blockade.

2.2.1 Is [redacted] (b) (4) bioequivalent to OPANA ER?

Yes. Peak plasma concentration and AUC of oxymorphone are bioequivalent between [redacted] (b) (4) and OPANA ER at 40 mg and 5 mg doses under fasting condition.

Efficacy and safety of [redacted] (b) (4) was established by demonstration of bioequivalence of the highest (40 mg) strength [redacted] (b) (4) with OPANA ER under fasting condition (Study # EN3288-103). With regard to intermediate strengths (7.5 – 30 mg), results of bioequivalence at the lowest (5 mg) tablet strengths compared to OPANA ER under fasting condition (Study # EN3288-105) along with similarity of intermediate tablet strength in vitro dissolution profiles was provided.

The bioequivalence studies (EN3288-104 and EN3288-105) were open-label, randomized, single-dose, 2-sequence, 4-period, replicate, crossover studies in healthy subjects receiving naltrexone to block opioid effects of oxymorphone.

The results of the ANOVA comparison of geometric mean results of oxymorphone AUC and Cmax for the three BE studies are provided in the table below. As indicated in the table, the analysis confirms that the 5 mg and 40 mg [redacted] (b) (4) tablets are bioequivalent to 5 mg and 40 mg OPANA ER, respectively under fasting condition. Bioequivalence was concluded if the 90% CI of the geometric mean ratio ([redacted] (b) (4) or EN3288 over OPANA ER) for oxymorphone AUC_{0-t} and C_{max} fall within the limits of 0.8 to 1.25.

Summary table indicating BE analysis of [redacted] (b) (4) compared to OPANA ER

Parameter	**Geometric Least Squares Means**		**Ratio of Means**	**90% Confidence Interval**
	EN3288	OPANA ER		
EN3288-103: Single 40 mg Oral Doses to Fasted Healthy Subjects*				
Cmax (ng/mL)	[redacted] (b) (4)			
AUC0-t (ng•h/mL)				
EN3288-105: Single 5 mg Oral Doses to Fasted Healthy Subjects				
Cmax (ng/mL)	0.352	0.360	0.98	0.93-1.03
AUC0-t (ng•h/mL)	5.04	4.82	1.05	1.01-1.09

*Pending confirmation of acceptance of data by Division of Scientific Investigations

Pharmacokinetic profile and parameters of (b) (4) ***(40 mg and 5 mg) under fasting condition***

Figure: Mean ±SE Oxymorphone Plasma Concentrations Versus Time After Single Oral Doses of EN3288 and OPANA ER **40 mg** to Fasted Subjects (EN3288-103).

Table: Plasma Pharmacokinetics of Oxymorphone **40 mg** Single Oral Dose to Fasted Healthy Subjects - Arithmetic Mean ± SD (%CV) (EN3288-103)

(b) (4)

Figure: Mean ±SE Oxymorphone Plasma Concentrations Versus Time After Single Oral **5 mg** Doses of EN3288 and OPANA ER to Fasted Subjects (EN3288-105)

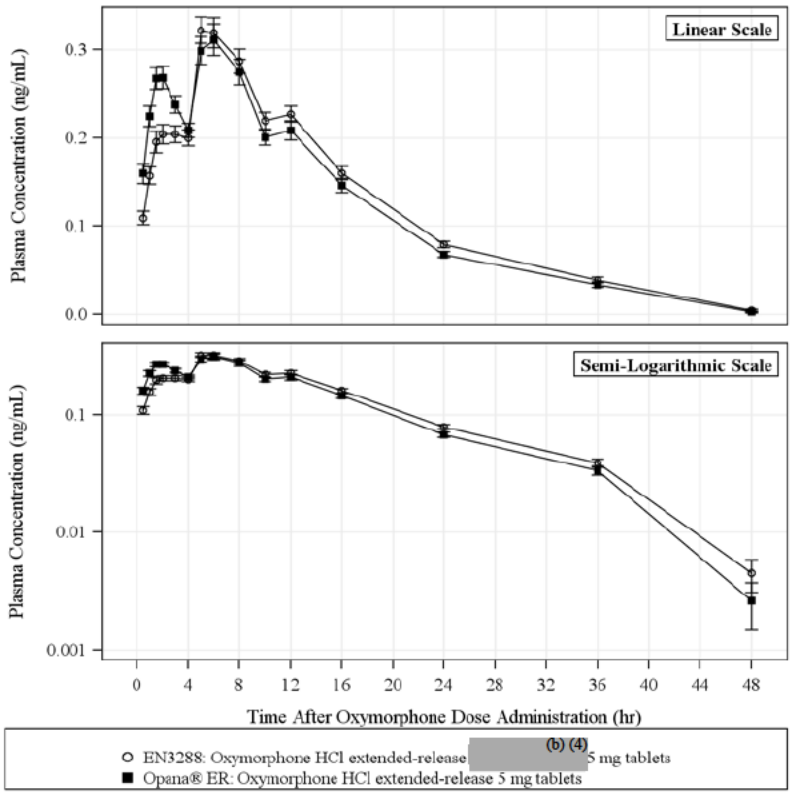


Table: Plasma Pharmacokinetics of Oxymorphone 5 mg After a Single Oral Dose of **5 mg** to Fasted Healthy Subjects - Arithmetic Mean±SD (%CV) (EN3288-105)

Parameter	EN3288 5 mg	OPANA ER 5 mg
AUC_{0-t} (ng•h/mL)	5.29±1.515 (28.7)	5.05±1.549 (30.7)
C_{max} (ng/mL)	0.370±0.1171 (31.7)	0.375±0.1144 (30.5)
T_{max} (h)[a]	5.0 (1.0-16.0)	6.0 (1.0-12.0)
C_t (ng/mL)	0.044±0.0146 (33.2)	0.043±0.0109 (25.1)

2.3 Intrinsic Factors

No new information was provided. (b) (4) NDA relies on previous findings from OPANA ER NDA.

2.4 Extrinsic Factors

Relevant extrinsic factors for this NDA include the effect of misuse and abuse on extended release characteristics of (b) (4) The applicant evaluated effect of the accidental misuse of (b) (4) following: a) consumption of alcohol, b) crushing by a pill crusher. The applicant evaluated intentional effect of intentional abuse of (b) (4) following: a) grinding (b) (4) and b) chewing. Extended release profile of (b) (4) is characterized by lower plasma levels and delayed time to peak plasma levels

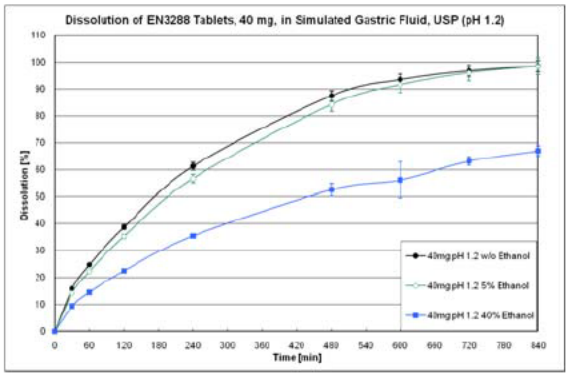
compared to equal dose of immediate release product. Peak plasma levels of 40 mg [redacted] taken intact under fasting condition are ~ 1/4th (~ 2 ng/mL) of that noted with 4 X 10 mg dose of OPANA IR (~8 ng/mL). Time to peak plasma levels is ~ 5 hours with [redacted] compared to ~ 0.5 hour with immediate release product. Hence, extended release profile of [redacted] under normal use or improper use is discussed with particular attention to peak plasma levels in the clinical pharmacology summary. Over all systemic profile in terms of AUC and Tmax is also discussed below and in individual study reviews.

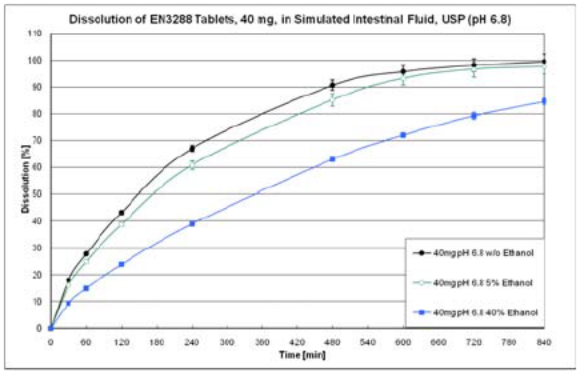
2.4.1 What is the effect of alcohol on pharmacokinetics of [redacted]

As such opioids, including oxymorphone, cause additive central nervous system depressive effects when consumed with alcohol. Additionally, accidental consumption of alcohol with regular doses of [redacted] may result in significantly high plasma levels of oxymorphone. Iin vitro alcohol interaction studies show that both [redacted] and OPANA ER (previous NDA observations) did not show any dose-dumping characteristics.This effect is probably related to oxymorphonedrug substance per se as opposed to the compromise of the ER characteristics of [redacted] and OPANA ER.

Previously, OPANA ER did not dose-dump in alcoholic solutions when evaluated in vitro. However, in vivo alcohol interaction was noted. Applicant conducted in vitro studies to evaluate dissolution characteristics of [redacted] in different concentrations of alcoholic solutions. Dissolution of [redacted] tablets in phosphate buffer solution is characterized by release of [redacted] of oxymorphone after 8 hours. Dose-dumping is typically concluded when most of the drug is released within couple of hours of initiating the dissolution experiment. As noted by the dissolution profile (simulated gastric fluid and intestinal fluid), [redacted] tablet did not dose-dump oxymorphone. In fact, release of oxymorphone from [redacted] appears to have decreased in 40% alcohol solution. Final assessment of these data are deferred to ONDQA.

Figures: Dissolution profile of [redacted] tablet in simulated gastric fluid (left) and intestinal fluid (right).





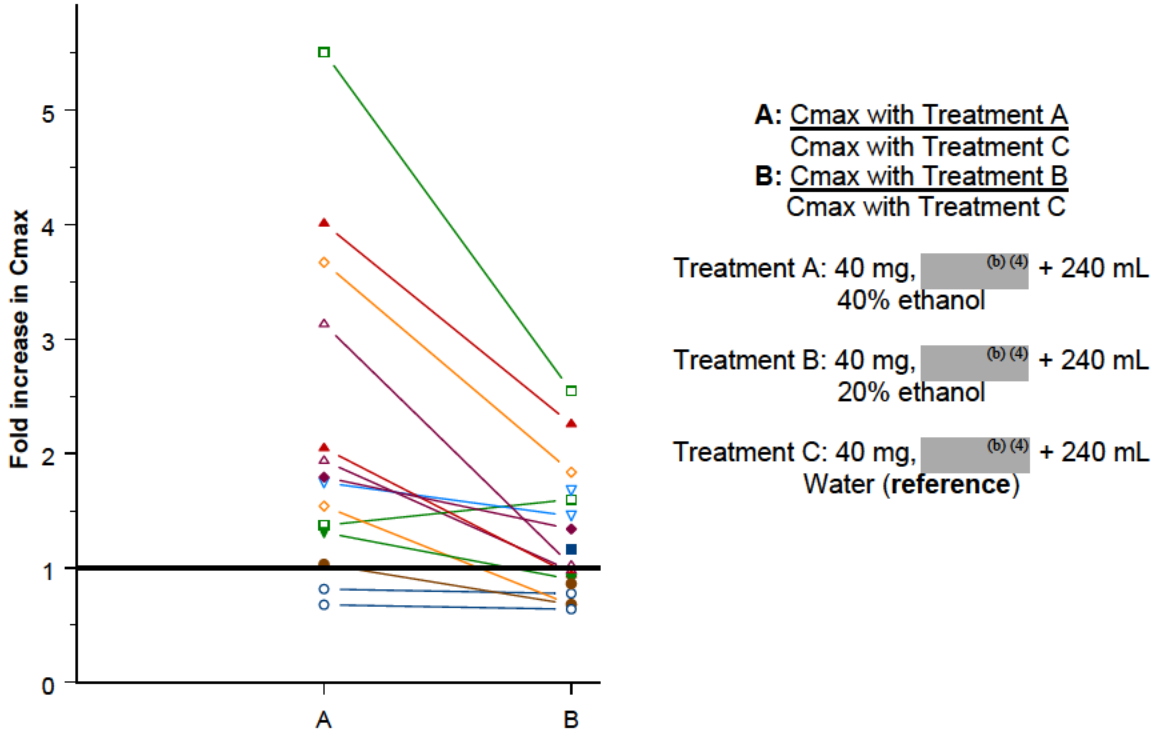
PK study # EN3288-107 was conducted to evaluate alcohol-drug interaction where effect of consuming 20% alcohol or 40% alcohol on PK of [redacted] This study was an open-label, randomized, single-dose, 3-period, 6 sequence crossover design. Subjects were randomly allocated to one of the 6 sequences to receive a single dose of EN3288 40 mg co-administered with either ethanol or water over 3 periods. Each EN3288 dose

administration was separated by a washout of at least 7 days. All treatments were to be administered to fasted subjects. The 3 treatments were:
A EN3288 40 mg + 240 mL 40% ethanol
B EN3288 40 mg + 240 mL 20% ethanol
C EN3288 40 mg + 240 mL of water (0% ethanol) (reference)

The ethanol solution was to be consumed as quickly as possible at the time of EN3288 administration. Eighteen (18) subjects were to be randomized to ensure that 12 subjects had evaluable pharmacokinetic data from 12 of the ethanol treatment arms and the water treatment arm. Hence, relative bioavailability but not bioequivalence information was derived from this study.

Results indicate that, similar to OPANA ER (noted in previous NDA), administration of [(b) (4)] with alcohol contained beverages (20% or 40%) will result in significant increase in peak plasma levels. On average, oxymorphone Cmax increased with the amount of ethanol consumed and was 1.14-fold and 1.80-fold higher with 20% and 40% ethanol, respectively. Noteworthy is the fact that in certain individuals maximum fold change in Cmax upto 2.5-fold or 5.5-fold were noted in 20% or 40% alcohol treatment groups compared to [(b) (4)] alone (see figure below).

Figure: Fold increase in Cmax following administration of [(b) (4)] with 40% alcohol (A) or 20% alcohol (B) compared to water (C, not shown) in individual subjects.



The results of the ANOVA comparison of 90% CI's of geometric mean ratio of oxymorphone AUC and Cmax provided in the Table below indicate that [(b) (4)] consumed with water is not bioequivalent (outside 0.8 – 1.25 limit) to [(b) (4)] consumed with either 20% (Cmax only) or 40% alcohol. It should be noted that the

alcohol drug interaction study was not powered to demonstrate bioequivalence. AUC of oxymorphone is similar between [(b) (4)] consumed with water and 20% alcohol containing solution. Slightly higher AUC (15% higher geometric mean ratio) was noted when [(b) (4)] was consumed with 40% alcohol beverage compared to water.

Parameter (unit)	Treatment[a]	n[b]	Geometric Least Squares Means[c]	Ratio of Least Squares Means	90% CI of the Ratio (A/C or B/C)	
					Lower	Upper
AUC_{0-t} (ng•h/mL)	A	14	33.1936	1.1539	1.0089	1.3199
	B	17	27.3132	0.9495	0.8378	1.0762
	C	17	28.7652			
AUC_{0-inf} (ng•h/mL)	A	12	34.5161	1.1403	0.9911	1.3120
	B	16	28.6886	0.9478	0.8352	1.0755
	C	17	30.2701			
C_{max} (ng/mL)	A	14	3.3302	1.7959	1.4947	2.1579
	B	17	2.1103	1.1381	0.9591	1.3505
	C	17	1.8543			

[a] A=EN3288 40 mg with 240 mL 40% ethanol; B=EN3288 40 mg with 240 mL 20% ethanol; C=EN3288 40 mg with 240 mL water

Table: Oxymorphone pharmacokinetics after each treatment administration are provided in the table below.

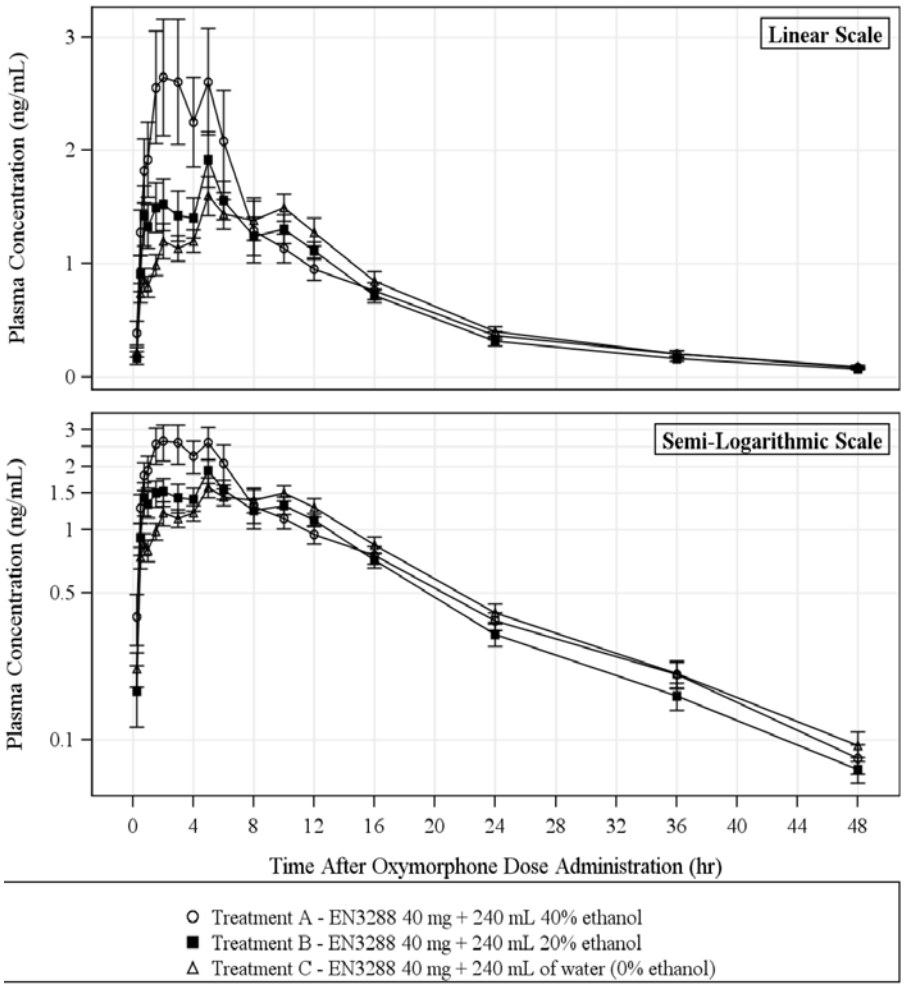
Parameter[a]	EN3288 40 mg Administered with 240 mL 40% Ethanol (N=14)	EN3288 40 mg Administered with 240 mL 20% Ethanol (N=17)	EN3288 40 mg Administered with 240 mL Water (N=17)
AUC_{0-t} (ng•h/mL)	35.57±14.136 (39.7)	28.38±8.800 (31.0)	29.96 ±9.218 (30.8)
AUC_{0-inf} (ng•h/mL)[b]	35.61±13.891 (39.0)	29.99±8.969 (29.9)	31.63±9.913 (31.3)
C_{max} (ng/mL)	3.94±2.307 (58.5)	2.34±1.118 (47.7)	1.99±0.757 (38.1)
T_{max} (h)[c]	2.0 (0.5-6.0)	5.0 (0.5-12.0)	5.0 (0.8-12.0)
C_t (ng/mL)	0.083±0.0372 (44.8)	0.072±0.0418 (57.9)	0.094±0.0624 (66.4)
λ_z (1/h)[b]	0.0801±0.01980 (24.7)	0.0743±0.01532 (20.6)	0.0708±0.02075 (29.3)
$t_{1/2}$ (h)[b]	9.2±2.28 (24.9)	9.8±2.61 (26.6)	10.7±3.48 (32.5)

Results indicate that [(b) (4)] is susceptible to alcohol consumption-related increase in plasma levels of oxymorphone. Significantly higher Cmax (Upper 90% CI's above 0.8 – 1.2) were noted in alcohol-treatment groups compared to [(b) (4)] taken with water under fasting condition.

Previously, OPANA ER also exhibited highly variable but significant alcohol-drug interaction. Following concomitant administration of 240 mL of 40% ethanol the Cmax increased on average by 70% and up to 270% in individual subjects. Following the concomitant administration of 240 mL of 20% ethanol, the Cmax increased on average by 31% and up to 260% in individual subjects. As noted with OPANA ER previously, a slight increase (15% increase) in AUC is noted when [(b) (4)] is taken with alcohol (20

or 40%, data not shown). Hence, (b) (4) and OPANA ER are similar in their susceptibility to alcohol-related drug interaction.

Figure: Plots of arithmetic mean oxymorphone concentrations versus time for (b) (4) taken with or without an alcoholic beverage are provided in the Figure below.



2.4.2 What is the effect of physical manipulation of (b) (4) tablet on its extended-release characteristics?

Although (b) (4) seems to resist crushing by pill crusher, it is susceptible to defeat of extended-release characteristics by other methods of physical manipulation. Cutting and grinding (b) (4) resulted in a significant increase in peak plasma levels compared to intact product.

Accidental misuse study: Pharmacokinetic study # EN3288-108 was conducted to evaluate safety and pharmacokinetics of (b) (4) under conditions of accidental or intentional misuse by breaking and/or crushing with different methods. This study was an open-label, randomized, 6-sequence, 6-period, crossover design. Subjects were randomized to receive the following treatments:

A EN3288 40 mg – intact tablet
B EN3288 40 mg – tablet tampered with a commercial pill crusher
C EN3288 40 mg – tablet cut (b) (4)
D EN3288 40 mg – tablet tampered (b) (4)
E OPANA ER 40 mg – tablet tampered with a commercial pill crusher
F OPANA 40 mg (4×10 mg) – intact tablets
The applicant compared bioavailability (Cmax and AUC) of (b) (4) following physical manipulation (Treatments B, C and D) with Treatment A (intact (b) (4) tablet) or Treatment F (40 mg immediate release tablets). The plasma concentration measurements (timing and assay range), sample size (29 subjects) were designed to accurately characterize the measures of systemic exposure to oxymorphone that provided evidence of bioequivalence.

The first step in misusing or abusing opioid drug products involves methods that would destroy the extended-release characteristics of drug product, followed later by oral consumption or nasal administration (snorting; not evaluated) or IV injection (not evaluated). Hence, pharmacokinetic analyses are conducted to understand the change in extended-release characteristics of drug products by comparing Cmax and AUC noted when the product is consumed under different conditions. Bioequivalence is concluded if the 90% CI of the geometric mean ratio of a treatment compared to appropriate reference for oxymorphone AUC_{0-t} and C_{max} fall within the limits of 0.8 to 1.25.

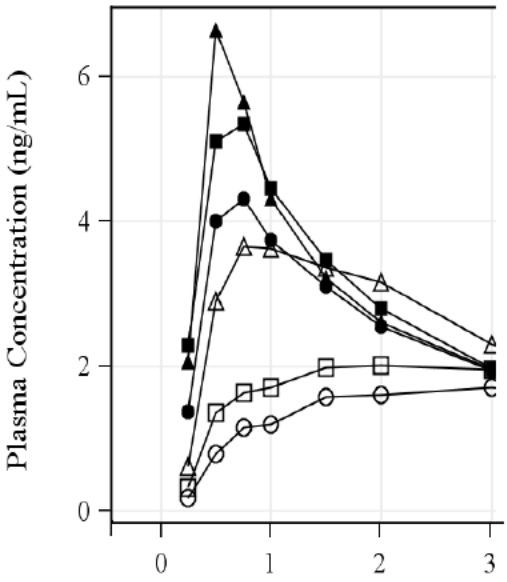


Figure: Mean plasma oxymorphone profiles over an initial 3 hour period with treatments as follows:

- ○ Treatment A: EN3288 40 mg - intact tablet
- □ Treatment B: EN3288 40 mg - (commercial pill crusher)
- △ Treatment C: EN3288 40 mg - (tablet cut (b) (4)
- ● Treatment D: EN3288 40 mg - (b) (4)
- ■ Treatment E: OPANA® ER 40 mg - (commercial pill crusher)
- ▲ Treatment F: OPANA 40 mg (4 × 10 mg) - intact tablets (reference product)

Classically, immediate release (IR) tablets produce peak plasma levels that are higher than extended-release drug products containing the same dose upon single dose administration. Use of such high Cmax values noted with OPANA IR tablets (See figure above) as reference would indicate a decrease in peak plasma levels to 0.4 – 0.7-fold when (b) (4) is consumed intact or under any condition of physical manipulation (See table below).

Table: Change in Cmax, with respect to OPANA IR 40 mg, when [redacted] 40 mg is consumed intact or following physical manipulation

Treatment	N	Geometric Least Squares Mean	Ratio of Least Squares Mean		Lower 90% CI	Upper 90% CI
A	29	3.4	A/F	0.42	0.37	0.48
B	29	3.3	B/F	0.41	0.36	0.47
C	29	5.1	C/F	0.63	0.55	0.72
D	29	5.3	D/F	0.65	0.57	0.75
E	29	6.5	E/F	0.79	0.69	0.91
F	29	8.1				

A [redacted] 40 mg – intact tablet
B [redacted] 40 mg – tablet tampered with a commercial pill crusher
C [redacted] 40 mg – tablet cut [redacted]
D [redacted] 40 mg – tablet tampered [redacted]
E OPANA ER 40 mg – tablet tampered with a commercial pill crusher
F OPANA 40 mg (4×10 mg) – intact tablets

Since the goal of this PK study is to understand whether the extended-release product can withstand physical tampering, PK results from an intact extended-release product should be used as reference. Use of IR tablets as a reference is masking the effects of physical manipulation which are obviously defeating the control release properties of [redacted] (see table below). Hence, from a clinical pharmacology perspective, bioavailability comparisons are appropriate using Treatment A or the intact extended-release tablet as reference. Using intact [redacted] (Treatment A) as reference, peak plasma levels of oxymorphone failed bioequivalence and were significantly higher when [redacted] was consumed following grinding and cutting [redacted] indicating loss of extended-release characteristics. However, data indicates that [redacted] resists physical crushing forces noted using a pill crusher as demonstrated by bioequivalence to intact [redacted] with respect to Cmax (see table below) and AUC (not shown).

Change in Cmax when [redacted] 40 mg is consumed following physical manipulation, with respect to intact [redacted] 40mg.

Treatment	N	Geometric Least Squares Mean	Ratio of Least Squares Mean		Lower 90% CI	Upper 90% CI
A	29	3.4	B/A	0.98	0.86	1.12
B	29	3.3	C/A	1.51	1.32	1.73
C	29	5.1	D/A	1.56	1.37	1.78
D	29	5.3				
E	29	6.5				
F	29	8.1				

When considering individual data, fold increase in Cmax as high as 4-fold were noted with cutting (Treatment C) and grinding (Treatment D) (See figure below). Fold change in Cmax for each individual were calculated by dividing Cmax noted for each treatment with Cmax noted with reference treatment A ((b) (4) 40 mg intact). As indicated previously by the bioequivalence was noted for Treatment B indicating no significant change compared to Treatment A.

With regard to AUC, bioequivalence was demonstrated between different methods of physical manipulation irrespective of the reference used (data not shown).

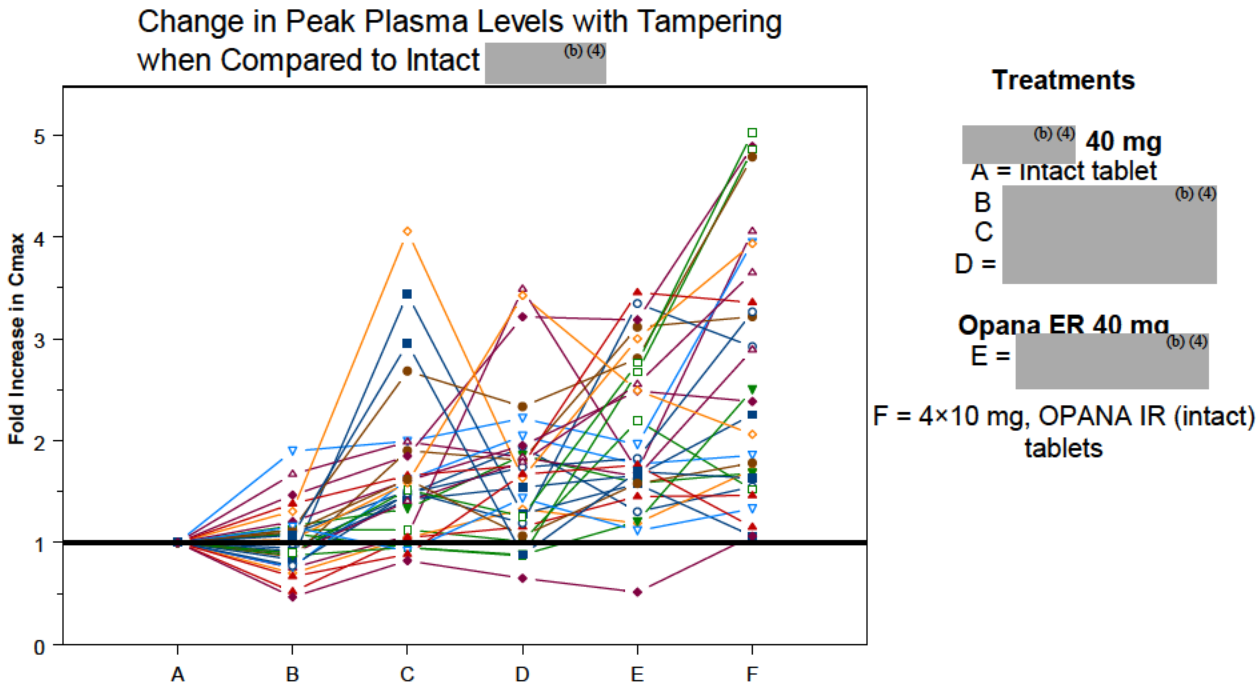


Table: Oxymorphone pharmacokinetics parameters after each treatment administration are provided in the Table below.

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	Treatment A (N=29)	Treatment B (N=29)	Treatment C (N=29)	Treatment D (N=29)	Treatment E (N=29)	Treatment F (N=29)
Drug Product[a]	**EN3288 40 mg**	**EN3288 40 mg**	**EN3288 40 mg**	**EN3288 40 mg**	**OPANA 40 mg**	**OPANA 4×10 mg**
Tampering Method	**Intact tablet**	**Commercial pill crusher**	**Cut** (b) (4)	(b) (4)	**Commercial pill crusher**	**Intact tablets**
$AUC_{0\text{-}t}$ (ng·h/mL)	46.58±12.468 (26.8)	43.44±12.156 (28.0)	44.70±14.317 (32.0)	40.68±11.570 (28.4)	43.64±13.397 (30.7)	45.18±13.863 (30.7)
$AUC_{0\text{-}inf}$ (ng·h/mL)	48.61±13.188 (27.1)	45.39±12.820 (28.2)	46.46±15.055 (32.4)	42.16±12.001 (28.5)	45.74±15.206 (33.2)	47.03±14.794 (31.5)
C_{max} (ng/mL)	3.66±1.616 (44.2)	3.51±1.201 (34.2)	5.67±2.824 (49.8)	6.39±5.556 (87.0)	7.02±2.917 (41.5)	9.41±6.626 (70.4)
T_{max} (h)[b]	5.0 (1.5-10.0)	5.0 (0.5-10.0)	1.0 (0.5- 6.0)	0.75(0.5- 6.0)	0.75(0.25-1.5)	0.5 (0.25-5.0)
C_t (ng/mL)	0.129±0.0721 (56.1)	0.118±0.0655 (55.6)	0.107±0.0771 (72.2)	0.094±0.0550 (58.6)	0.117±0.0951 (81.3)	0.113±0.0752 (66.3)
λ_z (1/h)	0.0756±0.02082 (27.5)	0.0704±0.01815 (25.8)	0.0718±0.01784 (24.9)	0.0712±0.01609 (22.6)	0.0701±0.01719 (24.5)	0.0713±0.01615 (22.7)
$t_{1/2}$ (h)	9.8±2.54 (25.9)	10.5±2.57 (24.6)	10.3±2.58 (25.2)	10.2±2.18 (21.4)	10.5±2.83 (26.9)	10.2±2.27 (22.2)
HVD (h)	10.3±3.99 (38.5)	9.1±2.84 (31.2)	4.3±2.41 (56.4)	3.5±2.47 (70.6)	2.6±1.48 (56.9)	1.7±1.44 (83.8)
MRT (h)	15.0±2.79 (18.6)	14.6±2.90 (19.9)	13.2±3.30 (25.0)	12.9±2.66 (20.7)	13.4±3.52 (26.3)	13.3±2.91 (22.0)
$AUMC_{0\text{-}inf}$ (ng·h^2/mL)	736±268.0 (36.4)	669±251.7 (37.6)	612±294.1 (48.0)	543±210.8 (38.8)	629±381.0 (60.6)	630±286.4 (45.5)
C_{max}/T_{max} (ng/mL·h)	1.0±0.74 (74.1)	1.8±1.96 (109.7)	5.7±4.24 (74.6)	8.8±11.61 (131.8)	11.3±8.15 (72.3)	18.0±16.92 (94.1)

Study of intentional abuse by chewing: Pharmacokinetic study # EN3288-109 was conducted to evaluate the effect of mastication on bioavailability of (b) (4) 40 mg. This was a randomized, double-blind, double-dummy, 4-period, 4-sequence, single-dose, crossover study in healthy, nondependent, recreational oral prescription opioid users experienced in mastication of ER opioid formulations. Unlike the previous bioavailability studies, subjects did not receive naltrexone to block opioid effects. Subjects able to tolerate and 30 mg OPANA IR tablets and able to show drug-liking effects compared to placebo during the qualification phase were randomized to receive Placebo or the following treatments: (The treatment arms in this PK sub-study were also as follows)

A EN3288 40 mg – intact tablet
B EN3288 40 mg – tablet ingested after mastication
C OPANA ER 40 mg – tablet ingested after mastication
D OPANA 10 mg (4×10 mg) – intact tablets

During the course of review, applicant was requested by the Agency to submit greater details provided to the subjects in the study as it relates to specific instructions on chewing. The excerpt of the information request and the applicant's response are included below.

> *1. In drug liking study EN3288-109, we note that you have recruited subjects experienced with chewing opioid products. We could not ascertain if the subjects were provided specific instructions on how to chew the treatments/tablets. Indicate details of instructions provided to subjects with regard to rate of chewing or duration of chewing and if the individual subjects followed those instructions.*
>
> **Endo Response**:
>
> No specific instructions with regard to rate of chewing or duration of chewing were given to the subjects. The subjects were instructed to "completely and carefully" chew the tablet for as long as possible. This instruction was given verbally to each individual subject just prior to administration of each treatment. A mouth and hand check was performed after ingestion of the tablets. The time the tablet allocated for chewing was given and the time that the subject indicated chewing was completed was recorded on source documentation.

In addition to pharmacokinetic assessments, a number of pharmacodynamic measures as it relates to drug effects were assessed over a 24 hour period. While pharmacokinetic analysis is discussed below, pharmacodynamic assessments are discussed by Controlled-Substance Staff reviewer Dr. James Tolliver.

The applicant compared bioavailability (Cmax and AUC) of (b) (4) following mastication (Treatments B) with Treatment A (intact (b) (4) 40 mg tablet) or Treatment D (40 mg immediate release tablets). As with BE studies, bioequivalence is concluded if the 90% CI of the geometric mean ratio of a treatment compared to appropriate reference for oxymorphone AUC_{0-t} and C_{max} fall within the limits of 0.8 to 1.25.

Using intact OPANA IR tablets (Treatment D) as reference, which has the highest Cmax compared to all treatment groups (See figure below), peak plasma levels following chewing ranged between 0.5 – 0.7-fold (See table below).

Treatment	N	Geometric Least Squares Mean (Cmax)	Ratio of Least Squares Mean		Lower 90% CI	Upper 90% CI
A	31	2.05	A/D	0.27	0.23	0.3
B	31	4.55	B/D	0.59	0.52	0.67
C	31	5.15	C/D	0.67	0.58	0.76
D	31	7.72				

A EN3288 40 mg – intact tablet
B EN3288 40 mg – tablet ingested after mastication
C OPANA ER 40 mg – tablet ingested after mastication
D OPANA 10 mg (4×10 mg) – intact tablets

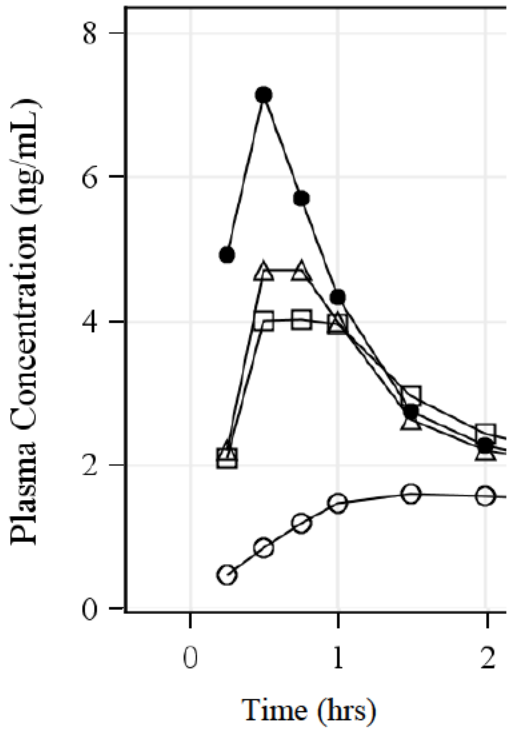


Figure: Mean plasma oxymorphone profiles over an initial 2 hour period with treatments as follows:

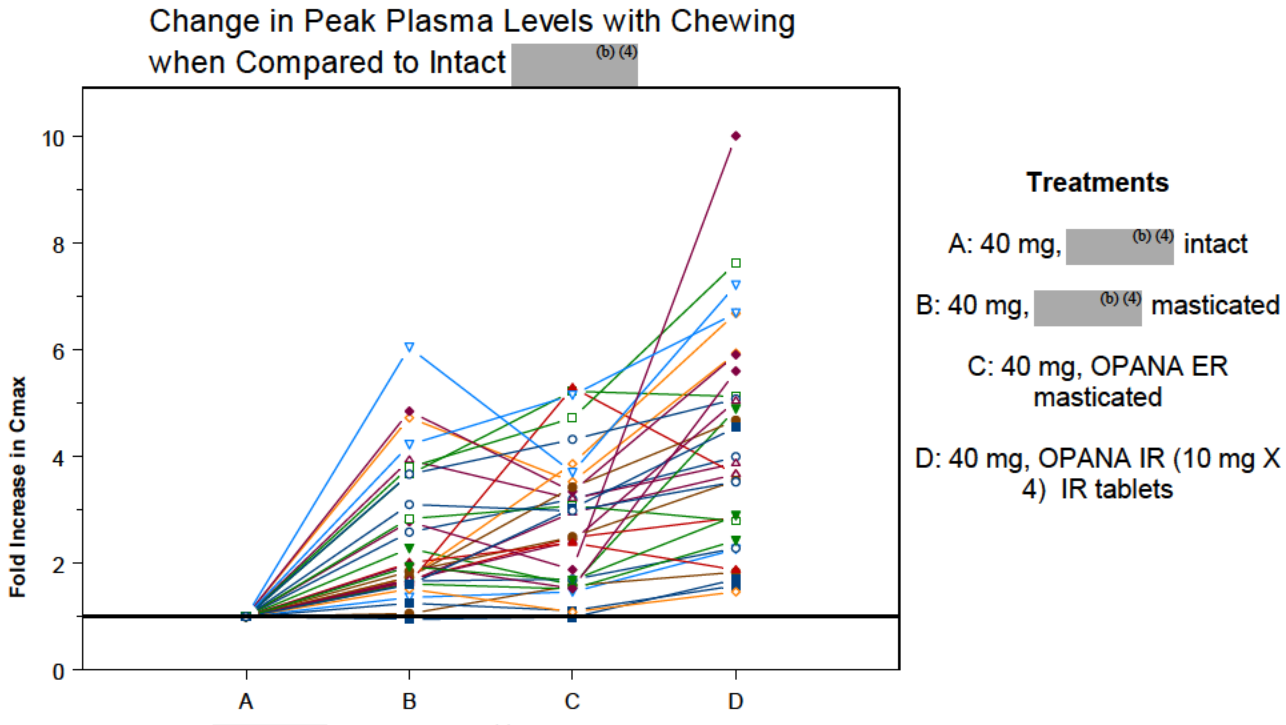
- Treatment A: EN3288 40 mg - intact tablet
- Treatment B: EN3288 40 mg - tablet ingested after mastication
- Treatment C: OPANA ER 40 mg – tablet ingested after mastication
- Treatment D: OPANA 40 mg (4 × 10 mg) – intact tablets (reference product)

As discussed in the previous study results, from a clinical pharmacology perspective it is important to understand if the product retains its extended-release characteristics under conditions of improper use. This can only be accomplished by utilizing intact extended-release product as a reference (Treatment A). Comparison with intact extended-release tablet indicates a 2.2-fold increase in Cmax when [redacted] (b) (4) is consumed after chewing (see table below).

	Treatment	N	Geometric Least Squares Mean	Ratio of Least Squares Mean		Lower 90% CI	Upper 90% CI
Cmax (ng/mL)	A	31	2.05				
	B	31	4.55	B/A	2.22	1.94	2.54
	C	31	5.15	C/A	2.51	2.19	2.87
	D	31	7.72				

A EN3288 40 mg – intact tablet
B EN3288 40 mg – tablet ingested after mastication
C OPANA ER 40 mg – tablet ingested after mastication
D OPANA 10 mg (4×10 mg) – intact tablets

When considering individual data, fold increase in Cmax as high as 6-fold were noted when [redacted] (b) (4) was consumed after chewing (Treatment B) (See figure below). Fold change in Cmax for each individual were calculated by dividing Cmax noted for each treatment with Cmax noted with reference treatment A ([redacted] (b) (4) 40 mg intact).



Intact or chewed [redacted] (b) (4) treatments were bioequivalent with respect to oxymorphone AUC.

Table: Oxymorphone pharmacokinetics after each treatment administration are provided in the table below.

	Treatment A (N=31)	Treatment B (N=31)	Treatment C (N=31)	Treatment D (N=31)
Drug Product[a]	**EN3288 40 mg**	**EN3288 40 mg**	**OPANA ER 40 mg**	**OPANA 4×10 mg**
Manipulation of Tablet	**Intact tablet**	**Masticated**	**Masticated**	**Intact tablets**
AUC_{0-t} (ng·h/mL)	30.16±8.441 (28.0)	32.24±9.987 (31.0)	31.79±8.158 (25.7)	33.54±10.558 (31.5)
AUC_{0-inf}[b] (ng·h/mL)	33.98±10.058 (29.6)	35.29±11.246 (31.9)	35.77±8.797 (24.6)	36.85±9.940 (27.0)
C_{max} (ng/mL)	2.17±0.774 (35.7)	5.16±2.838 (55.0)	5.67±2.612 (46.1)	8.69±4.822 (55.5)
T_{max} (h)[c]	3.0 (0.8-10.0)	0.8 (0.3-2.1)	0.8 (0.3-1.1)	0.5 (0.3-1.0)
C_t (ng/mL)	0.158±0.0710 (44.9)	0.140±0.0720 (51.4)	0.129±0.0515 (39.8)	0.146±0.0522 (35.8)
λ_z[b] (1/h)	0.0507±0.01475 (29.1)	0.0484±0.01238 (25.6)	0.0513±0.01529 (29.8)	0.0492±0.01395 (28.3)
$t_{1/2}$[b] (h)	15.3±6.47 (42.2)	15.2±3.68 (24.2)	14.7±4.70 (31.9)	15.3±4.88 (31.9)
HVD (h)	8.9±4.35 (48.7)	2.3±1.29 (57.1)	1.7±1.54 (89.6)	0.9±0.54 (59.5)
MRT[b] (h)	21.5±6.78 (31.6)	18.5±4.64 (25.1)	17.8±4.46 (25.1)	18.8±6.05 (32.1)
C_{max}/T_{max} (ng/mL·h)	1.1±0.89 (78.3)	7.6±5.63 (74.1)	9.8±6.70 (68.4)	22.1±20.66 (93.7)

[a] Source: EN3288-109 Clinical Study Report, Table 14.2.2.1

[b] N=23 for EN3288 40 mg, intact tablet; N=24 for EN3288 40 mg, masticated; N=25 for OPANA ER 40 mg masticated; N=22 for OPANA 4×10 mg, intact tablet

Analysis of pharmacodynamic effects with respect to drug-liking may be found in controlled substance staff review by Dr. James Tolliver.

Unlike the previous PK studies, naltrexone was not administered to block the opioid effects of oxymorphone in this drug-liking study. Additionally, this study was also placebo controlled. Hence, safety data across different treatments following single dose was reviewed. Of particular interest are typical opioid effect related side effects such as nausea, vomiting, pruritus, headache, dizziness and somnolence.

In the qualification phase, treatment emergent adverse events (TEAEs) occurred in 37 of 51 (73%) subjects after administration of OPANA 30 mg and in 6 of 51 (12%) subjects after administration of placebo. In the treatment phase, TEAEs occurred in 15 of 41 (37%) subjects after administration of treatment A (EN3288 intact); in 26 of 42 (62%) subjects after administration of treatment B (EN3288 masticated); in 34 of 43 (79%) subjects after administration of treatment C (OPANA ER masticated); and in 38 of 43 (88%) subjects after administration of treatment D (OPANA 4×10 mg intact). As shown in the table below, treatment related opioid effects were noted in higher frequency following consumption of (b) (4) (EN3288) by chewing compared to Placebo or intact (b) (4)

Table: Treatment emergent adverse effects following single dose administration.

Category	OPANA 30 mg (3×10 mg) tablets (N=51) n (%) During Qualification	Placebo (N=51) n (%)	EN3288 40 mg -intact (N=41) n (%)	EN3288 40 mg - tablet ingested after mastication (N=42) n (%)	OPANA ER 40 mg - tablet ingested after mastication (N=43) n (%)	OPANA 40 mg (4×10 mg) - intact (reference product) (N=43) n (%)
Pruritus	21 (41.2)	0	6 (14.6)	18 (42.9)	23 (53.5)	27 (62.8)
Nausea	14 (27.5)	2 (3.9)	4 (9.8)	8 (19.0)	9 (20.9)	13 (30.2)
Vomiting	3 (5.9)	0	1 (2.4)	2 (4.8)	6 (14.0)	5 (11.6)
Headache	3 (5.9)	2 (3.9)	4 (9.8)	4 (9.5)	7 (16.3)	7 (16.3)
Somnolence	3 (5.9)	0	2 (4.9)	0	3 (7.0)	5 (11.6)
Dizziness	4 (7.8)	1 (2.0)	1 (2.4)	2 (4.8)	3 (7.0)	5 (11.6)

2.5 General Biopharmaceutics

(b) (4) contains oxymorphone hydrochloride, a semi-synthetic opioid analgesic, and is supplied in 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg extended-release tablet strengths for oral administration. (b) (4) tablet is characterized by a (b) (4) (b) (4) The tablets contain the following inactive ingredients: hypromellose, polyethylene oxide, polyethylene glycol, α-tocopherol, citric acid, polyvinyl alcohol, titanium dioxide, macrogol and talc (See tablet composition in the table below).

Ingredient (mg)	5 mg	7.5 mg	10 mg	15 mg	20 mg	30 mg	40 mg	Function
Oxymorphone hydrochloride	5.0	7.5	10.0	15.0	20.0	30.0	40.0	Drug Substance
Polyethylene oxide (PEO) (b) (4)	(b) (4)							
(b) (4) HPMC (b) (4)								
Polyethylene glycol (b) (4) (PEG)[a]								
α-tocopherol (b) (4)								
Citric acid, anhydrous								
(b) (4)								
Total tablet weight	221.5	221.5	221.5	221.5	221.5	221.5	221.5	

(b) (4)

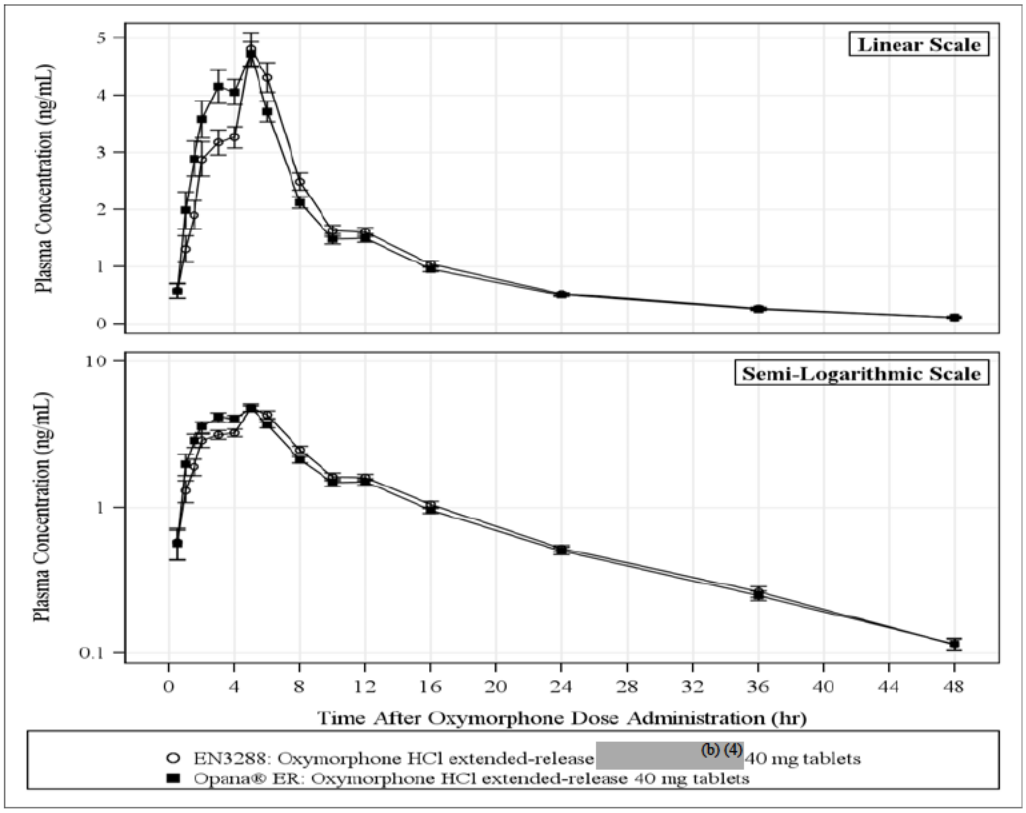
2.5.1 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The applicant established bioequivalence of the highest strength (40 mg) [redacted] with OPANA ER in healthy volunteers taking the FDA specified high fat meal. Previously, the applicant identified that OPANA ER has significant food effect. Agency recommended that OPANA ER should be dosed at least one hour prior to or two hours after eating. Since the two products are bioequivalent in fed state, same dosing recommendation should be made for [redacted]

In place of a food effect study, bioequivalence of 40 mg [redacted] tablet with marketed product OPANA ER was established under fed condition (Study # EN3288-104). The bioequivalence study EN3288-104 was an open-label, randomized, single-dose, 2-sequence, 4-period, replicate, crossover studies in healthy subjects receiving naltrexone to block opioid effects of oxymorphone.

The results of the ANOVA comparison of geometric mean results of oxymorphone AUC and Cmax for the three BE studies are provided in the table below. As indicated in the table below, the analysis confirms that the 40 mg [redacted] tablet is bioequivalent to 40 mg OPANA ER, respectively under fed condition. In BE studies, bioequivalence is concluded if the 90% CI of the geometric mean ratio [redacted] or EN3288 over OPANA ER) for oxymorphone AUC_{0-t} and C_{max} fall within the limits of 0.8 to 1.25.

Figure: Mean ±SE Oxymorphone Plasma Concentrations Versus Time After Single Oral Doses of EN3288 and OPANA ER 40 mg to Fed Subjects (EN3288-104).



Summary table indicating BE analysis of [redacted] (b) (4) compared to OPANA ER under fed condition

Parameter	Geometric Least Squares Means		Ratio of Means	90% Confidence Interval
	EN3288	OPANA ER		
EN3288-104: Single 40 mg Oral Doses to Healthy Subjects with a High-Fat Meal				
Cmax (ng/mL)	5.24	5.55	0.94	0.88-1.02
AUC0-t (ng•h/mL)	47.10	48.43	0.97	0.93-1.02

Table: Plasma Pharmacokinetics of Oxymorphone 40 mg Single Oral Dose to Fed Healthy Subjects - Arithmetic Mean ± SD (%CV) (EN3288-104)

Parameter	EN3288 40 mg	OPANA ER 40 mg
AUC_{0-t} (ng•h/mL)	[redacted]	50.16±14.910 (29.7)
AUC_{0-inf} (ng•h/mL)		52.29±15.980 (30.6)
C_{max} (ng/mL)		5.87±1.992 (33.9)
T_{max} (h)[a]		3.5 (1.0-6.0)
C_t (ng/mL)		0.12±0.087 (73.7)
λ_z (1/h)		0.0726±0.02108 (29.0)
$t_{1/2}$ (h)		10.5±4.12 (39.3)

Previously, during the review of NDA 21-610, clinical pharmacologist Dr. David Lee noted that the mean oxymorphone C_{max} in the fed state (4.25 ng/mL) was about 52% higher than the C_{max} in fasted state (2.79 ng/mL). Current dosing recommendations for OPANA ER indicate that the tablet should be dosed at least one hour prior to or two hours after eating. No change in dosing recommendation is needed taking into consideration the safety and efficacy of OPANA ER and bioequivalence of [redacted] (b) (4) to OPANA ER under fasting and fed condition.

2.6 Analytical

The method (AP LC/MS/MS 374.100) for determining oxymorphone/ 6-β-hydroxyoxymorphone in human plasma has been validated with a detection range of 0.02500/0.02500 to 10.00/10.00 ng/mL using an API 4000 LC/MS/MS system. The interface used with the API 4000 LC/MS/MS was a Turbo Ionspray®. The positive ions were measured in MRM mode. The analytes were quantitated using a solid phase extraction procedure. After extraction of a 200 µL sample, 10.00 µL was injected onto a LC/MS/MS system. The internal standard was (b) (4) (b) (4) Linear regression, with 1/x2 weighting, was used to obtain the best fit of the data for the calibration curves, which consisted of 9 samples with concentrations from 0.025/0.025 to 10/10 ng/mL. Quality control (QC) samples at low concentrations of 0.075/0.075 ng/mL (LQC), medium concentrations of 0.75/0.75 ng/mL (MQC) and high concentrations of 7.5/7.5 ng/mL (HQC), for oxymorphone/6-β-hydroxyoxymorphone prepared in human plasma, were analyzed with the assay validation to ensure acceptable assay precision and accuracy.

Intra-day precision (CV) and accuracy (bias) were evaluated from the mean concentration results of sets of 6 QC samples (at 3 concentrations) processed in each of 3 separate batch runs. In addition, 6 lower limit of quantification (LLOQ) and 6 upper limit of quantification (ULOQ) samples were included in each validation batch run. The results are presented in Table below.

Linearity of the calibration lines was confirmed by satisfactory precision and accuracy of the method over the calibration range.

Assay Intra-Day Validation Precision and Accuracy: Oxymorphone and 6-Hydroxy-Oxymorphone

Concentration [a] (ng/mL)	Oxymorphone		6-β-OH-Oxymorphone	
	Precision (CV%)	Accuracy (%Bias)	Precision (CV%)	Accuracy (%Bias)
LLOQ: 0.025	7.0% to 15.7%	-4.9% to 6.9%	6.1% to 12.5%	-12.3% to 8.3%
LQC: 0.075	3.7% to 5.9%	-4.9% to 8.8%	1.5% to 3.9%	-1.0% to 2.0%
MQC: 0.75	2.9% to 6.4%	-2.0% to 0.6%	2.6% to 5.8%	1.9% to 4.6%
HQC: 7.50	1.8% to 1.9%	-5.6% to -2.9%	1.5% to 2.5%	-2.3% to -1.4%
ULOQ: 10.0	1.7% to 4.1%	-8.4% to -3.0%	1.7% to 5.3%	-6.8% to -0.9%

The inter-day precision (CV) for QC samples for oxymorphone was within the range of 2.1% to 7.5% and the inter-day accuracy (bias) was within the range of -4.2% to 0.3%. The inter-day precision (CV) for 6-β-hydroxyoxymorphone QC samples was within the range of 1.9% to 4.3% and the inter-day accuracy (bias) was within the range of -1.9% to 2.9%. The inter-day precision for oxymorphone /6-β-hydroxyoxymorphone at the ULOQ was 3.6%/4.3% and at the LLOQ was 12.4%/12.8%. The inter-day accuracy for oxymorphone /6-β-hydroxyoxymorphone at the ULOQ was -5.7%/-3.4% and at the LLOQ was 2.9%/0.7%. The method was validated for analysis of concentrations >10 ng/mL by dilution of a 50 ng/mL sample with blank plasma. The precision and accuracy

of 6 samples were 1.7% and 0.8% for oxymorphone and -6.2% and -2.4% for 6-OH-oxymorphone.

The precision and accuracy of the analysis of samples for each study is summarized for oxymorphone and 6β-OH-oxymorphone in the two tables below. Two (2) QC samples at each of 3 concentrations were included in each assay batch run. A batch run was considered valid if 2/3 of QC sample results were within ±15% nominal values, and 50% of the QC sample results from each concentration were within ±15% nominal values.

Oxymorphone Assay Inter-day Precision and Accuracy During Study Sample Analysis

	Precision (%CV)[a]			Accuracy (%Bias)		
Study ID	LQC 0.075ng/mL	MQC 0.75ng/mL	HQC 7.50ng/mL	LQC 0.075ng/mL	MQC 0.75ng/mL	HQC 7.50ng/mL
EN3288-103	9.6%	7.6%	6.3%	-5.5%	-4.7%	-1.8%
EN3288-104	9.8%	4.9%	5.9%	-0.9%	-3.9%	-1.1%
EN3288-105	13.4%	7.8%	7.1%	-1.7%	-3.1%	-1.2%
EN3288-107	10.6%	7.2%	7.6%	-4.8%	-2.4%	-1.3%
EN3288-108	11.9%	7.5%	8.1%	-2.3%	1.5%	5.1%
EN3288-109	8.1%	7.9%	5.2%	-1.7%	-0.2%	7.1%

6-β-Hydroxy-Oxymorphone Assay Inter-day Precision and Accuracy During Study Sample Analysis

	Precision (%CV)[a]			Accuracy (%Bias)		
Study ID	LQC 0.075ng/mL	MQC 0.75ng/mL	HQC 7.50ng/mL	LQC 0.075ng/mL	MQC 0.75ng/mL	HQC 7.50ng/mL
EN3288-103	7.0%	5.7%	6.0%	-5.7%	-2.7%	-6.6%
EN3288-104	7.6%	4.8%	4.0%	-2.1%	-1.3%	-5.2%
EN3288-105	5.9%	4.8%	4.1%	-1.6%	-1.1%	-5.9%
EN3288-107	8.1%	4.4%	4.6%	-3.4%	-0.9%	-6.0%
EN3288-108	12.1%	5.0%	6.6%	1.8%	5.5%	0.2%
EN3288-109	7.9%	6.7%	5.5%	3.4%	6.7%	2.3%

A portion of the study samples were reanalyzed (incurred sample reanalysis) to provide evidence of the reproducibility of the sample concentration results. Assay reproducibility was established if at least 2/3 of the samples had repeat results within 20% of the original values. The results are provided in below and show that more than 2/3 (67%) reanalyzed samples had results within 20% of reported assay result.

Reanalysis of Incurred Samples

Study ID	Number of Samples Assayed (2/3 the Number)[a]	Number (Percent of Samples Assayed) Samples with Results within 20%	
		Oxymorphone	6β-OH-oxymorphone
EN3288-103	150 (100)	123 (82%)	141 (94%)
EN3288-104	149 (100)	120 (81%)	145 (97%)
EN3288-105	146 (98)	140 (96%)	145 (99%)
EN3288-107	104 (70)	94 (90%)	103 (99%)
EN3288-108	223 (149)	207 (93%)	214 (96%)
EN3288-109	205 (137)	183 (89%)	197 (96%)

3 Labeling

Since this NDA is based on establishing bioequivalence between [redacted] (b) (4) and OPANA ER, much of the proposed labeling is identical to the previously approved OPANA ER. The sponsor has replaced mention of brand name "OPANA ER" with oxymorphone extended release tablets. Clinical pharmacology relevant sections of proposed label are discussed below. Sponsor proposed text is indicated in regular font, while reviewer proposed text is indicated as bold or strike-through font for additions and deletions, respectively.

2 DOSAGE AND ADMINISTRATION

…

2.2 Initiating Therapy with OPANA ER

Administer [redacted] (b) (4) on an empty stomach, at least one hour prior to or two hours after eating *[see Clinical Pharmacology (12.3)]*.

…

12 CLINICAL PHARMACOLOGY

…

12.3 Pharmacokinetics

Absorption

[redacted] (b) (4)

The absolute oral bioavailability of oxymorphone is approximately 10%.

Steady-state levels are achieved after three days of multiple dose administration. Under both single-dose and steady-state conditions, dose proportionality has been established for the 5 mg, 10 mg, 20 mg, and 40 mg doses of oxymorphone hydrochloride extended-release tablets, for both peak plasma levels (Cmax) and extent of absorption (AUC) (see Table 4).

Table 4: Mean (±SD) Oxymorphone Hydrochloride Extended-Release Tablets Pharmacokinetic Parameters

Regimen	Dosage	C_{max} (ng/mL)	AUC (ng·hr/mL)	$T_{½}$ (hr)
Single Dose	5 mg	0.27±0.13	4.54±2.04	11.30±10.81
	10 mg	0.65±0.29	8.94±4.16	9.83±5.68
	20 mg	1.21±0.77	17.81±7.22	9.89±3.21
	40 mg	2.59±1.65	37.90±16.20	9.35±2.94
Multiple Dose[a]	5 mg	0.70±0.55	5.60±3.87	NA
	10 mg	1.24±0.56	9.77±3.52	NA
	20 mg	2.54±1.35	19.28±8.32	NA
	40 mg	4.47±1.91	36.98±13.53	NA

NA = not applicable
[a] Results after 5 days of q12h dosing.

Food Effect

Two studies examined the effect of food on the bioavailability of single doses of 20 and 40 mg of oxymorphone hydrochloride extended-release tablets in healthy volunteers. In both studies, after the administration of oxymorphone hydrochloride extended-release tablets, the Cmax was increased by approximately 50% in fed subjects compared to fasted subjects. A similar increase in Cmax was also observed with oxymorphone solution.

The AUC was unchanged in one study and increased by approximately 18% in the other study in fed subjects following the administration of oxymorphone hydrochloride extended-release tablets. Examination of the AUC suggests that most of the difference between fed and fasting conditions occurs in the first four hours after dose administration. After oral dosing with a single dose of 40 mg, a peak oxymorphone plasma level of 2.8 ng/ml is achieved at 1hour in fasted subjects and a peak of 4.25 ng/ml is achieved at 2 hours in fed subjects and that beyond the 12 hour time point, there is very little difference in the curves. (b) (4) As a result, REVOPAN should be dosed at least one hour prior to or two hours after eating [see Dosage and Administration (2.2)].

Ethanol Effect

In Vivo Oxymorphone Hydrochloride Extended-Release Tablets Formulation-Alcohol Interaction

Although in vitro studies have demonstrated that oxymorphone hydrochloride extended-release tablets do not release oxymorphone more rapidly in 500 mL of 0.1N HCl solutions containing ethanol (4%, 20%, and 40%), there is an in vivo interaction with alcohol. An in vivo study examined the effect of alcohol (40%, 20%, 4% and 0%) on the bioavailability of a single dose of 40 mg of oxymorphone hydrochloride extended-release tablets in healthy, fasted volunteers. The results showed that the oxymorphone mean AUC was 13% higher (not statistically significant) after co-administration of 240 mL of 40% alcohol. The AUC was essentially unaffected in subjects following the co-administration of oxymorphone hydrochloride extended-release tablets and ethanol (240 mL of 20% or 4% ethanol).

There was a highly variable effect on Cmax with concomitant administration of alcohol and oxymorphone hydrochloride extended-release tablets. The change in Cmax ranged from a decrease of 50% to an increase of 270% across all conditions studied. Following concomitant administration of 240 mL of 40% ethanol the Cmax increased on average by 70% and up to 270% in individual subjects. Following the concomitant administration of 240 mL of 20% ethanol, the Cmax increased on average by 31% and up to 260% in individual subjects. Following the concomitant administration of 240 mL of 4 % ethanol, the Cmax increased 7% on average and by as much as 110% for individual subjects. After oral dosing with a single dose of 40 mg in fasted subjects, the mean peak oxymorphone plasma level is 2.4 ng/mL and the median Tmax is 2 hours. Following co-administration of oxymorphone hydrochloride extended-release tablets and alcohol (240

mL of 40% ethanol) in fasted subjects, the mean peak oxymorphone level is 3.9 ng/mL and the median Tmax is 1.5 hours (range 0.75 – 6 hours).

(b) (4) co-administration of oxymorphone and ethanol must be avoided.

27 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

4.2 Individual Study Reviews

4.2.1 Study EN3288-103: BE study of 40 mg tablets in healthy subjects under fasted state

Study Design and Methods

This study was an open-label, randomized, 2-sequence, 4-period, crossover, replicated dosing design. Subjects were randomly allocated to receive a single dose of EN3288 or OPANA ER during alternate treatment periods. Each treatment period was separated by at least a 7-day washout. In total, each subject received 2 single doses of EN3288 and 2 single doses of OPANA ER.

Subjects included in each study were healthy males or females, of any race, between 18 and 45 years of age, inclusive. Plasma samples were obtained at 0 (predose, within 1 hour prior to administration of oxymorphone), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 hours after administration of oxymorphone in each period. Pharmacokinetic parameters were analyzed by a repeated measure ANOVA. Bioequivalence was demonstrated by 90% CIs for oxymorphone AUC0-t, AUC0-inf, and Cmax that were between 0.80 and 1.25.

Subject Disposition and Demographics

Three (3) out of 37 subjects who entered the study were administered naltrexone but not randomized to oxymorphone treatments, 2 because of an AE and 1 because the study panel was filled. Thirty-four (34) subjects were randomized. Three (3) subjects were administered only 1 dose of oxymorphone (1 each because of withdrawal of consent, physician decision, AE), so no data were available for pharmacokinetic analysis. All 3 subjects had been administered OPANA ER. Pharmacokinetic data were available from 31 subjects. There are data from 2 doses of each oxymorphone formulation for 30 subjects and data from 1 dose of each oxymorphone formulation for 1 subject.

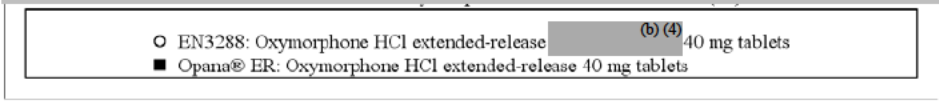
Category	EN3288-103
Number of Subjects	31
Age (years), mean±SD (range)	33.7±7.33 (20-44)
Gender, n (%)	
Male	13 (41.9%)
Female	18 (58.1%)
Ethnicity, n (%)	
Hispanic	27 (87.1%)
Non-Hispanic	4 (12.9%)
Race, n (%)	
White	24 (77.4%)
Black or African American	7 (22.6%)
Weight (kg), mean±SD (range)	73.05±9.913 (55.6-95.0)
Height (cm), mean±SD (range)	167±7.9 (151- 184)
BMI (kg/m^2), mean±SD (range)	26.26±2.204 (22.1-29.8)

Results: The results of the ANOVA comparison of geometric mean results of oxymorphone AUC and Cmax for the study #103 are provided in the Table below:

Parameter	Geometric Least Squares Means		Ratio of Means	90% Confidence Interval
	EN3288	OPANA ER		
EN3288-103: Single 40 mg Oral Doses to Fasted Healthy Subjects*				
Cmax (ng/mL)	(b) (4)			
AUC0-t (ng•h/mL)				

Mean ±SE Oxymorphone Plasma Concentrations Versus Time After Single Oral Doses of EN3288 and OPANA ER 40 mg to Fasted Subjects (EN3288-103).

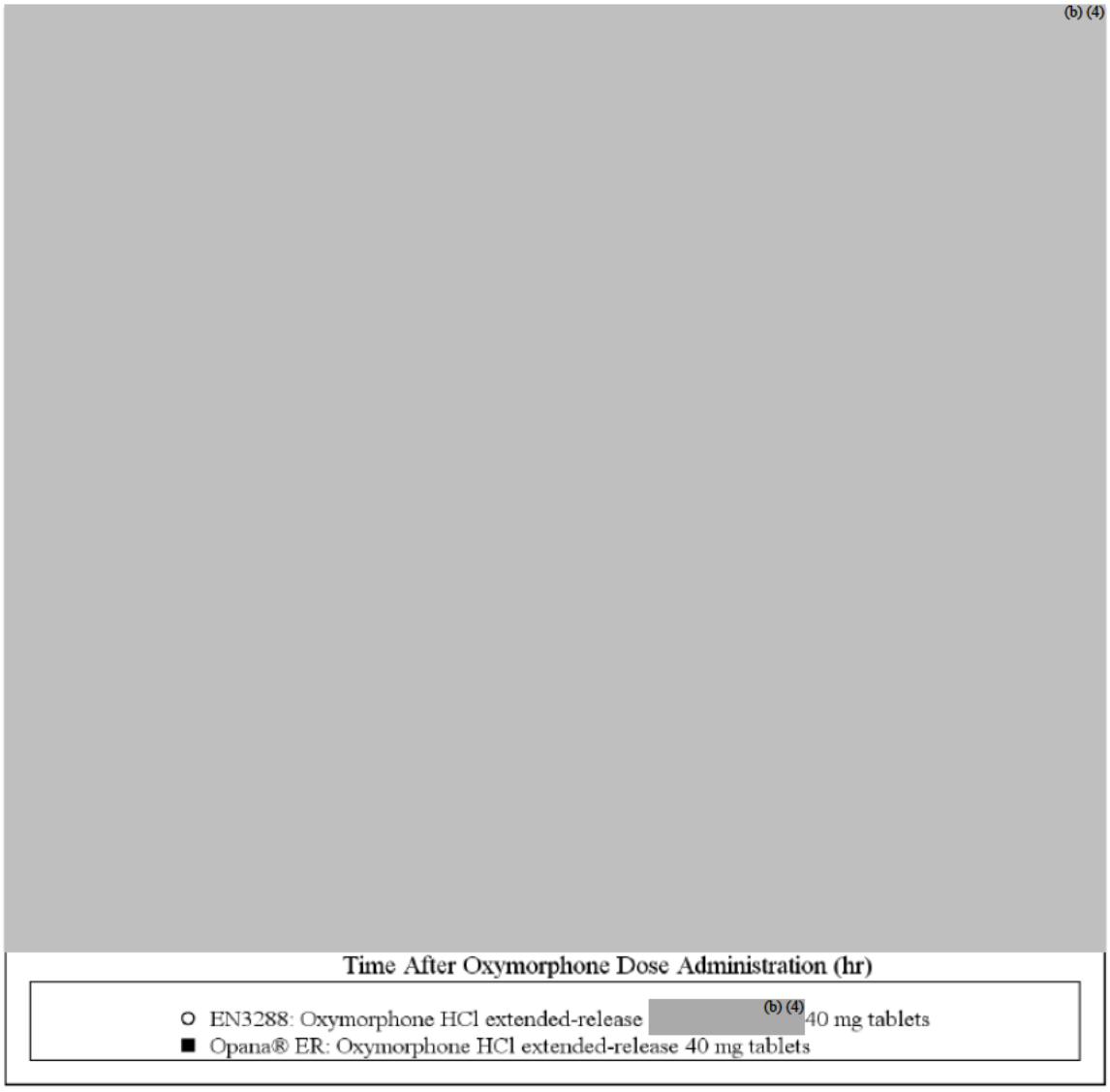
(b) (4)



Plasma Pharmacokinetics of Oxymorphone 40 mg Single Oral Dose to Fasted Healthy Subjects - Arithmetic Mean ± SD (%CV) (EN3288-103)

Parameter	EN3288 40 mg	OPANA ER 40 mg
AUC_{0-t} (ng•h/mL)	(b) (4)	50.16±14.910 (29.7)
AUC_{0-inf} (ng•h/mL)		52.29±15.980 (30.6)
C_{max} (ng/mL)		5.87±1.992 (33.9)
T_{max} (h)[a]		3.5 (1.0-6.0)
C_t (ng/mL)		0.12±0.087 (73.7)
λ_z (1/h)		0.0726±0.02108 (29.0)
$t_{1/2}$ (h)		10.5±4.12 (39.3)

Mean ±SE 6-β-Hydroxy-oxymorphone Plasma Concentrations Versus Time After Single Oral Doses of EN3288 and OPANA ER 40 mg to Fasted Subjects (EN3288-103)



Plasma Pharmacokinetics of 6-β-Hydroxy-oxymorphone after Single Oral Oxymorphone 40 mg Doses to Fasted Healthy Subjects – Arithmetic Mean±SD (%CV) (EN3288-103)

Parameter	EN3288 40 mg	OPANA ER 40 mg
AUC_{0-t} (ng•h/mL)	(b) (4)	29.78±10.506 (35.3)
AUC_{0-inf} (ng•h/mL)		37.85±15.883 (42.0)
C_{max} (ng/mL)		1.84±0.646 (35.2)
T_{max} (h)[a]		1.5 (0.5-6.0)
C_t (ng/mL)		0.235±0.1364 (58.0)
λ_z (1/h)		0.0434±0.01959 (45.1)
$t_{1/2}$ (h)		19.7±11.34 (57.6)

Conclusion: Bioequivalence of (b) (4) (oxymorphone HCl extended-release) 40 mg tablets to OPANA ER under fasting state was established by 90% CIs for oxymorphone AUC0-t and Cmax that were between 0.80 and 1.25.

4.2.2 Study EN3288-104: BE study of 40 mg tablets in healthy subjects under fed state

Study Design and Methods

This study was an open-label, randomized, 2-sequence, 4-period, crossover, replicated dosing design. Subjects were randomly allocated to receive a single dose of EN3288 or OPANA ER during alternate treatment periods. Each treatment period was separated by at least a 7-day washout. In total, each subject received 2 single doses of EN3288 and 2 single doses of OPANA ER.

Subjects were confined to the study unit beginning on the day prior to dosing (Day -1) until the morning of Day 3 (48 hours postdose). Blood samples for pharmacokinetics were obtained through 48 hours postdose.

Subjects included in each study were healthy males or females, of any race, between 18 and 45 years of age, inclusive.

Plasma samples were obtained at 0 (predose, within 1 hour prior to administration of oxymorphone), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 hours after administration of oxymorphone in each period. Pharmacokinetic parameters were analyzed by a repeated measure ANOVA. Bioequivalence was demonstrated by 90% CIs for oxymorphone AUC0-t, AUC0-inf, and Cmax that were between 0.80 and 1.25.

Subject Disposition and Demographics

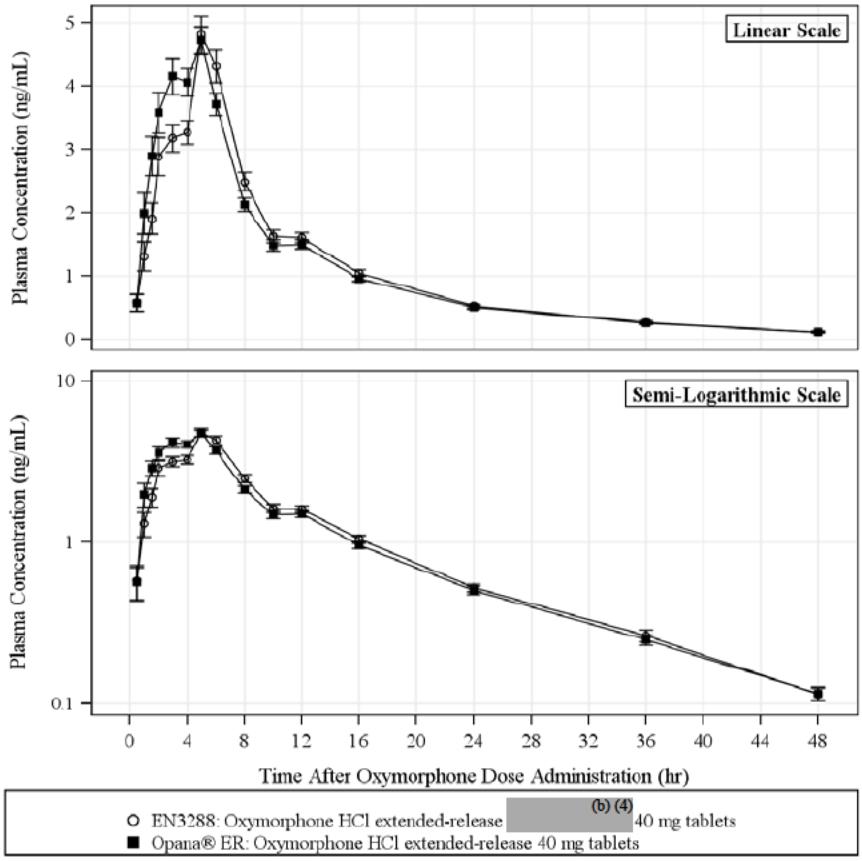
Six (6) out of 36 subjects who entered the study were administered naltrexone but not randomized to oxymorphone treatments because the study panel was filled. Pharmacokinetic data were available from all 30 subjects randomized. There are data from 2 doses of each oxymorphone formulation for 28 subjects and data from 1 dose of each oxymorphone formulation for 2 subjects.

Category	EN3288-104
Number of Subjects	30
Age (years), mean±SD (range)	34.4±7.74 (19-44)
Gender, n (%)	
Male	15 (50.0%)
Female	15 (50.0%)
Ethnicity, n (%)	
Hispanic	30 (100.0%)
Non-Hispanic	0
Race, n (%)	
White	27 (90.0%)
Black or African American	3 (10.0%)
Weight (kg), mean±SD (range)	71.50±12.029 (51.3-96.4)
Height (cm), mean±SD (range)	168±9.4 (145-185)
BMI (kg/m^2), mean±SD (range)	25.33±2.728 (20.9-29.8)

Results: The results of the ANOVA comparison of geometric mean results of oxymorphone AUC and Cmax for the study #104 are provided in the Table below:

Parameter	Geometric Least Squares Means		Ratio of Means	90% Confidence Interval
	EN3288	OPANA ER		
EN3288-104: Single 40 mg Oral Doses to Healthy Subjects with a High-Fat Meal				
Cmax (ng/mL)	5.24	5.55	0.94	0.88-1.02
AUC0-t (ng•h/mL)	47.10	48.43	0.97	0.93-1.02

Mean ±SE Oxymorphone Plasma Concentrations Versus Time After Single Oral Doses of EN3288 and OPANA® ER 40 mg to Subjects After a High-fat Meal (EN3288-104).



Plasma Pharmacokinetics of Oxymorphone 40 mg After a Single Oral Dose

Administered to Healthy Subjects After a High-fat Meal - Arithmetic Mean±SD (%CV) (EN3288-104)

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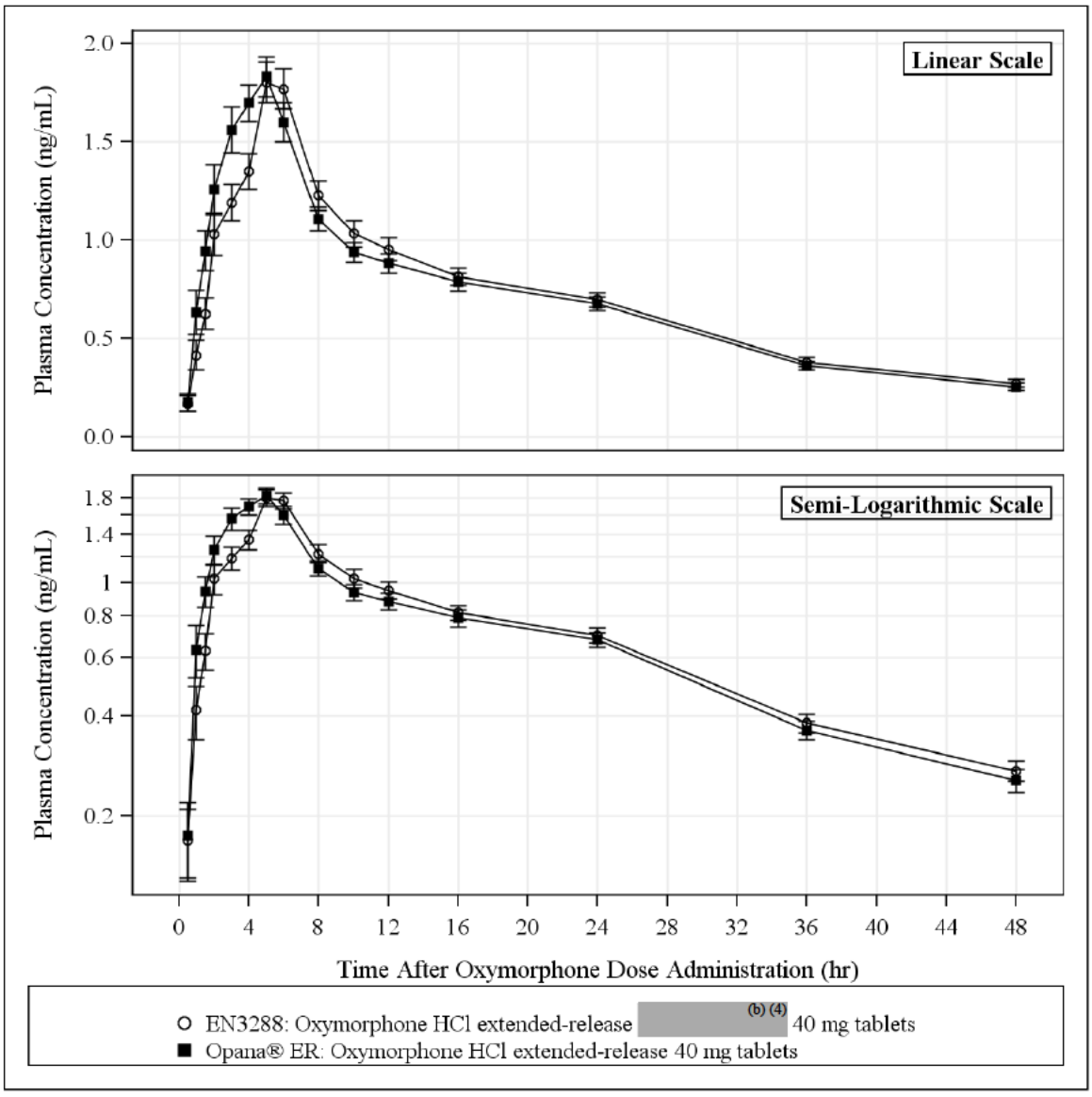
Parameter	EN3288 40 mg	OPANA ER 40 mg
AUC_{0-t} (ng•h/mL)	49.01±14.026 (28.6)	50.16±14.910 (29.7)
AUC_{0-inf} (ng•h/mL)	50.95±14.629 (28.7)	52.29±15.980 (30.6)
C_{max} (ng/mL)	5.63±2.255 (40.1)	5.87±1.992 (33.9)
T_{max} (h)[a]	5.0 (1.0-10.0)	3.5 (1.0-6.0)
C_t (ng/mL)	0.11±0.069 (62.2)	0.12±0.087 (73.7)
λ_z (1/h)	0.0740±0.02178 (29.4)	0.0726±0.02108 (29.0)
$t_{1/2}$ (h)	10.3±3.63 (35.2)	10.5±4.12 (39.3)

Mean ±SE 6-Hydroxy-oxymorphone Plasma Concentrations Versus Time After Single Oral Doses of EN3288 and OPANA® ER 40 mg to Subjects After a Meal (EN3288-104)



Plasma Pharmacokinetics of 6-β-Hydroxy-oxymorphone After Single Oral

Oxymorphone 40 mg Doses Administered to Healthy Subjects After a Meal-Arithmetic Mean±SD (%CV) (EN3288-104)

Parameter	EN3288 40 mg	OPANA ER 40 mg
AUC_{0-t} (ng•h/mL)	33.39±11.483 (34.4)	33.40±11.940 (35.7)
AUC_{0-inf} (ng•h/mL)	42.05±16.878 (40.1)	40.99±16.472 (40.2)
C_{max} (ng/mL)	2.23±0.866 (38.8)	2.24±0.889 (39.7)
T_{max} (h)[a]	5.0 (1.0-12.0)	4.0 (1.0-10.0)
C_t (ng/mL)	0.27±0.148 (54.5)	0.26±0.150 (58.4)
λ_z (1/h)	0.0425±0.01940 (45.7)	0.0458±0.02002 (43.7)
$t_{1/2}$ (h)	19.5±8.78 (45.0)	17.8±7.29 (41.1)

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Conclusion: Bioequivalence of (b) (4) (Oxymorphone HCl extended-release) 40 mg tablets to OPANA ER under fed state was established by 90% CIs for oxymorphone AUC0-t and Cmax that were between 0.80 and 1.25.

4.2.3 Study EN3288-105: BE study of 5 mg tablets in healthy subjects under fasted state

Study Design and Methods

This study was an open-label, randomized, 2-sequence, 4-period, crossover, replicated dosing design. Subjects were randomly allocated to receive a single dose of EN3288 or OPANA ER during alternate treatment periods. Each treatment period was separated by at least a 7-day washout. In total, each subject received 2 single doses of EN3288 and 2 single doses of OPANA ER.

Subjects were confined to the study unit beginning on the day prior to dosing (Day -1) until the morning of Day 3 (48 hours postdose). Blood samples for pharmacokinetics were obtained through 48 hours postdose.

Subjects included in each study were healthy males or females, of any race, between 18 and 45 years of age, inclusive.

Plasma samples were obtained at 0 (predose, within 1 hour prior to administration of oxymorphone), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 hours after administration of oxymorphone in each period. Pharmacokinetic parameters were analyzed by a repeated measure ANOVA. Bioequivalence was demonstrated by 90% CIs for oxymorphone AUC0-t, AUC0-inf, and Cmax that were between 0.80 and 1.25.

Subject Disposition and Demographics

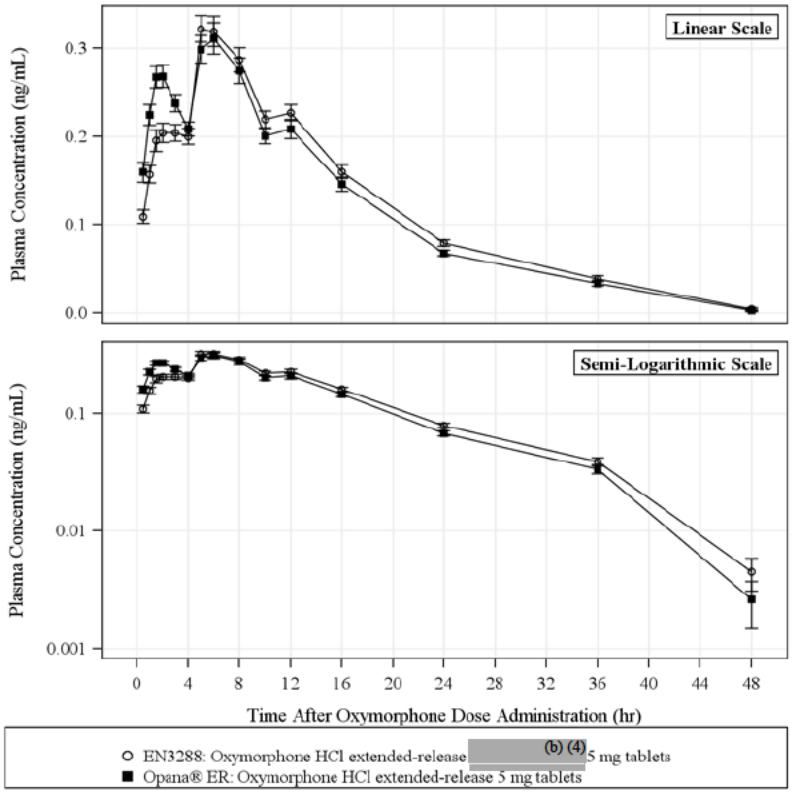
Thirty (30) subjects entered the study and were randomized for treatment with EN3288 and OPANA ER treatment. Two (2) subjects were administered only 1 dose of oxymorphone (1 each because of withdrawal of consent and a protocol violation), and they were not included in the pharmacokinetic analysis. Both subjects had been administered EN3288. Pharmacokinetic data were available from 28 subjects. There are data from 2 doses of each oxymorphone formulation for 27 subjects and data from 2 doses of OPANA ER and 1 dose of EN3288 for 1 subject.

Category	EN3288-105
Number of Subjects	28
Age (years), mean±SD (range)	34.7±7.55 (20-45)
Gender, n (%)	
Male	14 (50.0%)
Female	14 (50.0%)
Ethnicity, n (%)	
Hispanic	28 (100.0%)
Non-Hispanic	0
Race, n (%)	
White	24 (85.7%)
Black or African American	4 (14.3%)
Weight (kg), mean±SD (range)	70.80±8.747 (53.0-88.0)
Height (cm), mean±SD (range)	168±8.8 (152- 182)
BMI (kg/m^2), mean±SD (range)	25.18±2.519 (21.3-29.8)

Results: The results of the ANOVA comparison of geometric mean results of oxymorphone AUC and Cmax for the study #105 are provided in the Table below:

Parameter	Geometric Least Squares Means		Ratio of Means	90% Confidence Interval
	EN3288	OPANA ER		
EN3288-105: Single 5 mg Oral Doses to Fasted Healthy Subjects				
Cmax (ng/mL)	0.352	0.360	0.98	0.93-1.03
AUC0-t (ng•h/mL)	5.04	4.82	1.05	1.01-1.09

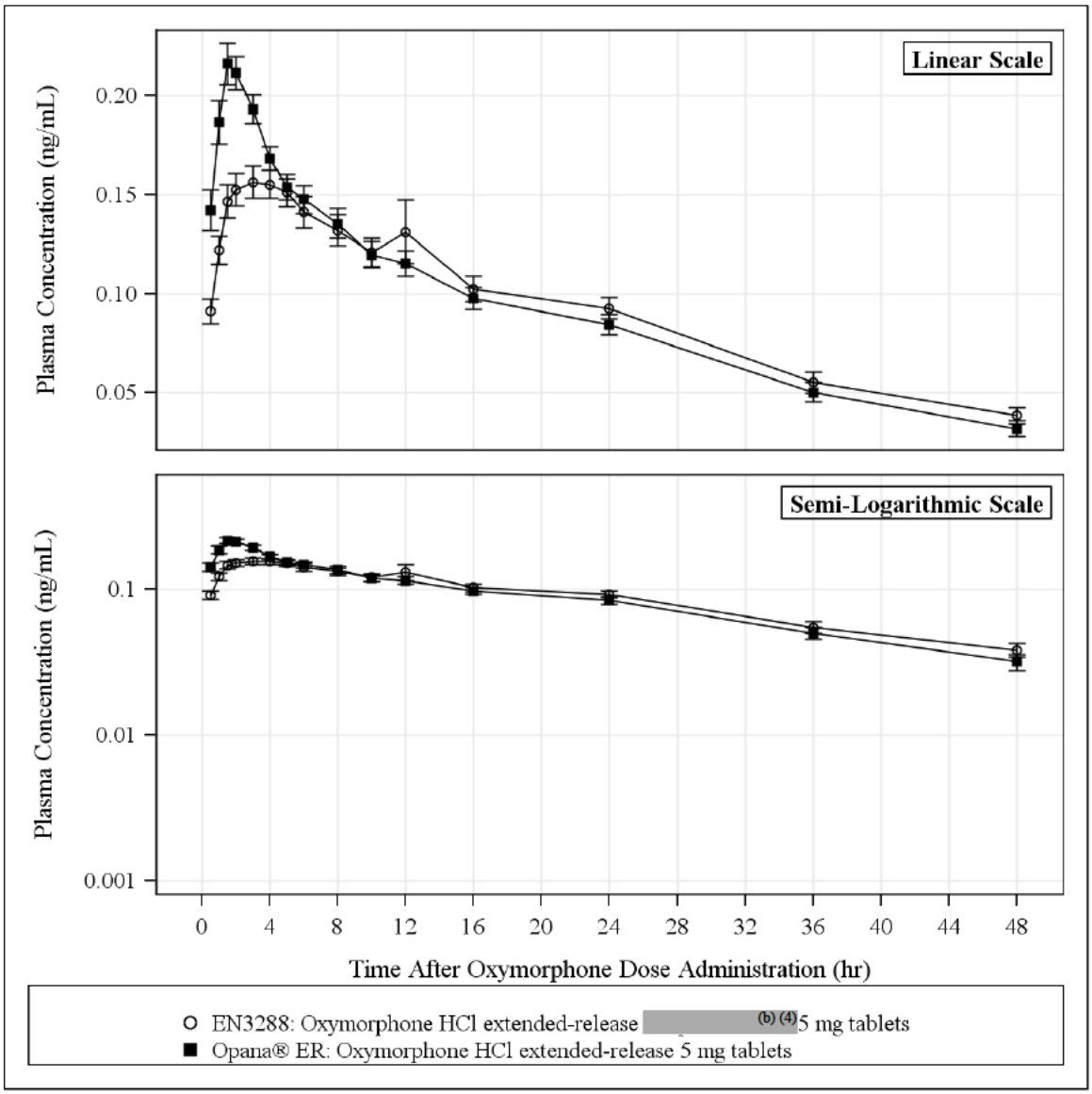
Mean ±SE Oxymorphone Plasma Concentrations Versus Time After Single Oral 5 mg Doses of EN3288 and OPANA ER to Fasted Subjects (EN3288-105)



Plasma Pharmacokinetics of Oxymorphone 5 mg After a Single Oral Dose of 5 mg to Fasted Healthy Subjects - Arithmetic Mean±SD (%CV) (EN3288-105)

Parameter	EN3288 5 mg	OPANA ER 5 mg
AUC_{0-t} (ng•h/mL)	5.29±1.515 (28.7)	5.05±1.549 (30.7)
C_{max} (ng/mL)	0.370±0.1171 (31.7)	0.375±0.1144 (30.5)
T_{max} (h)[a]	5.0 (1.0-16.0)	6.0 (1.0-12.0)
C_t (ng/mL)	0.044±0.0146 (33.2)	0.043±0.0109 (25.1)

Mean ±SE 6-β-Hydroxy-oxymorphone Plasma Concentrations versus Time After Single Oral 5 mg Doses of EN3288 and OPANA ER (56 Doses) to Fasted Subjects (EN3288-105)



Plasma Pharmacokinetics of 6-β-Hydroxy-oxymorphone After Single Oral 5 mg Oxymorphone Doses to Fasted Healthy Subjects - Arithmetic Mean±SD (%CV) (EN3288-105)

Parameter	EN3288 5 mg	OPANA ER 5 mg
AUC_{0-t} (ng•h/mL)	4.24±1.947 (46.0)	4.15±1.821 (43.9)
C_{max} (ng/mL)	0.204±0.1163 (56.9)	0.242±0.0683 (28.2)
T_{max} (h)[a]	3.0 (0.5-24.0)	1.5 (0.5-6.0)
C_t (ng/mL)	0.049±0.0217 (43.8)	0.048±0.0206 (42.9)

Conclusions: Bioequivalence of [redacted] (b) (4) (Oxymorphone HCl extended-release) 5 mg tablets to OPANA ER under fed state was established by 90% CIs for oxymorphone AUC0-t and Cmax that were between 0.80 and 1.25.

4.2.4 Study EN3288-107: Alcohol Interaction Study

Study Design and Methods: This study was an open-label, randomized, single-dose, 3-period, 6 sequence crossover design. Subjects were randomly allocated to one of the 6 sequences to receive a single dose of EN3288 40 mg co-administered with either ethanol or water over 3 periods. Each EN3288 dose administration was separated by a washout of at least 7 days. All treatments were to be administered to fasted subjects. The 3 treatments were:

A EN3288 40 mg + 240 mL 40% ethanol
B EN3288 40 mg + 240 mL 20% ethanol
C EN3288 40 mg + 240 mL of water (0% ethanol) (reference)

The ethanol solution was to be consumed as quickly as possible at the time of EN3288 administration. Subjects were confined to the study unit beginning on the day prior to dosing (Day -1) until the morning of Day 3 (48 hours postdose). Subjects were healthy males or females, of any race, between 22 and 45 years of age, inclusive, with a history of moderate ethanol consumption. Plasma samples were obtained at 0 (predose, within 1 hour prior to administration of oxymorphone) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 hours after administration of oxymorphone in each period.

Subject Disposition and Demographics

Two (2) of 22 subjects who entered the study were administered naltrexone but not randomized to oxymorphone treatments because the study panel was filled. Three subjects experienced vomiting within 2 hours of the first dose (administered with 240 mL 40% ethanol) and were excluded from the pharmacokinetic population. Pharmacokinetic data were available from 17 of 20 subjects randomized. There are data from 3 doses of each oxymorphone treatment for 14 subjects, who completed the study, and data from doses of EN3288 with 20% ethanol and with water for 3 subjects. These 3 subjects were excluded from the pharmacokinetic population because they experienced vomiting within 2 hours after the first dose of EN3288 40 mg administered with 40% ethanol, subsequently no valid pharmacokinetic data were available.

Demographics of the 17 subjects in the pharmacokinetic population are summarized in the table below.

Category	Pharmacokinetic Population (N=17)[a]
Age (years), mean±SD (range)	36.2±6.42 (22-45)
Gender, n (%)	
Male	14 (82.4%)
Female	3 (17.6%)
Ethnicity, n (%)	
Hispanic	8 (47.1%)
Non-Hispanic	9 (52.9%)
Race, n (%)	
White	14 (82.4%)
Black or African American	3 (17.6%)
Weight (kg), mean±SD (range)	84.94±8.758 (71.6-106.0)
Height (cm), mean±SD (range)	175±7.5 (162-188)
BMI (kg/m^2), mean±SD (range)	27.63±2.320 (22.6-31.8)

Subjects drank 240 mL 20% or 40% ethanol, equivalent to 2.5 or 5 standard drinks, within the 30 minutes following administration of EN3288 40 mg.

Results:
The results of the ANOVA comparison of geometric mean results of oxymorphone AUC and Cmax are provided in the Table below. The sample size was not based on statistical power. A sample size of 12 subjects was considered to provide adequate information for clinical interpretation. Eighteen (18) subjects were to be randomized to ensure that 12 subjects had evaluable pharmacokinetic data from 1 of the ethanol treatment arms and the water treatment arm.

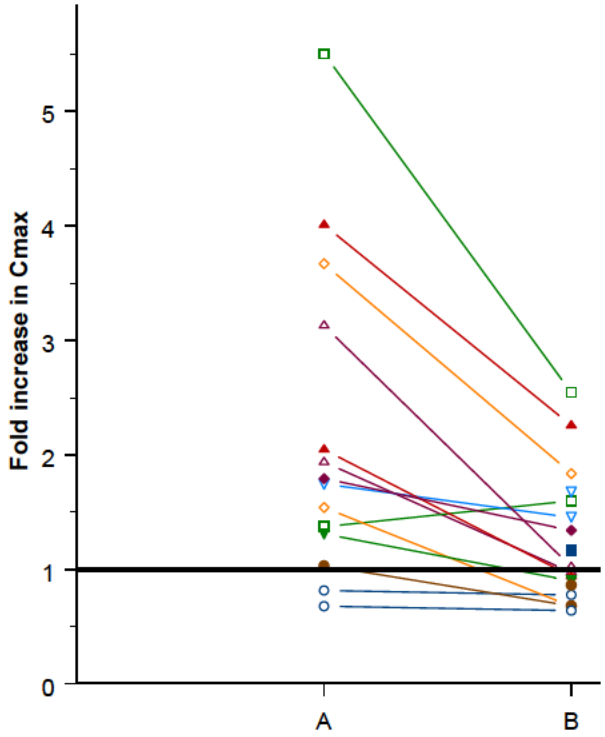
Parameter (unit)	Treatment[a]	n[b]	Geometric Least Squares Means[c]	Ratio of Least Squares Means	90% CI of the Ratio (A/C or B/C)	
					Lower	Upper
AUC_{0-t} (ng•h/mL)	A	14	33.1936	1.1539	1.0089	1.3199
	B	17	27.3132	0.9495	0.8378	1.0762
	C	17	28.7652			
AUC_{0-inf} (ng•h/mL)	A	12	34.5161	1.1403	0.9911	1.3120
	B	16	28.6886	0.9478	0.8352	1.0755
	C	17	30.2701			
C_{max} (ng/mL)	A	14	3.3302	1.7959	1.4947	2.1579
	B	17	2.1103	1.1381	0.9591	1.3505
	C	17	1.8543			

[a] A=EN3288 40 mg with 240 mL 40% ethanol; B=EN3288 40 mg with 240 mL 20% ethanol; C=EN3288 40 mg with 240 mL water

Results indicate that [redacted] is susceptible to alcohol consumption-related interaction as seen by a significantly higher Cmax (Upper 90% CI's above 0.8 – 1.2) in alcohol-treatment groups compared to [redacted] taken with water under fasting condition.

On average, oxymorphone Cmax increased with the amount of ethanol consumed and was 1.14-fold and 1.80-fold higher with 20% and 40% ethanol, respectively. Noteworthy is the fact that in certain individuals maximum fold change in Cmax upto 2.5-fold or 5.5-fold were noted in 20% or 40% alcohol treatment groups compared to [redacted] alone (see figure below).

Figure: Fold increase in Cmax following administration of [(b) (4)] with 40% alcohol (A) or 20% alcohol (B) compared to water (C, not shown) in individual subjects.



A: Cmax with Treatment A / Cmax with Treatment C
B: Cmax with Treatment B / Cmax with Treatment C

Treatment A: 40 mg, [(b) (4)] + 240 mL 40% ethanol

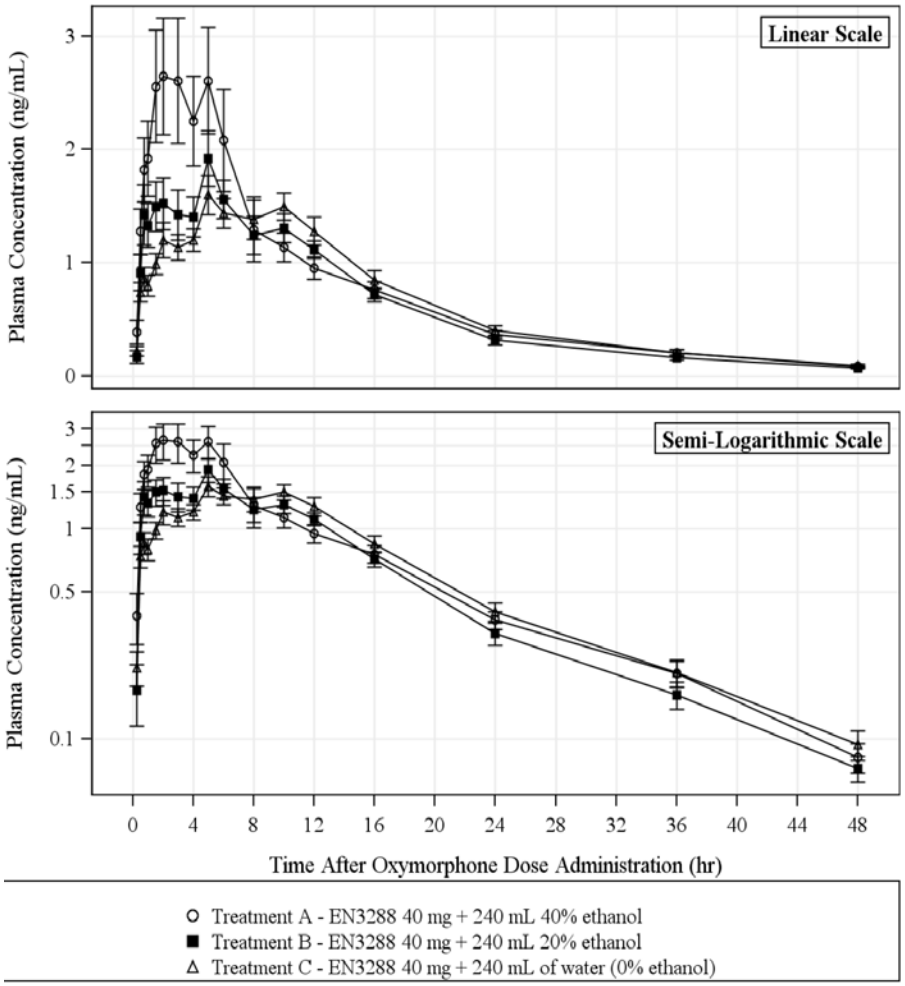
Treatment B: 40 mg, [(b) (4)] + 240 mL 20% ethanol

Treatment C: 40 mg, [(b) (4)] + 240 mL Water (**reference**)

Previously, OPANA ER also exhibited highly variable but significant alcohol-drug interaction. Following concomitant administration of 240 mL of 40% ethanol the Cmax increased on average by 70% and up to 270% in individual subjects. Following the concomitant administration of 240 mL of 20% ethanol, the Cmax increased on average by 31% and up to 260% in individual subjects. As noted with OPANA ER previously, a slight but significant increase (15% increase) in AUC is noted when [(b) (4)] is taken with alcohol (20 or 40%, data not shown). Hence, [(b) (4)] and OPANA ER are similar in their susceptibility to alcohol-related drug interaction.

Plots of arithmetic mean oxymorphone concentrations versus time are provided in the Figure below.

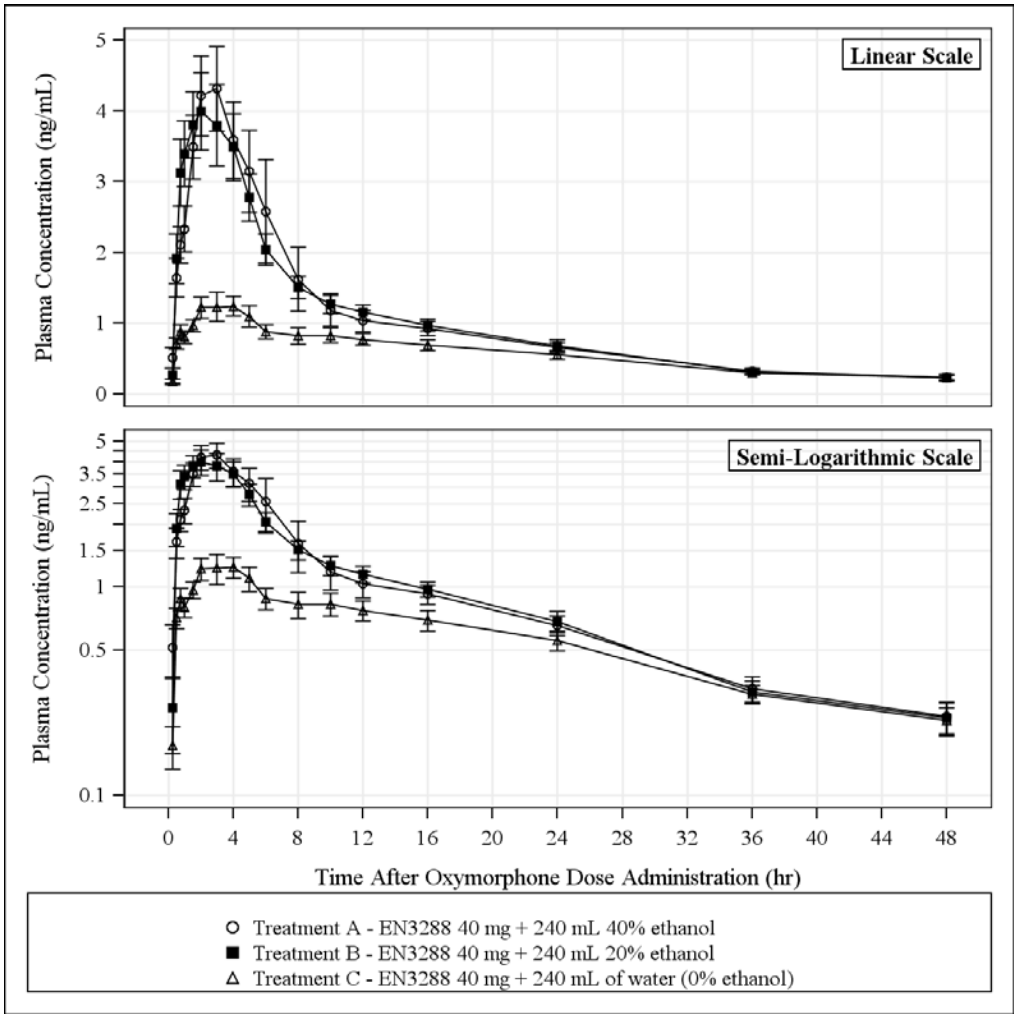
Mean ±SE Oxymorphone Plasma Concentrations Versus Time After Single Oral Doses of EN3288 40 mg Administered with Ethanol Solutions or Water to Fasted Subjects (N=14 for EN3288 40 mg with 240 mL 40% Ethanol; N=17 for EN3288 40 mg with 240 mL 20% Ethanol; N=17 for EN3288 40 mg with 240 mL Water)



Plasma Pharmacokinetics of Oxymorphone After a Single Oral EN3288 40 mg Dose Administered with Ethanol or Water to Healthy Subjects - Arithmetic Mean±SD (%CV)

Parameter[a]	EN3288 40 mg Administered with 240 mL 40% Ethanol (N=14)	EN3288 40 mg Administered with 240 mL 20% Ethanol (N=17)	EN3288 40 mg Administered with 240 mL Water (N=17)
AUC_{0-t} (ng•h/mL)	35.57±14.136 (39.7)	28.38±8.800 (31.0)	29.96 ±9.218 (30.8)
AUC_{0-inf} (ng•h/mL)[b]	35.61±13.891 (39.0)	29.99±8.969 (29.9)	31.63±9.913 (31.3)
C_{max} (ng/mL)	3.94±2.307 (58.5)	2.34±1.118 (47.7)	1.99±0.757 (38.1)
T_{max} (h)[c]	2.0 (0.5-6.0)	5.0 (0.5-12.0)	5.0 (0.8-12.0)
C_t (ng/mL)	0.083±0.0372 (44.8)	0.072±0.0418 (57.9)	0.094±0.0624 (66.4)
λ_z (1/h)[b]	0.0801±0.01980 (24.7)	0.0743±0.01532 (20.6)	0.0708±0.02075 (29.3)
$t_{1/2}$ (h)[b]	9.2±2.28 (24.9)	9.8±2.61 (26.6)	10.7±3.48 (32.5)

Mean ±SE 6-β-Hydroxy-oxymorphone Plasma Concentrations Versus Time After Single Oral Doses of EN3288 40 mg Administered with Ethanol Solutions or Water to Fasted Subjects (N=14 for EN3288 40 mg with 240 mL 40% Ethanol; N=17 for EN3288 40 mg with 240 mL 20% Ethanol; N=17 for EN3288 40 mg with 240 mL water)



Plasma Pharmacokinetics of 6-β-Hydroxy-oxymorphone After Single Oral Doses of EN3288 40 mg Administered with Ethanol or Water to Healthy Subjects - Arithmetic Mean±SD (%CV)

Parameter[a]	EN3288 40 mg Administered with 240 mL 40% Ethanol (N=14)	EN3288 40 mg Administered with 240 mL 20% Ethanol (N=17)	EN3288 40 mg Administered with 240 mL Water (N=17)
AUC_{0-t} (ng•h/mL)	49.85±24.595 (49.3)	47.55±16.640 (35.0)	27.44±11.392 (41.5)
AUC_{0-inf} (ng•h/mL)[b]	55.24±27.052 (49.0)	53.81±18.984 (35.3)	34.89±17.305 (49.6)
C_{max} (ng/mL)	5.54±2.629 (47.4)	5.07±2.066 (40.7)	1.47±0.822 (55.9)
T_{max} (h)[c]	2.5 (1.0-6.0)	2.0 (0.8-5.0)	3.0 (0.8-8.0)
C_t (ng/mL)	0.224±0.1585 (70.7)	0.236±0.1740 (73.9)	0.230±0.1434 (62.4)
λ_z (1/h)[c]	0.0557±0.01733 (31.1)	0.0531±0.02201 (41.4)	0.0426±0.01890 (44.4)
$t_{1/2}$ (h)[c]	13.6±4.26 (31.3)	17.2±12.24 (71.2)	22.3±18.38 (82.3)

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Conclusion: As previously noted with OPANA ER, (b) (4) is also susceptible to alcohol consumption-related increase in systemic levels of oxymorphone.

4.2.5 Study EN3288-108: Effect of physical tampering on pharmacokinetics of [redacted]

Study Design and Methods

This study was an open-label, randomized, 6-sequence, 6-period, crossover design. Each subject was randomly allocated to a treatment sequence, and received a single dose of EN3288 40 mg intact or after physical tampering via several methods, OPANA ER 40 mg crushed, or OPANA 40 mg (4×10 mg) intact tablets over the 6 treatment periods. Each dose was administered under fasted conditions and was separated by at least a 7 day washout period. The 6 treatments were identified as follows:

A EN3288 40 mg – intact tablet
B EN3288 40 mg – tablet tampered with a commercial pill crusher
C EN3288 40 mg – tablet cut [redacted]
D EN3288 40 mg – tablet tampered [redacted]
E OPANA ER 40 mg – tablet tampered with a commercial pill crusher
F OPANA 40 mg (4×10 mg) – intact tablets (reference product)

Subjects were confined to the study unit beginning on the day prior to dosing (Day -1) until the morning of Day 3 (48 hours postdose). Blood samples for pharmacokinetics were obtained through 48 hours postdose. Subjects were healthy males or females, of any race, between 18 and 45 years of age, inclusive. Plasma samples were obtained at 0 (predose, within 1 hour prior to administration of oxymorphone) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 hours after administration of oxymorphone in each period.

Sample size

The intra-subject coefficients of variation (CV) for AUC0-inf and Cmax for oxymorphone were up to 22% in study EN3288-101. With 18 subjects, the 90% CIs of the geometric mean ratio (test/reference) of the pharmacokinetic parameters (AUC and Cmax) would be R/1.135 and R*1.135, where R is the estimated geometric mean ratio. Approximately 30 subjects were to be randomized to ensure that 18 subjects completed the study.

Subject Disposition and Demographics
Three (3) of 35 subjects who entered the study were administered naltrexone but not randomized to oxymorphone treatments; 2 because they experienced AEs and 1 because the study panel was filled. Two subjects vomited within 12 hours of the first dose administered (EN3288 and OPANA) and 1 subject was discontinued from the study for a protocol violation after only 1 dose. Pharmacokinetic data were available from 29 of 32 subjects randomized. There are data from all 6 doses of oxymorphone formulation for 29 subjects, who completed the study. Their demographics are summarized in the Table below.

Category	Pharmacokinetic Population (N=29)
Age (years), mean±SD (range)	34.1±7.62 (20-45)
Gender, n (%)	
Male	18 (62.1%)
Female	11 (37.9%)
Ethnicity, n (%)	
Hispanic	29 (100%)
Race, n (%)	
White	24 (82.8%)
Black or African American	5 (17.2%)
Weight (kg), mean±SD (range)	72.84±8.726 (58.5-90.0)
Height (cm), mean±SD (range)	169±7.0 (155-185)
BMI (kg/m^2), mean±SD (range)	25.63±3.115 (20.2-29.9)

The results of the ANOVA comparison of geometric mean results of oxymorphone AUC and Cmax are provided in the table below.

Parameter (unit)	Treatment[a]	n[b]	Geometric Least Squares Means[c]	Ratio of Least Squares Means		90% CI of the Ratio	
						Lower	Upper
AUC_{0-t}	A	29	45.0073	A/F	1.0389	0.9835	1.0974
(ng·h/mL)	B	29	42.0208	B/F	0.9700	0.9183	1.0246
	C	29	42.7008	C/F	0.9857	0.9331	1.0412
	D	29	39.1295	D/F	0.9033	0.8551	0.9541
	E	29	41.7014	E/F	0.9626	0.9113	1.0168
	F	29	43.3206				
				B/A	0.9336	0.8839	0.9862
				C/A	0.9488	0.8982	1.0022
				D/A	0.8694	0.8231	0.9184
				B/E	1.0077	0.9539	1.0644
AUC_{0-inf}	A	29	46.8820	A/F	1.0419	0.9861	1.1008
(ng·h/mL)	B	29	43.8458	B/F	0.9744	0.9222	1.0296
	C	29	44.3532	C/F	0.9857	0.9329	1.0415
	D	29	40.5414	D/F	0.9010	0.8527	0.9520
	E	29	43.5082	E/F	0.9669	0.9151	1.0216
	F	29	44.9969				
				B/A	0.9352	0.8852	0.9882
				C/A	0.9461	0.8954	0.9996
				D/A	0.8648	0.8184	0.9137
				B/E	1.0078	0.9538	1.0648
C_{max}	A	29	3.4030	A/F	0.4184	0.3658	0.4784
(ng/mL)	B	29	3.3344	B/F	0.4099	0.3585	0.4688
	C	29	5.1488	C/F	0.6330	0.5535	0.7239
	D	29	5.3234	D/F	0.6545	0.5723	0.7484
	E	29	6.4818	E/F	0.7969	0.6968	0.9113
	F	29	8.1341				
				B/A	0.9798	0.8568	1.1206
				C/A	1.5130	1.3230	1.7303
				D/A	1.5643	1.3679	1.7890
				B/E	0.5144	0.4498	0.5883

(b) (4)

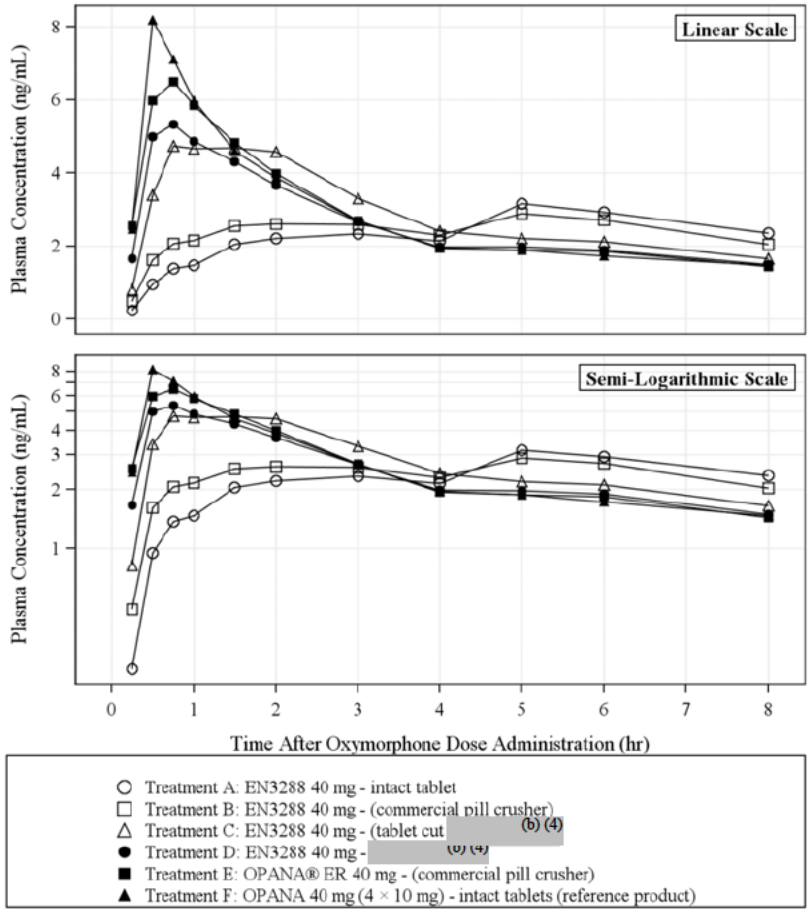
Immediate release (IR) tablets produce peak plasma levels that are higher than extended-release drug products containing the same dose upon single dose administration. Use of such high Cmax values noted with OPANA IR tablets (See figure below) as reference

would indicate a decrease in peak plasma levels to 0.4 – 0.7-fold when [(b) (4)] is consumed intact or under any condition of physical manipulation (See above table).

Since the goal of this PK study is to understand whether the extended-release product can withstand physical tampering, PK results from an intact extended-release product should be used as reference. Use of IR tablets as a reference is masking the effects of physical manipulation which are obviously defeating the control release properties of [(b) (4)] (see above table). Hence, from a clinical pharmacology perspective, bioavailability comparisons are appropriate using Treatment A or the intact extended-release tablet as reference. Using intact [(b) (4)] (Treatment A) as reference, peak plasma levels of oxymorphone failed bioequivalence and were significantly higher when [(b) (4)] was consumed following cutting [(b) (4)] and grinding indicating loss of extended-release characteristics. However, data indicates that [(b) (4)] resists physical crushing forces noted using a pill crusher as demonstrated by bioequivalence to intact [(b) (4)] with respect to Cmax and AUC.

Plots of arithmetic mean oxymorphone concentrations versus time for the first 8 hours after dosing are provided in the figure below.

Mean Oxymorphone Plasma Concentrations Versus Time (0-8 Hours) After Single Oral Doses of Intact and Tampered EN3288 40 mg, Tampered OPANA ER 40 mg, and Intact OPANA 4×10 mg Tablets Administered to Fasted Healthy Subjects (N=29)



Oxymorphone pharmacokinetics after each treatment administration are provided in the Table below.

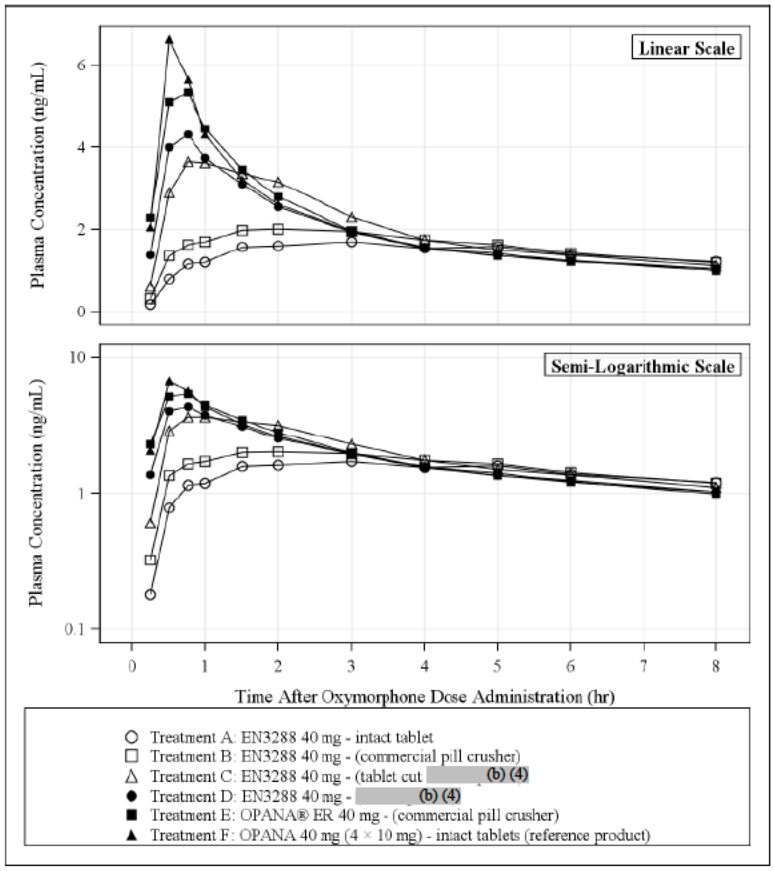
Plasma Pharmacokinetics of Oxymorphone After Single Oral Doses of Intact and Tampered EN3288 40 mg, Tampered OPANA ER 40 mg, and Intact OPANA 4×10 mg Tablets Administered to Fasted Healthy Subjects - Arithmetic Mean±SD (%CV)

	Treatment A (N=29)	Treatment B (N=29)	Treatment C (N=29)	Treatment D (N=29)	Treatment E (N=29)	Treatment F (N=29)
Drug Product[a]	EN3288 40 mg	EN3288 40 mg	EN3288 40 mg	EN3288 40 mg	OPANA 40 mg	OPANA 4×10 mg
Tampering Method	Intact tablet	Commercial pill crusher	Cut (b) (4)	(b) (4)	Commercial pill crusher	Intact tablets
AUC_{0-t} (ng·h/mL)	46.58±12.468 (26.8)	43.44±12.156 (28.0)	44.70±14.317 (32.0)	40.68±11.570 (28.4)	43.64±13.397 (30.7)	45.18±13.863 (30.7)
AUC_{0-inf} (ng·h/mL)	48.61±13.188 (27.1)	45.39±12.820 (28.2)	46.46±15.055 (32.4)	42.16±12.001 (28.5)	45.74±15.206 (33.2)	47.03±14.794 (31.5)
C_{max} (ng/mL)	3.66±1.616 (44.2)	3.51±1.201 (34.2)	5.67±2.824 (49.8)	6.39±5.556 (87.0)	7.02±2.917 (41.5)	9.41±6.626 (70.4)
T_{max} (h)[b]	5.0 (1.5-10.0)	5.0 (0.5-10.0)	1.0 (0.5- 6.0)	0.75(0.5- 6.0)	0.75(0.25-1.5)	0.5 (0.25-5.0)
C_t (ng/mL)	0.129±0.0721 (56.1)	0.118±0.0655 (55.6)	0.107±0.0771 (72.2)	0.094±0.0550 (58.6)	0.117±0.0951 (81.3)	0.113±0.0752 (66.3)
λ_z (1/h)	0.0756±0.02082 (27.5)	0.0704±0.01815 (25.8)	0.0718±0.01784 (24.9)	0.0712±0.01609 (22.6)	0.0701±0.01719 (24.5)	0.0713±0.01615 (22.7)
$t_{1/2}$ (h)	9.8±2.54 (25.9)	10.5±2.57 (24.6)	10.3±2.58 (25.2)	10.2±2.18 (21.4)	10.5±2.83 (26.9)	10.2±2.27 (22.2)
HVD (h)	10.3±3.99 (38.5)	9.1±2.84 (31.2)	4.3±2.41 (56.4)	3.5±2.47 (70.6)	2.6±1.48 (56.9)	1.7±1.44 (83.8)
MRT (h)	15.0±2.79 (18.6)	14.6±2.90 (19.9)	13.2±3.30 (25.0)	12.9±2.66 (20.7)	13.4±3.52 (26.3)	13.3±2.91 (22.0)
$AUMC_{0-inf}$ (ng·h^2/mL)	736±268.0 (36.4)	669±251.7 (37.6)	612±294.1 (48.0)	543±210.8 (38.8)	629±381.0 (60.6)	630±286.4 (45.5)
C_{max}/T_{max} (ng/mL·h)	1.0±0.74 (74.1)	1.8±1.96 (109.7)	5.7±4.24 (74.6)	8.8±11.61 (131.8)	11.3±8.15 (72.3)	18.0±16.92 (94.1)

Plasma Pharmacokinetics of 6-β-Hydroxy-oxymorphone after Single Oral Doses of Intact and Tampered EN3288 40 mg, Tampered OPANA ER 40 mg, and Intact OPANA 4×10 mg Tablets Administered to Fasted Healthy Subjects – Arithmetic Mean±SD (%CV)

	Treatment A (N=29)	Treatment B (N=29)	Treatment C (N=29)	Treatment D (N=29)	Treatment E (N=29)	Treatment F (N=29)
Drug Product[a]	EN3288 40 mg	EN3288 40 mg	EN3288 40 mg	EN3288 40 mg	OPANA 40 mg	OPANA 4×10 mg
Tampering Method	Intact tablet	Commercial pill crusher	Cut (b) (4)	(b) (4)	Commercial pill crusher	Intact tablets
AUC_{0-t} (ng·h/mL)	35.14±13.274 (37.8)	35.51±13.865 (39.0)	38.23±13.137 (34.4)	35.14±15.569 (44.3)	37.96±15.158 (39.9)	38.43±11.894 (31.0)
AUC_{0-inf} (ng·h/mL)[b]	44.51±22.353 (50.2)	45.34±19.792 (43.7)	46.49±16.741 (36.0)	40.79±18.825 (46.2)	44.77±19.896 (44.4)	43.51±13.758 (31.6)
C_{max} (ng/mL)	2.10±0.786 (37.5)	2.53±1.080 (42.7)	4.31±1.778 (41.3)	5.09±3.091 (60.7)	5.99±2.365 (39.4)	7.82±4.207 (53.8)
T_{max} (h)[c]	2.0 (0.5- 6.0)	1.5 (0.5-5.0)	1.0 (0.5-3.0)	0.75 (0.25- 2.0)	0.75 (0.25-1.5)	0.5 (0.25- 4.0)
C_t (ng/mL)	0.285±0.1764 (61.9)	0.271±0.1546 (57.0)	0.236±0.1469 (62.4)	0.217±0.1221 (56.2)	0.265±0.1638 (61.9)	0.251±0.1598 (63.7)
λ_z (1/h)[b]	0.0422±0.01994 (47.2)	0.0387±0.01824 (47.2)	0.0447±0.02024 (45.2)	0.0436±0.01811 (41.5)	0.0438±0.01936 (44.2)	0.0464±0.01642 (35.4)
$t_{1/2}$ (h)[b]	20.1±9.79 (48.8)	21.4±8.40 (39.3)	18.2±6.84 (37.5)	18.5±7.23 (39.2)	18.4±6.50 (35.4)	16.5±4.87 (29.5)
HVD (h)	10.4±5.43 (52.4)	8.0±3.28 (41.2)	3.0±1.20 (39.9)	2.1±0.99 (47.2)	1.5±0.64 (41.9)	1.4±1.86 (131)
MRT (h)[b]	29.3±12.59 (43.0)	29.1±9.79 (33.6)	24.1±9.06 (37.6)	23.8±8.31 (34.9)	23.5±7.57 (32.2)	21.3±5.61 (26.4)
$AUMC_{0-inf}$ (ng·h^2/mL)[b]	1490±1515.3 (101.7)	1376±904.3 (65.7)	1167±759.2 (65.0)	971±557.8 (57.5)	1107±692.5 (62.5)	954±475.6 (49.8)
C_{max}/T_{max} (ng/mL·h)	1.2±0.73 (62.0)	2.4±1.98 (81.7)	5.1±3.71 (73.4)	8.0±7.43 (93.5)	10.1±6.40 (63.4)	15.8±13.29 (84.3)

Mean 6-β-Hydroxy-oxymorphone Plasma Concentrations Versus Time (0 to 8 Hours) After Single Oral Doses of Intact and Tampered EN3288 40 mg, Tampered OPANA ER 40 mg, and Intact OPANA 4×10 mg Tablets Administered to Fasted Healthy Subjects (N=29)



Conclusions:

While tampering with a pill crusher resisted loss of extended-release characteristics of (b) (4) cutting and grinding resulted in immediate release of oxymorphone from (b) (4)

4.2.6 Study EN3288-109: Effects of Mastication on pharmacokinetics of (b) (4)

Study Design and Methods

This was a randomized, double-blind, double-dummy, 4-period, 4-sequence, single-dose, crossover study in healthy, nondependent, recreational oral prescription opioid users experienced in mastication of ER opioid formulations. Each subject participated in a screening visit, a qualification phase, and a treatment phase consisting of 4 treatment periods.

Subjects attended a randomized, double-blind qualification phase consisting of a 3-night confinement period in which he/she received either OPANA 10 mg (3×10 mg) or placebo in a randomized crossover manner to ensure that he/she could consistently discriminate between active drug and placebo and could tolerate the 30 mg dose. Each dose administration in the qualification phase was separated by approximately 24 hours. In addition, the tests that were administered demonstrated that each subject was able to complete and feel comfortable with the pharmacodynamic measures, that he/she could follow directions, and was cooperative.

The following 5 measures contributed to the decision regarding eligibility into the treatment phase: Visual Analog Scale (VAS) for Drug Liking ('at this moment'), VAS for Overall Drug Liking, VAS for High, VAS for Good Effects, and Price Value Assessment.

There was a washout period of at least 72 hours between the end of the qualification phase and the beginning of the first treatment period.

The treatments were identified as follows:

A EN3288 40 mg – intact tablet

B EN3288 40 mg – tablet ingested after mastication

C OPANA ER 40 mg – tablet ingested after mastication

D OPANA 10 mg (4×10 mg) – intact tablets (reference product)

Each subject was randomly assigned to receive a single dose of the study drug over the 4 periods.

Each dose was administered under fasted conditions and separated by at least a 4 day washout period. The treatments were administered in a double-blind, double-dummy manner with the intact tablets (active and/or placebo) administered first followed by the masticated tablet (either EN3288, OPANA ER, or placebo).

A common placebo and unmatched active tablets (all of similar size) were utilized for the study; therefore, doses were administered by an unblinded site pharmacist or designated site personnel who had no other responsibilities for the study.

Pharmacodynamic assessments were obtained at various times through 24 hours postdose in each treatment period and included visual analog scales (VAS) for Drug Liking 'at this moment', Overall Drug Liking, Any Drug Effects, Good Drug Effects, Bad Drug Effects, High, Sick, Take Drug Again, Difficulty Chewing, and Overall Chewing Experience;

Addiction Research Center Inventory (ARCI) for the Morphine Benzedrine Group (MBG); Price Value Assessment; and pupillometry.

At the end of Period 4, an interview session was conducted with the subject individually followed by an optional group session of approximately 5 subjects per group to explore other potential methods of oral abuse of prescription opioids. The interviews were conducted by the investigator or other qualified site personnel designated by the investigator. The interviewer verbally asked questions to the subject and recorded the responses. The questions were not specific to the treatments received in order to maintain the blinding of the study. It was expected that the individual interviews would take approximately 10 to 15 minutes per subject, and the group interviews would take approximately 15 to 30 minutes per group. The interview sessions were to complete on the same day.

Plasma samples were obtained at 0 (predose, within 1 hour prior to administration of oxymorphone) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 hours after administration of oxymorphone in each period.

Subject Disposition and Demographics

In the qualification phase, 51 subjects were enrolled into the study and were administered OPANA 30 mg. Of these, 43 (84%) subjects completed the qualification phase and passed the eligibility criteria. Of the 8 subjects who were not randomized in the treatment phase, 6 (12%) could not discriminate between active treatment and placebo, 1 (2%) had an AE (tachycardia) while receiving placebo, and 1 (2%) receiving OPANA discontinued because of subject decision.

A total of 43 subjects were randomized into the treatment phase. Of these subjects, 41 (95%) completed the study and were included in the pharmacodynamic analysis; 2 (5%) subjects were discontinued due to TEAEs (vomiting). Thirty-one (31) subjects were included in the pharmacokinetic analysis; 6 vomited within 12 hours of a dose and 4 had predose 6-OH-oxymorphone concentrations >5% Cmax. A summary of demographics for the analysis populations in study EN3288-109 is provided in the table below.

Category	Pharmacodynamic Population (N=41)	Pharmacokinetic Population (N=31)
Age (years), mean±SD (range)	25.5±5.59 (18-46)	25.7±5.78 (19-46)
Gender, n (%)		
Male	35 (85.4%)	27 (87.1%)
Female	6 (14.6%)	4 (12.9%)
Ethnicity, n (%)		
Hispanic or Latino	5 (12.2%)	3 (9.7%)
Not Hispanic or Latino	36 (87.8%)	28 (90.3%)
Race, n (%)		
Asian	2 (4.9%)	2 (6.5%)
White	38 (92.7%)	29 (93.5%)
Other	1 (2.4%)	0
Weight (kg), mean±SD (range)	75.20±11.376 (55.8-104.9)	77.23±11.231 (56.1-104.9)
Height (cm), mean±SD (range)	177±8.3 (161-196)	177±7.6 (163-196)
BMI (kg/m^2), mean±SD (range)	23.94±2.853 (18.7-29.7)	24.51±2.666 (19.5-29.7)

Results: The results of the ANOVA comparison of geometric mean results of oxymorphone AUC and Cmax are provided in the table below.

Parameter (unit)	Treatment[a]	n[b]	Geometric Least Squares Means[c]	Ratio of Least Squares Means		90% CI of the Ratio	
						Lower	Upper
AUC_{0-t}	A	31	28.9115	A/D	0.9075	0.8633	0.9539
(ng·h/mL)	B	31	30.6828	B/D	0.9631	0.9161	1.0124
	C	31	30.6995	C/D	0.9636	0.9167	1.0129
	D	31	31.8592				
				B/A	1.0613	1.0096	1.1156
				C/A	1.0618	1.0101	1.1163
				B/C	0.9995	0.9508	1.0506
AUC_{0-inf}	A	23	32.7126	A/D	0.9371	0.8805	0.9974
(ng·h/mL)	B	24	33.6741	B/D	0.9647	0.9070	1.0260
	C	25	34.4435	C/D	0.9867	0.9284	1.0487
	D	22	34.9066				
				B/A	1.0294	0.9703	1.0921
				C/A	1.0529	0.9944	1.1149
				B/C	0.9777	0.9228	1.0358
C_{max}	A	31	2.0492	A/D	0.2655	0.2320	0.3039
(ng/mL)	B	31	4.5555	B/D	0.5903	0.5158	0.6756
	C	31	5.1509	C/D	0.6675	0.5833	0.7638
	D	31	7.7170				
				B/A	2.2231	1.9427	2.5440
				C/A	2.5136	2.1963	2.8769
				B/C	0.8844	0.7729	1.0121

[a] A = EN3288 40 mg, intact tablet; B = EN3288 40 mg, masticated; C = OPANA ER 40 mg, masticated; D = OPANA 4×10 mg, intact tablets

[b] One observation per subject, when available

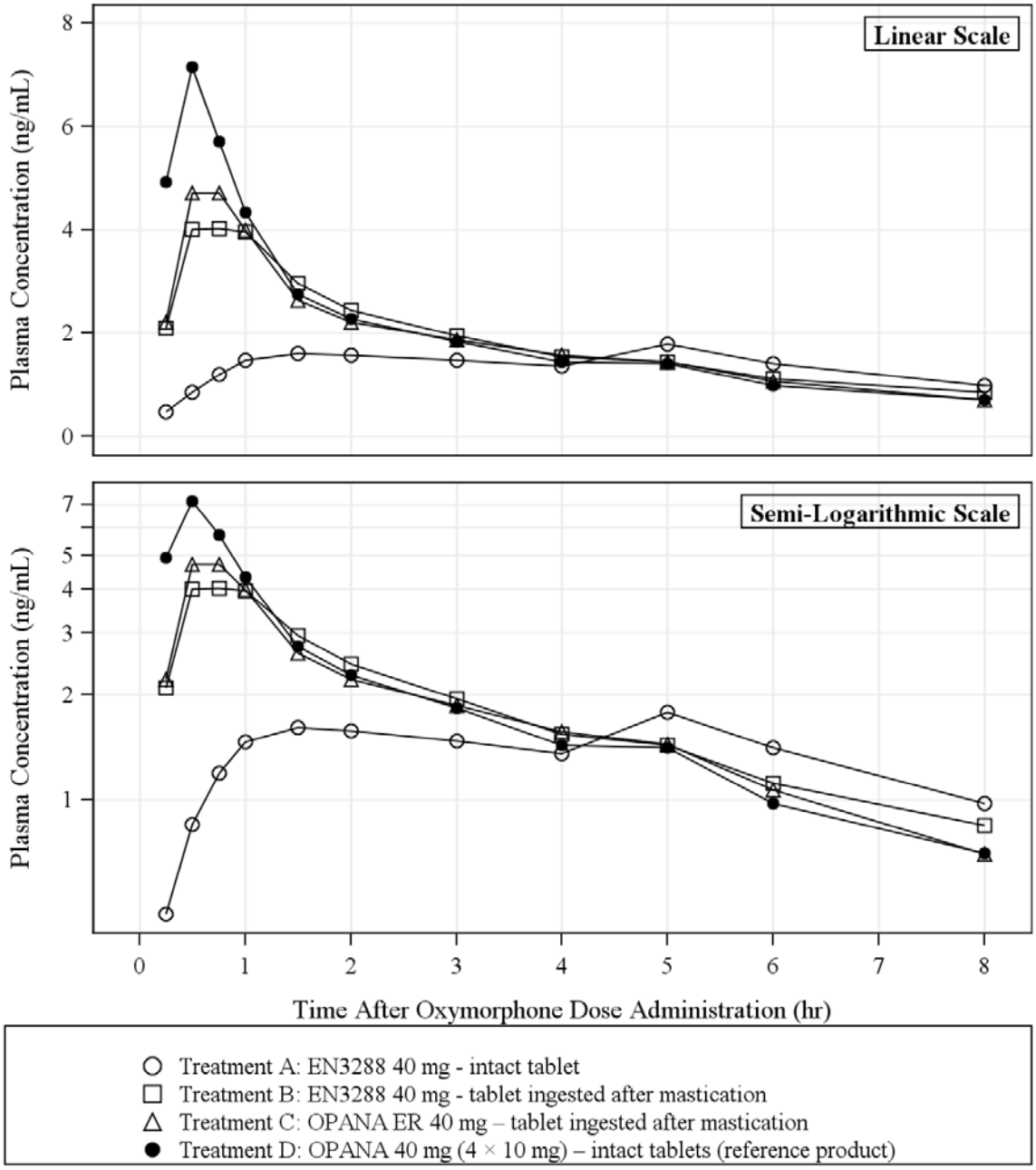
The applicant compared bioavailability (Cmax and AUC) of [redacted] (b) (4) following mastication (Treatments B) with Treatment A (intact [redacted] (b) (4) 40 mg tablet) or Treatment D (40 mg immediate release tablets). As with BE studies, bioequivalence is concluded if the 90% CI of the geometric mean ratio of a treatment compared to appropriate reference for oxymorphone AUC_{0-t} and C_{max} fall within the limits of 0.8 to 1.25.

Using intact OPANA IR tablets (Treatment D) as reference, which has the highest Cmax compared to all treatment groups (See figure below), peak plasma levels following chewing ranged between 0.5 – 0.7-fold (See table above).

Plots of arithmetic mean oxymorphone concentrations versus time for the first 8 hours after dosing are provided in the figure below.

Mean Oxymorphone Plasma Concentrations Versus Time (0-8 Hours) After Single Oral Doses of Intact and Masticated EN3288 40 mg, Masticated

OPANA ER 40 mg, and Intact OPANA 4×10 mg Tablets Administered to Fasted Healthy Subjects (N=31)



Plasma Pharmacokinetics of Oxymorphone After Single Oral Doses of Intact and Masticated EN3288 40 mg, Masticated OPANA ER 40 mg, and Intact OPANA 4×10

mg Tablets Administered to Fasted Healthy Subjects - Arithmetic Mean±SD (%CV)

	Treatment A (N=31)	Treatment B (N=31)	Treatment C (N=31)	Treatment D (N=31)
Drug Product[a]	**EN3288 40 mg**	**EN3288 40 mg**	**OPANA ER 40 mg**	**OPANA 4×10 mg**
Manipulation of Tablet	**Intact tablet**	**Masticated**	**Masticated**	**Intact tablets**
AUC_{0-t} (ng·h/mL)	30.16±8.441 (28.0)	32.24±9.987 (31.0)	31.79±8.158 (25.7)	33.54±10.558 (31.5)
AUC_{0-inf}[b] (ng·h/mL)	33.98±10.058 (29.6)	35.29±11.246 (31.9)	35.77±8.797 (24.6)	36.85±9.940 (27.0)
C_{max} (ng/mL)	2.17±0.774 (35.7)	5.16±2.838 (55.0)	5.67±2.612 (46.1)	8.69±4.822 (55.5)
T_{max} (h)[c]	3.0 (0.8-10.0)	0.8 (0.3-2.1)	0.8 (0.3-1.1)	0.5 (0.3-1.0)
C_t (ng/mL)	0.158±0.0710 (44.9)	0.140±0.0720 (51.4)	0.129±0.0515 (39.8)	0.146±0.0522 (35.8)
λ_z[b] (1/h)	0.0507±0.01475 (29.1)	0.0484±0.01238 (25.6)	0.0513±0.01529 (29.8)	0.0492±0.01395 (28.3)
$t_{1/2}$[b] (h)	15.3±6.47 (42.2)	15.2±3.68 (24.2)	14.7±4.70 (31.9)	15.3±4.88 (31.9)
HVD (h)	8.9±4.35 (48.7)	2.3±1.29 (57.1)	1.7±1.54 (89.6)	0.9±0.54 (59.5)
MRT[b] (h)	21.5±6.78 (31.6)	18.5±4.64 (25.1)	17.8±4.46 (25.1)	18.8±6.05 (32.1)
C_{max}/T_{max} (ng/mL·h)	1.1±0.89 (78.3)	7.6±5.63 (74.1)	9.8±6.70 (68.4)	22.1±20.66 (93.7)

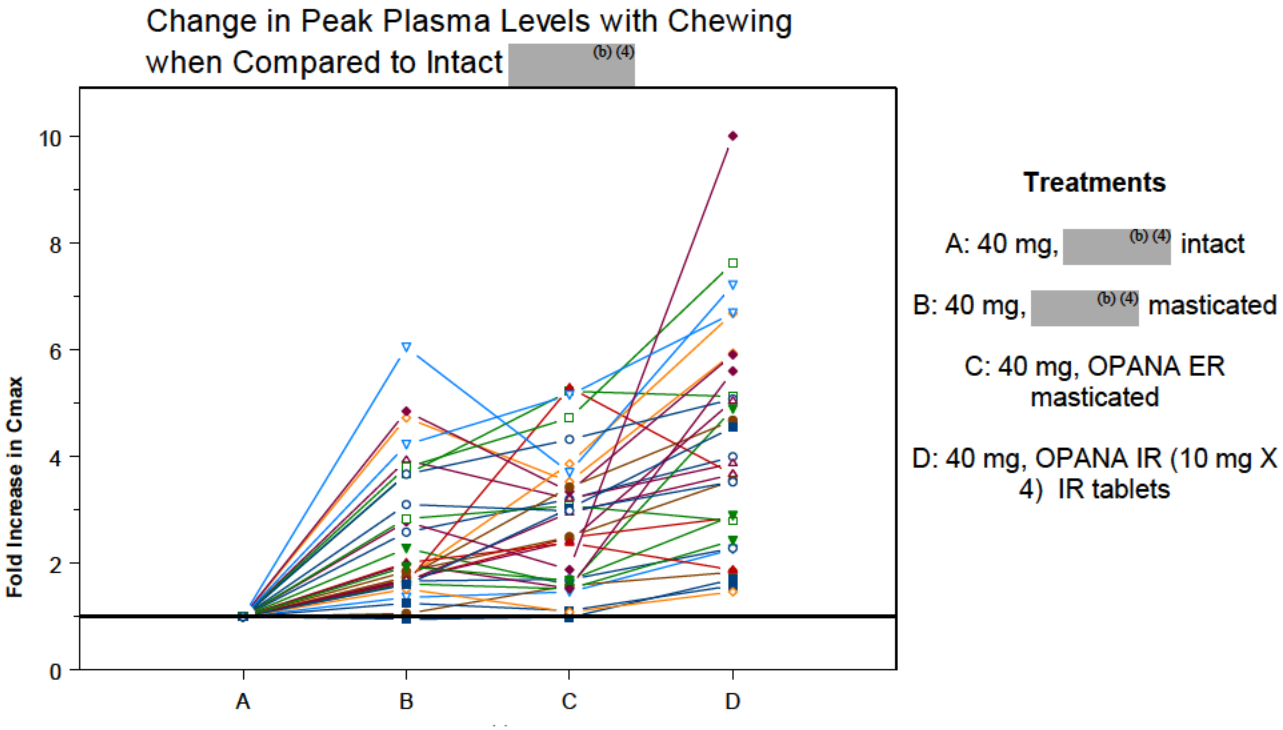
[a] Source: EN3288-109 Clinical Study Report, Table 14.2.2.1

[b] N=23 for EN3288 40 mg, intact tablet; N=24 for EN3288 40 mg, masticated; N=25 for OPANA ER 40 mg masticated; N=22 for OPANA 4×10 mg, intact tablet

Analysis of pharmacodynamic effects may be found in controlled substance staff review by Dr. James Tolliver.

As discussed in the previous study results, from a clinical pharmacology perspective it is important to understand if the product retains its extended-release characteristics under conditions of improper use. This can only be accomplished by utilizing intact extended-release product as a reference (Treatment A). Comparison with intact extended-release tablet indicates a 2.2-fold increase in Cmax when (b) (4) is consumed after chewing.

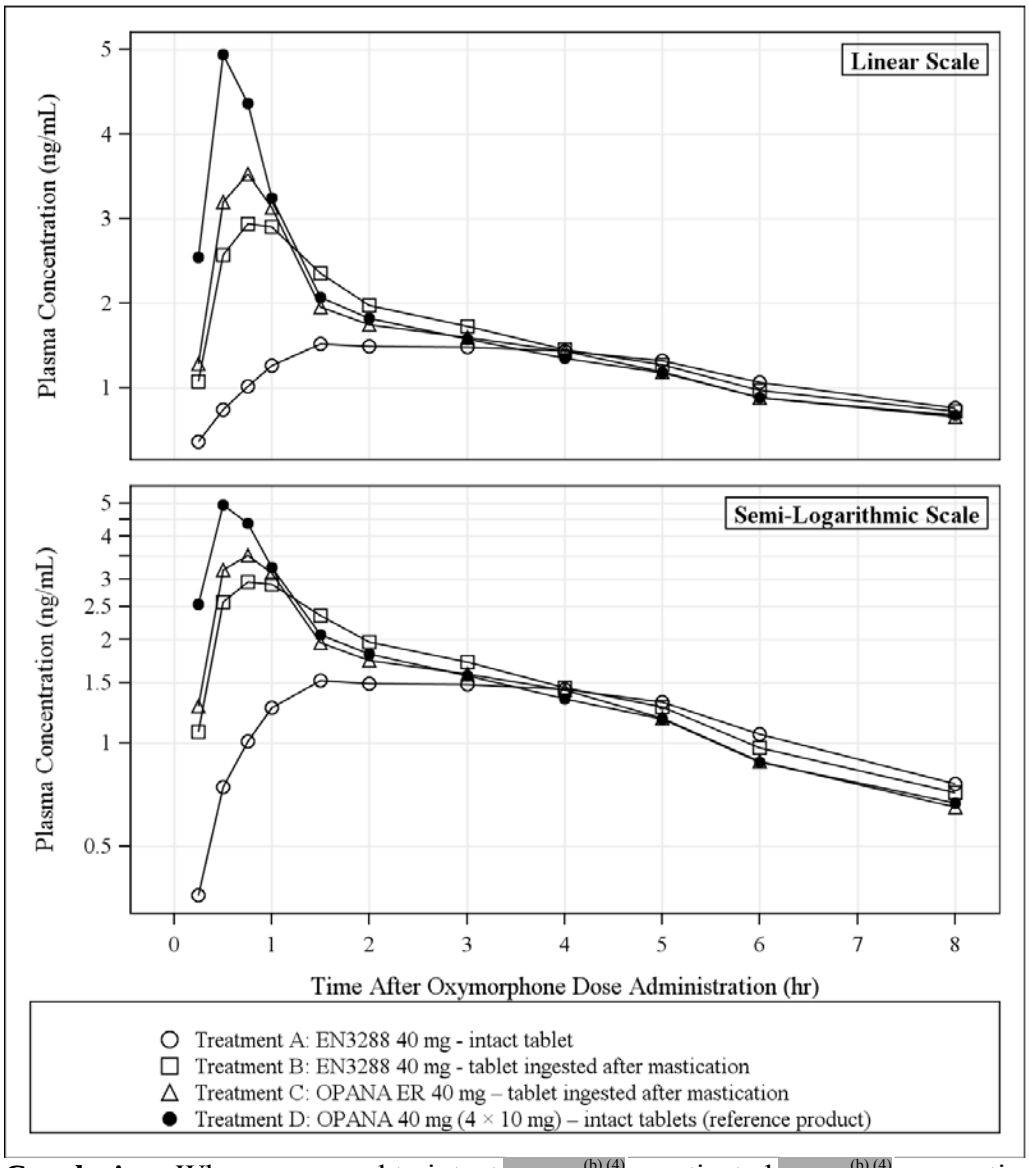
When considering individual data, fold increase in Cmax as high as 6-fold were noted when (b) (4) was consumed after chewing (Treatment B) (See figure below). Fold change in Cmax for each individual were calculated by dividing Cmax noted for each treatment with Cmax noted with reference treatment A ((b) (4) 40 mg intact).



Plasma Pharmacokinetics of 6-β-Hydroxy-oxymorphone After Single Oral Doses of Intact and Masticated EN3288 40 mg, Masticated OPANA ER 40 mg, and Intact OPANA 4×10 mg Tablets Administered to Fasted Healthy Subjects - Arithmetic Mean±SD (%CV)

	Treatment A (N=31)	Treatment B (N=31)	Treatment C (N=31)	Treatment D (N=31)
Drug Product[a]	EN3288 40 mg	EN3288 40 mg	OPANA ER 40 mg	OPANA 4×10 mg
Manipulation of Tablet	Intact tablet	Masticated	Masticated	Intact tablets
AUC_{0-t} (ng·h/mL)	31.88±10.312 (32.4)	33.51±10.749 (32.1)	33.10±8.967 (27.1)	34.19±9.401 (27.5)
C_{max} (ng/mL)	1.78±0.580 (32.6)	3.53±1.181 (33.49)	3.91±1.316 (33.6)	5.48±1.685 (30.7)
T_{max} (h)[b]	3.0 (1.0-6.1)	0.8 (0.5-3.1)	0.8 (0.5-3.0)	0.6 (0.3-1.0)
C_t (ng/mL)	0.438±0.2096 (47.8)	0.374±0.1797 (48.0)	0.376±0.1574 (41.9)	0.382±0.1881 (49.2)
HVD (h)	8.1±4.92 (61.0)	2.6±1.22 (46.4)	1.9±1.13 (58.4)	1.1±0.66 (59.7)
C_{max}/T_{max} (ng/mL·h)	0.9±0.55 (64.8)	4.6±2.70 (59.2)	5.5±2.45 (44.6)	11.6±7.55 (65.4)

Mean <u>6-β-Hydroxy-oxymorphone</u> Plasma Concentrations Versus Time (0 to 8 Hours) After Single Oral Doses of Intact and Masticated EN3288 40 mg, Masticated OPANA ER 40 mg, and Intact OPANA 4×10 mg Tablets Administered to Fasted Healthy Subjects (N=31)



Conclusion: When compared to intact [redacted] (b) (4) masticated [redacted] (b) (4) or masticated OPANA ER resulted in dose dumping.

4.2.7 OCP Filing Memo

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**201655**	**Brand Name**	**Oxymorphone HCl (b) (4) extended-release tablet (b) (4)**
OCP Division (I, II, III, IV, V)	**DCP2**	**Generic Name**	**Oxymorphone HCl**
Medical Division	**DAAP**	**Drug Class**	**Opioid**
OCP Reviewer	**Srikanth C. Nallani, Ph.D.**	**Indication(s)**	**Moderate to severe pain**
OCP Team Leader	**Suresh Doddapaneni, Ph.D.**	**Dosage Form**	**Tablet**
Pharmacometrics Reviewer		**Dosing Regimen**	**BID**
Date of Submission	**7/7/2010**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**12/15/2010**	**Sponsor**	**Endo Pharmaceuticals**
Medical Division Due Date	**12/15/2010**	**Priority Classification**	**Priority**
PDUFA Due Date	**1/7/2010**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				**BE Based NDA**
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**1**	**1**	
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	**X**	**6**	**6**	**See Below**
Healthy Volunteers-				
single dose:	**X**	**6**	**6**	See details below
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				**Biowaiver Request for intermediate strengths (7.5 to 30 mg) submitted based on dissolution and product quality information.**
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				

Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**3**	**3**	**BE studies evaluating alcohol interaction (#107), physical tampering (crushing, grinding) of product (# 108) and chewing (#109)with IR tablet as reference .**
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:	**X**	**3**	**3**	**Fasted and Fed BE studies for 40 mg (#103,#104). Fasting BE study for 5 mg (#105).**
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping	**X**	**1**	**-**	**In vitro data is noted for reference only. ONDQA will review this in vitro study.**
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**7**	**7**	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			Plan involves establishing BE with approved Opana ER. Clinical formulation is all to-be-marketed formulation.
2	Has the applicant provided metabolism and drug-drug interaction information?			X	No new info.

3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	No new info
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	No PGx data submitted
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies			X	BE based NDA and hence no new info.

	for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?				
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	No pediatric submission is included with respect to exclusivity. Agency indicated as follows to sponsor at the Pre-NDA meeting: “Since your product does not represent a new indication, dosage form, active ingredient, dosing regimen or route of administration, PREA is not triggered and no studies in the pediatric population will be required.”
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and	X			

	breadth of investigation to meet basic requirements for approvability of this product?				
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
___Yes_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.
Please identify and list any potential review issues to be forwarded to the Applicant for the 60-day letter.

General notes on submitted clinical pharmacology studies are appended to this memo at the end.

DSI consult needed

Pivotal BE Study # EN3288-103:

Study Title: An open-label, randomized, single-dose, four-period, replicate, crossover study to determine the bioequivalence of EN3288 (Oxymorphone HCl extended-release (b) (4) formulation) 40 mg compared to Opana® ER (Oxymorphone HCl extended-release) 40 mg in healthy subjects under fasted conditions.

Name and Address of Investigator
Axel Juan, MD SeaView Research, Inc. 3898 NW 7th Street Miami, FL 33126

(b) (4)

Comments to sponsor for Filing letter
In drug liking study EN3288-109, we note that you have recruited subjects experienced with chewing opioid products. We could not ascertain if the subjects were provided specific instructions on how to chew to treatments. Indicate the details of instructions provided to subjects with regard to rate of chewing or duration of chewing?

Srikanth C. Nallani, Ph.D.	8/13/10
Reviewing Clinical Pharmacologist	Date
Suresh Doddapaneni, Ph.D.	
Team Leader/Supervisor	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SRIKANTH C NALLANI
12/14/2010

SURESH DODDAPANENI
12/15/2010

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 201-655 (000)	**Reviewer:** Sandra Suarez Sharp, Ph.D	
Division:	DAAP		
Sponsor:	ENDO Pharmaceuticals	**Team Leader:** Angelica Dorantes, Ph.D .	
Trade Name:	--	**Supervisor:** Patrick J. Marroum, Ph.D	
Generic Name:	Oxymorphone HCl (b) (4) (b) (4) ER Tablet	**Date Assigned:**	Jul 12, 2010
Indication:	relief of moderate to severe pain	**Date of Review:**	Nov 15, 2010
Formulation/strengths	ER Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	**CDER Stamp Date**	**Date of informal/Formal Consult**	**PDUFA DATE**
July 7, 2010 Sep 14, 2010 Dec 6, 2010	July 7, 2010	Jul 8, 2010	Dec 2010
Type of Submission:	Original NDA		
Type of Consult:	Dissolution method and specifications/waiver request for lower strengths		

REVIEW SUMMARY:

OPANA® (oxymorphone HCl) immediate release tablet was approved by the Agency under NDA 21-611 on June 22, 2006. The sponsor, ENDO, has developed a (b) (4) extended-release tablet for oxymorphone HCl. This New Drug Application is based on establishing bioequivalence to OPANA® ER (NDA 21-610), which was approved by FDA on June 22, 2006.

The (b) (4) formulation product is intended to be dosed twice-daily and will be available in the same dosage strengths as OPANA ER (5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg). The oxymorphone HCl (b) (4) extended-release tablet is intended to be indicated for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. It is proposed that the dosing and administration will be identical to the reference OPANA ER (oxymorphone HCl) Extended-Release Tablets.

The development program for Oxymorphone ER (b) (4) tablets consisted of the following studies:

- Two bioequivalence studies for the highest (40 mg) and lowest (5 mg) tablet strengths to the marketed product, OPANA ER (EN3288-103 and EN3288-105, respectively).
- Waiver request based on dissolution profile comparisons: The bioequivalence of intermediate tablet strengths was established by the proportional similarity of all tablet strength formulas, and the similarity of dissolution profiles.
- Food effect study: the 40 mg tablet was administered with a high fat meal (EN3288-104).
- In vivo (study EN3288-107) and vitro dose dumping effect of concurrent administration of ethanol on the oxymorphone HCl (b) (4) extended-release tablets.
- The tamper-resistant characteristics of oxymorphone HCl (b) (4) extended-release tablets were explored in in vitro tampering studies and in vivo studies EN3288-108 and EN3288-109.

All batches of oxymorphone HCl (b) (4) ER tablet and other products used in the clinical studies were manufactured by Pharmaceutical Manufacturing Research Services (PMRS) at Horsham, PA, USA which is the commercial manufacturing site. The oxymorphone HCl (b) (4) ER tablet clinical trial formulation is the same as the to-be-marketed formulation.

The biopharmacetics review focuses on the dissolution method and specification, the waiver request based on the dissolution profile comparisons supporting the approvability of the intermediate strengths, and the in vitro alcohol interaction study. The BE studies and in vivo alcohol interaction study are being reviewed by OCP.

The dissolution method and specifications being proposed by the sponsor for all the strengths of Oxymorphone ER (b) (4) tablets are as follows:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Acceptance criteria
Oxymorphone HCl	ER Tablet	II (paddle)	50	phosphate buffer, pH 4.5	900, 37 °C ± 0.5 °C	1 hour: (b) (4) 2 hours: (b) (4) dissolved 8 hours: NLT (b) (4)

These proposed ranges are based on the in vitro performance of BA/BE batches, stability batches, and on the Agency's recommendations dated November 23, 2010. Section 3.2.P.5.1 Drug Product Specifications has been updated accordingly (refer to submission dated Dec 6, 2010). The proposed dissolution method and specifications are acceptable.

The dissolution profiles of all 7 strengths of oxymorphone hydrochloride (b) (4) ER tablets in three different media (pH 1.2, 4.5 and 6.8) were determined. Similarity factors (f2 values) higher than 50 demonstrated that all 7 strengths of oxymorphone hydrochloride (b) (4) ER tablets exhibit similar dissolution profiles. Therefore, the waiver request of the in vivo BE requirements for the lower strengths is granted.

Dissolution of the 5 mg and 40 mg oxymorphone HCl (b) (4) extended-release tablets was unaffected by addition of 5% ethanol to the media. In contrast, dissolution rates of both 40 mg and 5 mg oxymorphone HCl (b) (4) extended-release tablet were slower when 40% ethanol was added to the dissolution media.

Numerous in vitro studies were conducted to demonstrate the (b) (4) characteristics of the oxymorphone (b) (4) ER tablets by evaluation of changes in the rate of release of the drug from the drug product if it is misused either intentionally or unintentionally. The in vitro studies evaluated the extractability of the drug from the formulation under the effects of pH, temperature, alcohol concentration, solvent volume and polarity, at various exposure times in combination with agitation on disruption or destruction of the drug product (b) (4). The destruction of the drug product (b) (4) also included increasing the total surface area of the tablet from intact to being "crushed" (b) (4) or cut (b) (4) Oxymorphone HCl (b) (4) tablets do not show good resistance to tampering employed by recreational abusers or experienced abusers (b) (4)

RECOMMENDATION:
The ONDQA/biopharmaceutics team has reviewed NDA 201-655 (000) submitted on July 7, 2010, Sep 14,

2010, and Dec 6, 2010. The dissolution method and specifications proposed by the sponsor on submission dated Dec 6, 2010 are acceptable.

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: ADorantes, SPatwardhan, DChristodoulou, CBertha

INTRODUCTION

Oxymorphone hydrochloride (HCl) tablets are currently marketed in the United States (US), under the trade name OPANA® and are available in both an immediate-release (IR) and an extended-release (ER) dosage form. The IR form is available in dosage strengths of 5 mg and 10 mg and the ER form is available in dosage strengths of 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg. In the US, oxymorphone is a Schedule II controlled substance under the US Controlled Substances Act of 1970.

OPANA® ER (oxymorphone HCl) Extended-Release Tablets are indicated for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid therapy for an extended period of time. OPANA ER tablets incorporate the TIMERx®-N controlled-release matrix to provide delivery of oxymorphone over a 12-hour dosing interval and are therefore dosed twice daily.

Endo Pharmaceuticals Inc. and its partner, Grünenthal GmbH (Aachen, Germany), have developed a (b) (4) extended-release formulation of oxymorphone HCl that according to them reduces accidental misuse (ie, breaking and/or crushing for patient convenience) and to deter certain methods of intended abuse (ie, crushing for snorting and/or injection).

Clinical Pharmacology Background

According to the sponsor, the absolute oral bioavailability of oxymorphone is approximately 10%. Steady-state levels are achieved after three days of multiple dose administration. Under both single-dose and steady state conditions, dose proportionality has been established for the 5 mg, 10 mg, 20 mg, and 40 mg tablet strengths for both peak plasma levels (Cmax) and extent of absorption (AUC)[1]. After a single oral dose of OPANA ER 40 mg, oxymorphone Cmax (mean±SD) and AUC (mean±SD) were 2.59±1.65 ng/mL and 37.90±16.20 ng*h/mL, respectively. Mean (±SD) oxymorphone half life ranged from 9.35±2.94 hours to 11.30±10.81 hours in the single dose studies.

[1] Drugs at the FDA

Table 1. Mean (±SD) OPANA ER Pharmacokinetic Parameters

Regimen	Dosage	Cmax	AUC	T ½
		(ng/mL)	(ng·hr/mL)	(hr)
Single Dose	5 mg	0.27±0.13	4.54±2.04	11.30±10.81
	10 mg	0.65±0.29	8.94±4.16	9.83±5.68
	20 mg	1.21±0.77	17.81±7.22	9.89±3.21
	40 mg	2.59±1.65	37.90±16.20	9.35±2.94
Multiple Dosea	5 mg	0.70±0.55	5.60±3.87	NA
	10 mg	1.24±0.56	9.77±3.52	NA
	20 mg	2.54±1.35	19.28±8.32	NA
	40 mg	4.47±1.91	36.98±13.53	NA

CHEMISTRY

Formulation

Oxymorphone hydrochloride, a semi-synthetic opioid analgesic, is supplied in 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg (b) (4) extended-release tablet strengths for oral administration. The principal mechanism of drug release of the oxymorphone HCl (b) (4) extended-release tablets is via (b) (4) The composition of the product is given in Table 3.

Table 2. Composition of 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg Oxymorphone Hydrochloride (b) (4) ER Tablets (%w/w basis)

Ingredient (%w/w)	**5 mg**	**7.5 mg**	**10 mg**	**15 mg**	**20 mg**	**30 mg**	**40 mg**	**Function**
Oxymorphone hydrochloride	2.33	3.49	4.65	6.98	9.30	13.95	18.60	Drug Substance
Polyethylene oxide (PEO) (b) (4)	(b) (4)							
Hypromellose (b) (4) (HPMC) (b) (4)								
Polyethylene glycol (b) (4) (PEG)a								
α-tocopherol (b) (4)								
Citric acid, anhydrous								
(b) (4)								
(b) (4)								

Table 3. Oxymorphone HCl (b) (4) ER Tablet (EN3288), OPANA ER and OPANA IR Batches Used in Clinical Trials Listed by Study Number

Study Number	Product	Strength	Lot Number
EN3288-103	EN3288	40 mg	B09056B1
	OPANA ER	40 mg	401569NV
EN3288-104	EN3288	40 mg	B09056B2
	OPANA ER	40 mg	401569NV
EN3288-105	EN3288	5 mg	B09051B1
	OPANA ER	5 mg	401557NV
EN3288-107	EN3288	40 mg	B09056B3
EN3288-108	EN3288	40 mg	B09056G
	OPANA ER	40 mg	401791NV
	OPANA IR	10 mg	401845NV
EN3288-109	EN3288	40 mg	B09056H
	OPANA ER	40 mg	401787NV
	OPANA IR	10 mg	401855NV

Reviewer's Comments

(b) (4) *the ratio of PEO to total weight of the dosage form is within the limits defined by the SUPAC-MR guidance up to and including Level II (≤ 10%) for the bracket 40 mg, 30 mg, and 15 mg and the bracket for 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg). The sponsor conducted two BE studies (comparing the 40 mg and 5 mg strengths to their respective references) which are sufficient to link all the strengths using dissolution profile comparisons.*

Proposed Dissolution Method

The following table summarizes the proposed dissolution method and specification for Oxymorphone ER (b) (4) Tablets:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)
Oxymorphone HCl	ER Tablet	II (paddle)	50	phosphate buffer, pH 4.5	900, 37 °C ± 0.5 °C

It is noted that this dissolution method is the same as that approved for oxymorphone HC ER tablets[2] and it is also approved for Opana ER Tablets.

[2] FDA dissolution method database online

Mean dissolution results for oxymorphone HCl (b) (4) extended-release tablet batches (EN3288) used in human clinical trials are summarized in Table 4. The mean dissolution profiles are represented in Figure 1 and Figure 2 for the 40 mg and 5 mg tablets, respectively.

Table 4. Mean Dissolution Profiles of Oxymorphone HCl (b) (4) Extended-Release Tablet Batches Used in Clinical Trials

Batch Number	Strength	Mean Percent of Labeled Amount Dissolved by Hour[a]								
		0	0.5	1	2	4	8	10	12	14
B09056 (n=12)	40 mg	0	(b) (4)							
B09051 (n=12)	5 mg	0								

a In-vitro dissolution testing for the EN3288, 5 mg and 40 mg tablets was performed by (b) (4)

Figure 1. Dissolution Profiles of EN3288 40 mg Tablets and OPANA ER 40 mg Tablets Used in Bioequivalence Studies EN3288-103 and EN3288-104

Figure 2. Dissolution Profiles of EN3288 5 mg Tablets and OPANA ER 5 mg Tablets Used in Bioequivalence Study EN3288-105.

Dissolution Profiles of All Seven Strengths of Oxymorphone Hydrochloride (b) (4) Extended-Release Tablets

The dissolution profiles of all 7 strengths of oxymorphone hydrochloride (b) (4) extended-release tablets in the pH 4.5 medium (the primary method) are shown in Figure 3. The f2 values provided in Table 5 demonstrate that all 7 strengths of oxymorphone hydrochloride (b) (4) extended-release tablets exhibit similar dissolution profiles. In addition, the sponsor was requested to provide f2 testing considering the (b) (4) (b) (4) strength as a reference given that the lower strengths (5 mg to 15 mg) are not proportionally similar to the 40 mg strength. The f2 values were > 40 indicating similar dissolution profiles.

Figure 3. Dissolution Profiles of All Seven Strengths of Oxymorphone Hydrochloride (b) (4) (b) (4) Extended-Release Tablets in pH 4.5 Medium (N=12).

Table 5. Similarity Factor (f2) of the Dissolution Profiles of All Seven Strengths of Oxymorphone Hydrochloride TR ER Tablets in pH 4.5 Medium

Reference Product versus Test Product	**Similarity factor (f2)**
40 mg (Lot B09056) versus 5 mg (Lot B09051)	68.5
40 mg (Lot B09056) versus 5 mg (Lot B09052)	71.3
40 mg (Lot B09056) versus 5 mg (Lot B09053)	67.8
40 mg (Lot B09056) versus 7.5 mg (Lot B09142)	70.9
40 mg (Lot B09056) versus 10 mg (Lot B09054)	77.3
40 mg (Lot B09056) versus 15 mg (Lot B09143)	91.2
40 mg (Lot B09056) versus 20 mg (Lot B09055)	83.7
40 mg (Lot B09056) versus 30 mg (Lot B09144)	97.6
40 mg (Lot B09056) versus 40 mg (Lot B09057)	90.6
40 mg (Lot B09056) versus 40 mg (Lot B09058)	88.1

Dissolution profiles, using the FDA published method but in 3 different media (pH 1.2, 4.5, and 6.8), were generated on oxymorphone hydrochloride (b) (4) extended-release tablets 5 mg (Figure 4), 20 mg (Figure 5), and 40 mg strengths (Figure 6) in support of the waiver request of BE studies for the lower strengths. Similarity factor (f2) values depicted in Table 6 demonstrate that dissolution profiles are similar in pH 1.2, 4.5, and 6.8 media for the 5 mg, 20 mg, and 40 mg strengths. Therefore, the waiver request of the in vivo BE requirements for the lower strengths is granted.

Figure 4. Dissolution Profiles of 5 mg Oxymorphone Hydrochloride (b) (4) Extended-Release Tablets in pH 1.2, 4.5, and 6.8 Media (N=12)

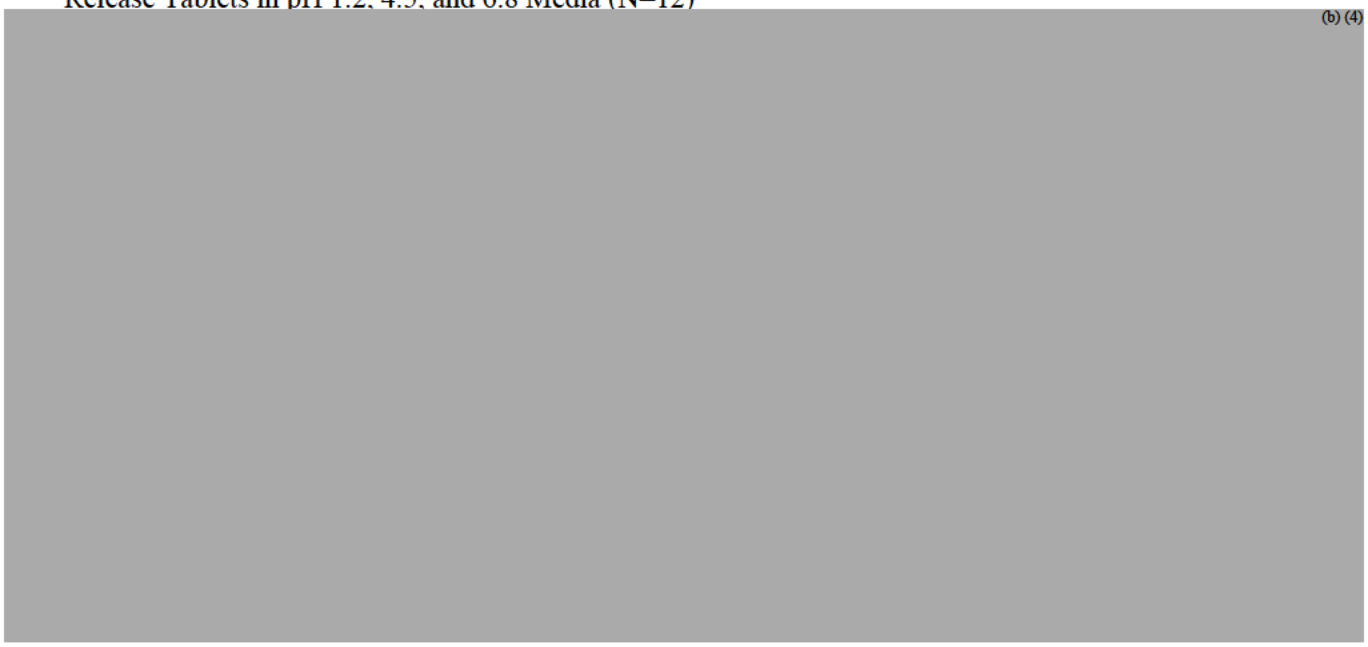


Figure 5. Dissolution Profiles of 20 mg Oxymorphone Hydrochloride (b) (4) Extended-Release Tablets in pH 1.2, 4.5, and 6.8 Media (N=12).

Figure 6. Dissolution Profiles of 40 mg Oxymorphone Hydrochloride (b) (4) Extended-Release Tablets in pH 1.2, 4.5, and 6.8 Media (N=12).

Table 6. Similarity Factor (f2) of the Dissolution Profiles of Oxymorphone Hydrochloride (b) (4) Extended-Release Tablets, 5 mg, 20 mg, and 40 mg, in pH 1.2, 4.5, and 6.8 Media

Reference Product versus Test Product	Similarity factor (f2)
5 mg (Lot HLTU37), pH 4.5 versus pH 1.2	76.8
5 mg (Lot HLTU37), pH 4.5 versus pH 6.8	84.6
20 mg (Lot B09055), pH 4.5 versus pH 1.2	68.2
20 mg (Lot B09055), pH 4.5 versus pH 6.8	89.5
40 mg (Lot HLTX61), pH 4.5 versus pH 1.2	68.8
40 mg (Lot HLTX61), pH 4.5 versus pH 6.8	95.6
40 mg (Lot HLTX61) versus 5 mg (Lot HLTU37) in pH 1.2	66.3
40 mg (Lot HLTX61) versus 20 mg (Lot B09055) in pH 1.2	82.8
40 mg (Lot HLTX61) versus 5 mg (Lot HLTU37) in pH 4.5	60.0
40 mg (Lot HLTX61) versus 20 mg (Lot B09055) in pH 4.5	85.3
40 mg (Lot HLTX61) versus 5 mg (Lot HLTU37) in pH 6.8	66.6
40 mg (Lot HLTX61) versus 20 mg (Lot B09055) in pH 6.8	76.1

Comparison of dissolution profiles between the oxymorphone hydrochloride (b) (4) ER tablets and the OPANA ER tablets were conducted using the FDA published dissolution method. According to the sponsor, the similarity factor (f2) values demonstrate that the dissolution profiles of the oxymorphone hydrochloride (b) (4) extended-release tablets are similar to those of respective OPANA ER tablets (Table 7).

Table 7. Similarity Factor (f2) of the Dissolution Profiles Between OPANA® ER Tablets and Oxymorphone Hydrochloride (b) (4) Extended-Release Tablets ((b) (4) in pH 4.5 Medium (N=12 unless noted)

Reference Product versus Test Product	Similarity factor (f2)
5 mg, OPANA ER (Lot 63481-907[a], 400816NV[b], 401397 NV[a]) versus (b) (4) (Lot B09051)	81.0
5 mg, OPANA ER (Lot 63481-907[a], 400816NV[b], 401397 NV[a]) versus (b) (4) (Lot B09052)	78.3
5 mg, OPANA ER (Lot 63481-907[a], 400816NV[b], 401397 NV[a]) versus (b) (4) (Lot B09053)	81.7
7.5 mg, OPANA ER (Lot 401033NV[b]) versus (b) (4) (Lot B09142)	71.5
10 mg, OPANA ER (Lot 400835NV[b], 400879NV[b]) versus (b) (4) (Lot B09054)	73.1
15 mg, OPANA ER (Lot 401155NV[b]) versus (b) (4) (Lot B09143)	72.9
20 mg, OPANA ER (Lot 400934NV[b], 400943NV[b]) versus (b) (4) (Lot B09055)	67.5
30 mg, OPANA ER (Lot 401447NV[b]) versus (b) (4) (Lot B09144)	70.2
40 mg, OPANA ER (Lot 400914NV[b], 400935NV[b]) versus (b) (4) (Lot B09056)	65.9
40 mg, OPANA ER (Lot 400914NV[b], 400935NV[b]) versus (b) (4) (Lot B09057)	66.4
40 mg, OPANA ER (Lot 400914NV[b], 400935NV[b]) versus (b) (4) (Lot B09058)	64.4

[a] N=3
[b] N=6

In Vitro Alcohol Interaction Study

The dissolution of 40 mg oxymorphone HCl (b) (4) extended-release tablets was studied in dissolution media containing 5% and 40% ethanol by (b) (4)

The 900 mL dissolution media at 37°C were:

- USP Simulated Gastric Fluid without Pepsin, pH 1.2
- 5% Ethanol and 95% USP Simulated Gastric Fluid without Pepsin, pH 1.2
- 40% Ethanol and 60% USP Simulated Gastric Fluid without Pepsin, pH 1.2
- USP Simulated Intestinal Fluid without Pancreatin, pH 6.8
- 5% Ethanol and 95% USP Simulated Intestinal Fluid without Pancreatin, pH 6.8
- 40% Ethanol and 60% USP Simulated Intestinal Fluid without Pancreatin, pH 6.8

The dissolution apparatus was: USP <711> Apparatus 2 (paddles) at 50 rpm.
The results measured over 14 hours (840 minutes) are represented in Figures 7 and 8 in different media.

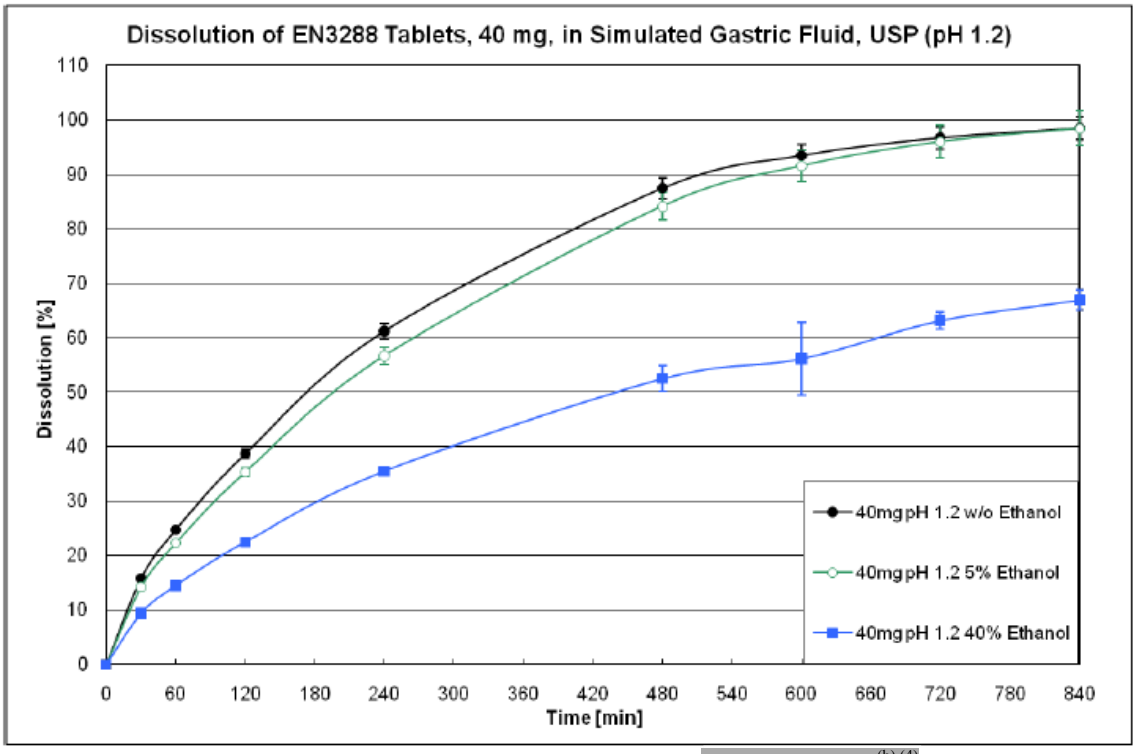


Figure 7. Dissolution Profile of 40 mg Oxymorphone HCl [redacted] (b) (4) Extended- Release Tablet (EN3288) Batch No. HLTX61-1: Ethanolic USP Simulated Gastric Fluid Without Pepsin, pH 1.2.

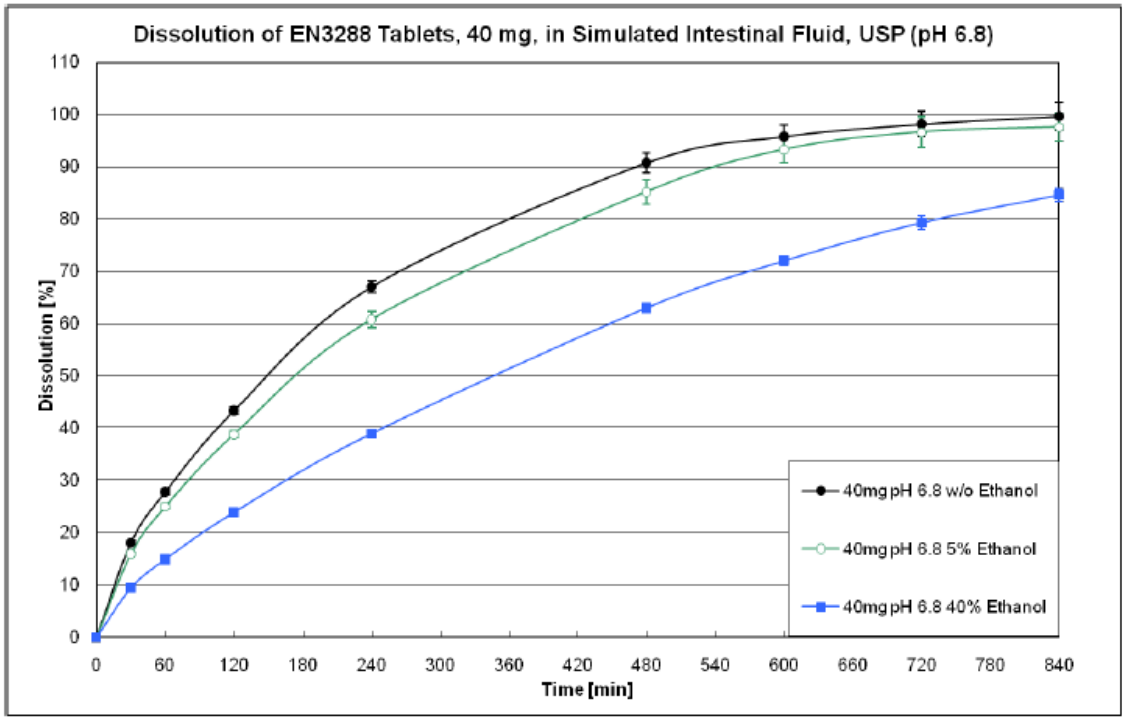


Figure 8. Dissolution Profile of 40 mg Oxymorphone HCl [redacted] (b) (4) Extended- Release Tablet (EN3288) Batch No. HLTX61-1: Ethanolic USP Simulated intestinal Fluid, pH 6.8.

According to the sponsor, dissolution of 40 mg oxymorphone HCl (b) (4) extended-release tablet (EN3288) was unaffected by addition of 5% ethanol to the media. In contrast, dissolution rates of both 40 mg and 5 mg oxymorphone HCl (b) (4) extended-release tablet (EN3288) were slower when 40% ethanol was added to the dissolution media.

Dissolution of Tablets after Tampering

According to the sponsor, numerous in vitro studies were conducted to demonstrate the TR characteristics of this formulation by evaluation of changes in the rate of release of the drug from the drug product if it is misused either intentionally or unintentionally. The sponsor states that the in vitro studies evaluated the extractability of the drug from the formulation under the effects of pH, temperature, alcohol concentration, solvent volume and polarity, at various exposure times in combination with agitation on disruption or destruction of the drug product (b) (4) The destruction of the drug product (b) (4) also included increasing the total surface area of the tablet from intact to being "crushed", (b) (4) or cut up into pieces. The in vitro dissolution results for tablets manipulated to increase surface area are presented (Figure 9) since the tablets administered in the in vivo study were manipulated in a similar manner.

In vitro dissolution testing of intact and tampered oxymorphone HCl (b) (4) extended release tablets, 40 mg (GRT6008 (b) (4), Lots HLT61-1 and CTX73) was performed using USP <711> Apparatus 2, at 50 rpm, in 900 mL of pH 4.5 phosphate buffer at 37°C. Dissolution results were reported over 120 minutes (2 hours).

Figure 9. Dissolution Profiles of Oxymorphone HCl (b) (4) Extended- Release Tablets (40 mg) Intact and Tampered with in Various Ways, Compared to Tampered OPANA ER (USP <711> Apparatus 2 at 50 rpm; 900 mL pH 4.5 Phosphate Buffer at 37°C; GRT6008 (b) (4) = Oxymorphone HCl (b) (4) Extended-Release Tablets, EN3288).

Reviewer's Comments

According to the sponsor, a typical IR profile is observed for OPANA ER tablets, 40 mg after tampering (b) (4) *In comparison, the sponsor states that the ER property of oxymorphone HCl* (b) (4) *ER tablets is still maintained to various degrees, depending on the surface area exposed. However, this conclusion is based on the results of one tablet. In addition, it is shown in Figure 9 that after one hour the % dissolved difference is about* (b) (4)*. Therefore, the TR characteristics of the drug are inconclusive from biopharmaceutics perspective.*

Dissolution Specifications

The following dissolution specifications are proposed by the sponsor:

Acceptance criteria
1 hour (b) (4) 2 hours: (b) (4) 10 hours: NLT (b) (4)

However, the following dissolution specifications are proposed by this reviewer based on the average data from several clinical/stability batches (see Tables 8 to 10; data taken from batch analysis report (3.2.P.5). Figure 10 shows that the dissolution profiles for the 10 mg strengths under stability studies up to 12 months meet the proposed dissolution specifications. The dissolution profiles for the rest of the strengths under stability studies also meet this reviewer's proposed specifications (data not shown in here).

Acceptance criteria
1 hour: (b) (4) 2 hours: (b) (4) 8 hours: NLT (b) (4)

Table 8. Batch Analyses of 5 mg Tablets

Batch No.	**B09051**	**B09052**	**B09053**
Dosage Strength	**5 mg**	**5 mg**	**5 mg**
1 hour	(b) (4)		
2 hours			
10 hours			

Table 9. Batch Analyses of 7.5, 10, 15, 20, and 30 mg Tablets

Dissolution, mean (range)	**B09142**	**B09054**	**B09143**	**B09055**	**B09144**
Dosage Strength	**7.5 mg**	**10 mg**	**15 mg**	**20 mg**	**30 mg**
1 hour	(b) (4)				
2 hours					
10 hours					

Table 10. Batch Analyses of 40 mg Tablets

Batch No.	**B09056**	**B09057**	**B09058**
Dosage Strength	**40 mg**	**40 mg**	**40 mg**
1 hour	(b) (4)		
2 hours			
10 hours			

Figure 10. Dissolution profiles for the 10 mg strength (B09054) of Oxymorphone HCL ER tablets at 0, 3, 6, 9 and 12 months stability testing.

On November 23, 2010 the sponsor was requested to consider the following recommendations:

1. Using your proposed dissolution method, the following dissolution acceptance criteria are recommended for all the strengths of Oxymorphone extended-release tablets:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Acceptance criteria
Oxymorphone HCl	ER Tablet	II (paddle)	50	phosphate buffer, pH 4.5	900, 37 °C ± 0.5 °C	1 hour: (b) (4) 2 hours: (b) (4) (b) (4) 8 hours: NLT (b) (4)

The recommended ranges are based on the mean dissolution target values (b) (4) from the clinical and stability batches for all the strengths. Please revise your dissolution acceptance criteria accordingly.

On December 6, 2010 the sponsor submitted the following response regarding the Nov 23, 2010 request:

"The Sponsor agrees to meet the Reviewers' recommendations as follows: We agree with the acceptance criterion of NLT [redacted] at 8 hours. Further, based on your recommendation of [redacted] variation, the Sponsor has reviewed the available release and stability data for all seven strengths, and the statistical analysis of the data. We are able to meet a [redacted] acceptance criteria range for the 1 hour and 2 hour dissolution timepoints, with an acceptance range that maintains the upper limit of the specification as originally proposed".

A summary of registration batch dissolution stability data at 1 hour and 2 hours is listed in Table 11. The sponsor states that among the seven strengths, there is a range in the mean dissolution percent at 1 hour of [redacted] and at 2 hours of [redacted] In addition, linear regression of the registration lot data shows a slight positive slope over projected shelf life in percent dissolution at 1 hour and 2 hours (Figures 11 and 12).

Based on these factors and an examination of all available data, the Sponsor has [redacted] the lower limit and maintained the upper limit of the acceptance criteria for dissolution at 1 hour and 2 hours. The proposed acceptance criteria (Table 12) meet the recommended [redacted] variation.

Table 11. Summary of All Dissolution Data for Registration Batches (T=0 to 12 months) at 25°C/60%RH.

Strength (mg)	Duration (months)	60 Tablets/Bottle (range[a], mean)	100 Tablets/Bottle (range[a], mean)
5	12	[redacted]	
7.5	6		
10	12		
15	6		
20	12		
30	6		
40	12		

a Range represents individual values

Table 12. Dissolution Acceptance Criteria for Oxymorphone Hydrochloride (b) (4) Extended-release Tablets (All 7 Strengths)

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Acceptance criteria
Oxymorphone HCl	ER Tablet	II (paddle)	50	phosphate buffer, pH 4.5	900, 37 °C ± 0.5 °C	1 hour: (b) (4) 2 hours: (b) (4) 8 hours: NLT (b) (4)

(b) (4)

Figure 11. Linear Regression Analysis of Dissolution at 1 Hour.

Figure 12. Linear Regression Analysis of Dissolution at 2 Hours.

Reviewer's Comments
The sponsor's proposed dissolution ranges are acceptable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANDRA SUAREZ
12/08/2010

PATRICK J MARROUM
12/08/2010

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**201655**	**Brand Name**	**Oxymorphone HCl (b) (4) extended-release tablet (b) (4)**
OCP Division (I, II, III, IV, V)	**DCP2**	**Generic Name**	**Oxymorphone HCl**
Medical Division	**DAAP**	**Drug Class**	**Opioid**
OCP Reviewer	**Srikanth C. Nallani, Ph.D.**	**Indication(s)**	**Moderate to severe pain**
OCP Team Leader	**Suresh Doddapaneni, Ph.D.**	**Dosage Form**	**Tablet**
Pharmacometrics Reviewer		**Dosing Regimen**	**BID**
Date of Submission	**7/7/2010**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**12/15/2010**	**Sponsor**	**Endo Pharmaceuticals**
Medical Division Due Date	**12/15/2010**	**Priority Classification**	**Priority**
PDUFA Due Date	**1/7/2010**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				**BE Based NDA**
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**1**		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	**X**	**6**		**See Below**
Healthy Volunteers-				
single dose:	**X**	**6**		See details below
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				**Biowaiver Request for intermediate strengths (7.5 to 30 mg) submitted based on dissolution and product quality information.**
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**3**		**BE studies evaluating alcohol interaction (#107), physical tampering (crushing, grinding) of product (# 108) and chewing (#109)with IR tablet as reference .**
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:	**X**	**3**		**Fasted and Fed BE studies for 40 mg (#103,#104). Fasting BE study for 5 mg (#105).**
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping	**X**	**1**		**In vitro data is noted for reference only. ONDQA will review this in vitro study.**
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**7**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			Plan involves establishing BE with approved Opana ER. Clinical formulation is also to-be-marketed formulation.
2	Has the applicant provided metabolism and drug-drug interaction information?			X	No new info.
3	Has the sponsor submitted	X			

	bioavailability data satisfying the CFR requirements?				
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	No new info
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	No PGx data submitted
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	BE based NDA and hence no new info.
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might			X	

	affect the pharmacokinetic or pharmacodynamics?				
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	No pediatric submission is included with respect to exclusivity. Agency indicated as follows to sponsor at the Pre-NDA meeting: "Since your product does not represent a new indication, dosage form, active ingredient, dosing regimen or route of administration, PREA is not triggered and no studies in the pediatric population will be required."
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
___Yes_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.
Please identify and list any potential review issues to be forwarded to the Applicant for the 60-day letter.

General notes on submitted clinical pharmacology studies are appended to this memo at the end.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

DSI consult needed

Pivotal BE Study # EN3288-103:

Study Title: An open-label, randomized, single-dose, four-period, replicate, crossover study to determine the bioequivalence of EN3288 (Oxymorphone HCl extended-release (b) (4) formulation) 40 mg compared to Opana® ER (Oxymorphone HCl extended-release) 40 mg in healthy subjects under fasted conditions.

Name and Address of Investigator
Axel Juan, MD SeaView Research, Inc. 3898 NW 7th Street Miami, FL 33126

(b) (4)

Comments to sponsor for Filing letter

In drug liking study EN3288-109, we note that you have recruited subjects experienced with chewing opioid products. We could not ascertain if the subjects were provided specific instructions on how to chew to treatments. Indicate the details of instructions provided to subjects with regard to rate of chewing or duration of chewing and if the individual subjects followed those instructions.

Srikanth C. Nallani, Ph.D.	8/13/10
Reviewing Clinical Pharmacologist	Date
Suresh Doddapaneni, Ph.D.	
Team Leader/Supervisor	Date

NDA 201655

Oxymorphone Extended Release

[redacted] (b) (4)

Drug Sponsor: Endo Pharmaceuticals

Background

- Drug Product (5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg tablets):
  - Reformulation of Opana ER (oxymorphone HCl) tablets
  - [redacted] (b) (4) ER formulation to reduce
    - accidental misuse (i.e., breaking, and/or crushing for patient convenience) and
    - to deter certain methods of intended abuse (i.e., crushing for snorting and/or injection).
- Indication and Usage:
  - Same as Opana ER
  - Relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time
- Other Oxymorphone products
  - Opana IR
  - Opana ER
  - Numorphan (rectal suppositories, discontinued)
- Other approved ER opioids modified to reduce abuse or tampering
  - Oxycontin (Oxycodone ER reformulation, approved in 2009)
  - Embeda (morphine sulfate with naltrexone sequestered, approved in 2009)

Clin Pharm-Related Regulatory History

- PIND meeting: 5/22/2009
- Pre-NDA meeting: 4/6/2010
- *Important notes from PIND meeting:*
  - The Sponsor inquired where the bar is being set for tamper-resistant products, i.e., do tamper resistant formulations need to protect the casual abuser, or are they expected to thwart the kitchen chemist?
  - Response: The three levels of data fall roughly into the following categories:
    - In vitro data
    - PK data
    - Clinical (Drug liking)
  - *BE based NDA approach acceptable… for the fed study, 90% CI of Cmax should be considered as part of the bioequivalence acceptance criteria.*
- *Important notes from Pre-NDA meeting:*
  - We told the sponsor to submit PK study reports for developmental formulations
  - We told the sponsor that since their product does not represent a new indication, dosage form, active ingredient, dosing regimen or route of administration, PREA is not triggered and no studies in the pediatric population will be required.

Clinical Pharmacology Database

- Plan:
  - Establish BE with Opana ER
    - Establish BE at 40 mg and 5 mg strengths –
      - Two PK studies (#103 and #105)
      - One PK study assessed fed condition BE, instead of a food-effect study (#104)
    - CMC submission to bridge intermediate strengths
      - Dissolution similarity
  - Assess safety/bioavailability following:
    - Alcohol coadministration – 1 PK study (#107)
    - Physical manipulation – 2 PK studies (#108, 109)
      - A) Cutting
      - B) Crushing (b) (4)
      - C) Chewing (drug liking study)
  - All of the above studies indicated will be reviewed
    - Test formulation studies will not be reviewed for PK

40 mg BE Studies: Fasted & Fed

Study # 3288-103: Fasted BE study

- Open-label, randomized, 2-sequence, 4-period, 2-treatment, replicate crossover, single 40 mg doses.
- Treatments (n=31) while fasting:
  - 40 mg, EN3288 Tab, single oral dose
  - 40 mg, OPANA ER Tab, single oral dose reference
- All subjects received naltrexone 50 mg (3 oral doses) during each study period to block opiate effects
- Washout: 7 days

Study # 104: Fed BE study

- All above considerations
- Treatments (N=30) administered under standard high-fat meal
- Note: Opana ER has food effect. Cmax increases by 50% with food

5 mg BE Study: Fasted

Study # 3288-105: Fasted BE study

- Open-label, randomized, 2-sequence, 4-period, 2-treatment, replicate crossover, single 40 mg doses.
- Treatments (n=31) while fasting:
  - 5 mg, EN3288 Tab, single oral dose
  - 5 mg, OPANA ER Tab, single oral dose reference
- All subjects received naltrexone 50 mg (3 oral doses) during each study period to block opiate effects
- Washout: 7 days

5 mg and 40 mg tablet strengths appear bioequivalent (not final assessment)

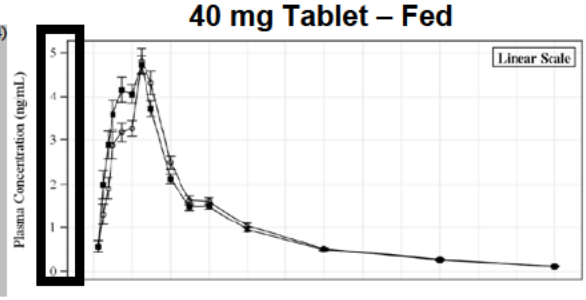
Parameter	Geometric LSM		Ratio	90% CI
	EN3288	OPANA ER		
EN3288-103: Single 40 mg Oral Doses to Fasted Healthy Subjects				
AUC0-t (ng•h/mL)	(b) (4)			
AUC0-inf (ng•h/mL)				
Cmax (ng/mL)				
EN3288-104: Single 40 mg Oral Doses to Healthy Subjects after a Meal				
AUC0-t (ng•h/mL)	47.10	48.43	0.97	0.93-1.02
AUC0-inf (ng•h/mL)	48.98	50.46	0.97	0.93-1.02
Cmax (ng/mL)	5.24	5.55	0.94	0.88-1.02
EN3288-105: Single 5 mg Oral Doses to Fasted Healthy Subjects				
AUC0-t (ng•h/mL)	5.04	4.82	1.05	1.01-1.09
Cmax (ng/mL)	0.352	0.360	0.98	0.93-1.03

5 mg and 40 mg tablet strengths appear bioequivalent (not final assessment)

40 mg Tablet – Fasting

(b) (4)

40 mg Tablet – Fed



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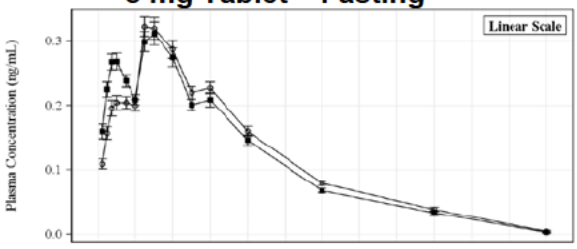
5 mg Tablet – Fasting



Alcohol Interaction Study

- Study # 3288-107: Relative BA when administered with alcohol while fasting
- Open-label, randomized, 6-sequence, 3-period, 3-treatment, crossover, single 40 mg doses
- Treatments (n= 17 for PK) while fasting
  - A: 40 mg, EN3288 Tab + 240 mL 40% ethanol
  - B: 40 mg, EN3288 Tab +240 mL 20% ethanol
  - C: 40 mg, EN3288 Tab + 240 mL water, reference
- Note: Treatment arm of 4% ethanol (beer) not studied
  - Sponsor's Reason: 4% ethanol had no effect on OPANA ER
- Washout: 7 days
- All subjects received naltrexone 50 mg (3 oral doses) during each study period to block opiate effects

Sponsor's notes on alcohol interaction study results

> The results were similar to those observed for oxymorphone when ethanol was co-administered with OPANA ER (section 5.3.2, Table 60). On average, oxymorphone Cmax tended to be increased in a dose dependent manner related to the amount of ethanol consumed and was 1.14-fold and 1.80-fold higher with 20% and 40% ethanol, respectively. Oxymorphone AUC was not increased when EN3288 was co-administered with 20% ethanol and increased 1.15-fold when co-administered with 40% ethanol. In contrast, systemic exposure to 6-OH-oxymorphone reached an asymptote with 240 mL 20% ethanol (AUC0-t increased 1.76-fold and Cmax increased 3.51-fold), and consumption of twice as much ethanol had no additional effect (AUC0-t increased 1.83-fold and Cmax increased 3.79-fold). The greater increase in systemic exposure to 6-OH-oxymorphone than oxymorphone when EN3288 was administered with ethanol indicates a effect upon oxymorphone disposition (metabolism) rather than a physico-chemical effect upon the dosage form. In light of no increase in the in vitro dissolution rates of oxymorphone from EN3288 in the presence of 40% ethanol (section 2.4.3), these increases in systemic exposure to oxymorphone and 6-OH-oxymorphone are considered to have been a result of physiological effects of ethanol upon first pass elimination of oxymorphone and its metabolite rather than physical effects of ethanol upon release of oxymorphone from the tablet.

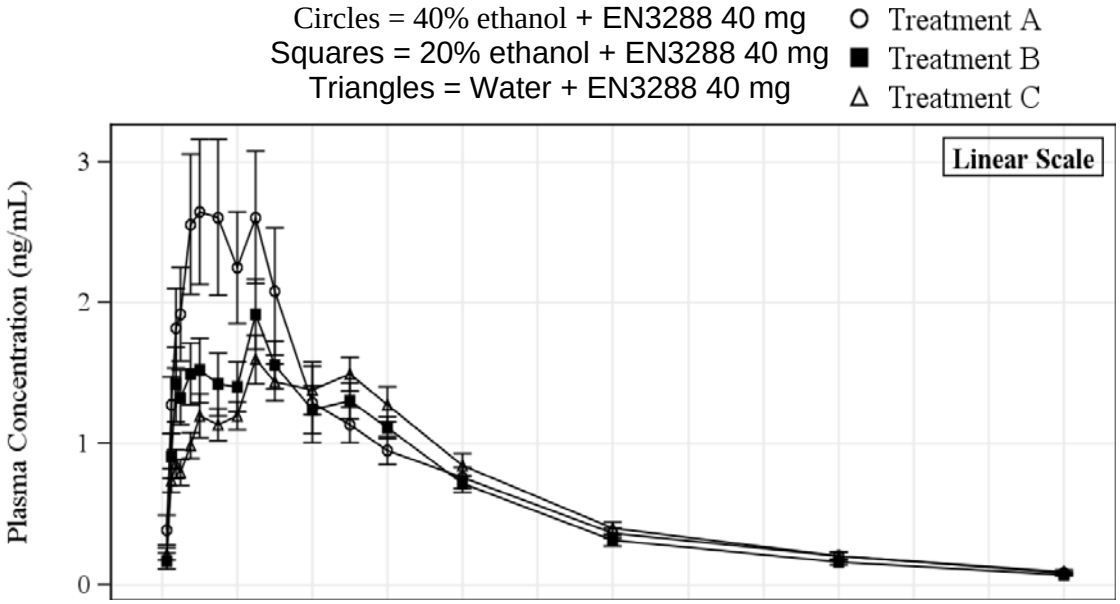
Significant effect noted with 40% Alcohol

Parameter (unit)	Treatment[a]	n[b]	Geometric Least Squares Means[c]	Ratio of Least Squares Means	90% CI of the Ratio (A/C or B/C)	
					Lower	Upper
AUC_{0-t} (ng•h/mL)	A	14	33.1936	1.1539	1.0089	1.3199
	B	17	27.3132	0.9495	0.8378	1.0762
	C	17	28.7652			
AUC_{0-inf} (ng•h/mL)	A	12	34.5161	1.1403	0.9911	1.3120
	B	16	28.6886	0.9478	0.8352	1.0755
	C	17	30.2701			
C_{max} (ng/mL)	A	14	3.3302	1.7959	1.4947	2.1579
	B	17	2.1103	1.1381	0.9591	1.3505
	C	17	1.8543			

Significant effect noted with 40% Alcohol

Lack of in vitro in vivo correlation was also noted

- Opana ER does not dissolve in alcohol in vitro (label)
- Reformulated oxymorphone ER dissolution is decreased in 40% alcohol

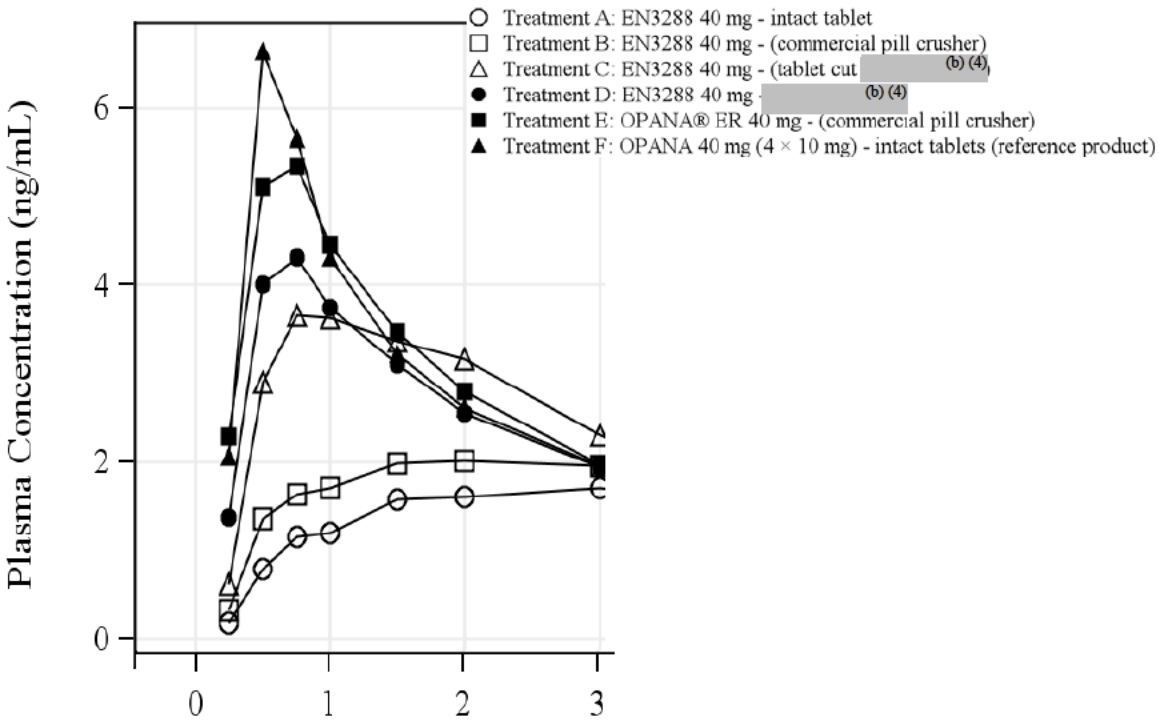


Product Tampering BA/BE study

- Study # 3288-108: Open-label, randomized, 6-sequence, 6-period, 6-treatment, crossover, single 40 mg dose
- Treatments (n=29 in each) while fasting
  - A: 40 mg, EN3288 Tab, Intact
  - B: 40 mg, EN3288 Tab, Pill crusher tampered
  - C: 40 mg, EN3288 Tab, Cut
  - D: 40 mg, EN3288 Tab, (b) (4) tampered
  - E: 40 mg, OPANA ER Tab Pill crusher tampered, comparator
  - F: 40 mg, OPANA IR 4x10 mg tablet intact **reference**
- All subjects received naltrexone 50 mg (3 oral doses) during each study period to block opiate effects
- Washout: 7 days

Cutting and Grinding defeat TR properties (w.r.t. Cmax)

- 4 X 10 mg tablet cohort has higher Cmax compared to 40 mg
  - This group is not appropriate reference
- Pill crusher data appears BE
- Cutting and Grinding defeat TR properties (w.r.t. Cmax)
  - Relative to intact tablet



Cutting and Grinding defeat TR properties (w.r.t. Cmax)

	Comparison	Ratio	Lower 90% CI	Upper 90% CI
Cmax	B/A	0.9798	0.8568	1.1206
	C/A	1.5130	1.3230	1.7303
	D/A	1.5643	1.3679	1.7890
	B/E	0.5144	0.4498	0.5883
AUC	B/A	0.9336	0.8839	0.9862
	C/A	0.9488	0.8982	1.0022
	D/A	0.8694	0.8231	0.9184
	B/E	1.0077	0.9539	1.0644

EN3288 40 mg

A = Intact tablet
B = Pill crusher
C = Cut (b) (4)
D = (b) (4)

Opana ER 40 mg

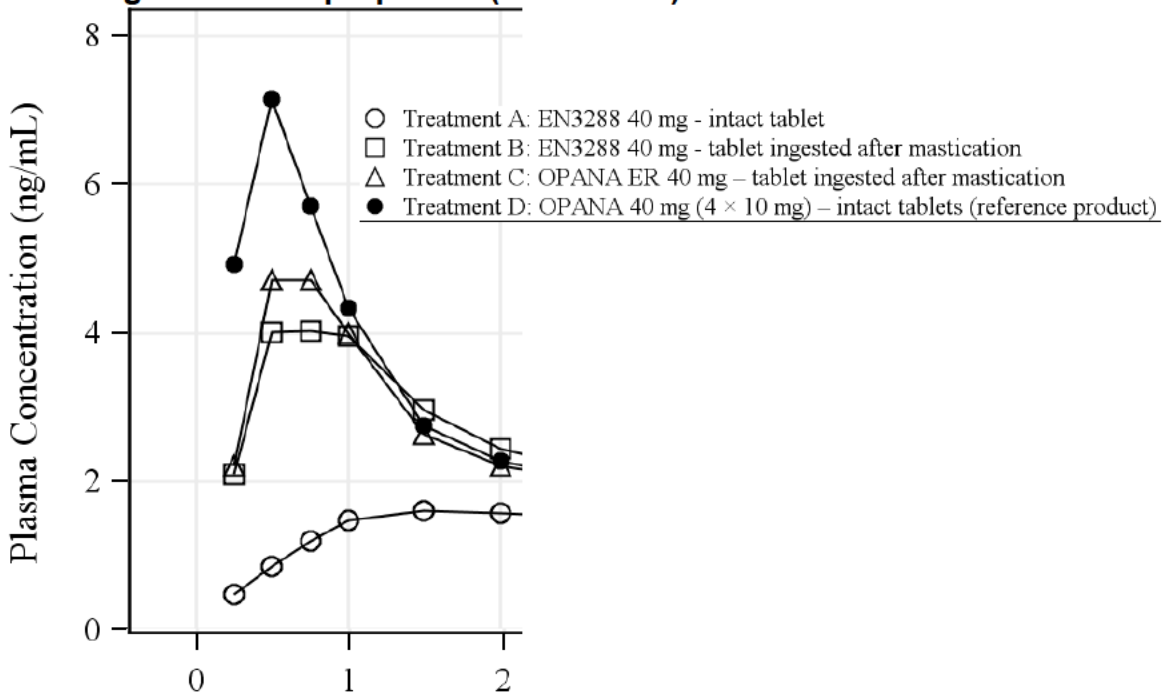
E = Pill crusher;

F = 4×10 mg, Intact tablets (data not shown)

Mastication (chewing) on drug liking, BA/BE

- Study # 3288-109: Double -blind, double-dummy, randomized, 4-sequence, 4-period, 4-treatment, crossover, single 40 mg dose
  - Opioid users experienced in mastication of opioid formulations
  - **Mastication procedure not explained in protocol/report**
- Treatments (n=31 for PK, n=41 for PD)
  - A: 40 mg, EN3288 Tab intact
  - B: 40 mg, EN3288 Tab masticated
  - C: 40 mg, OPANA ER Tab masticated comparator
  - D: 40 mg, OPANA 4x10 mg IR Tab, **intact reference**
- **Note: 4 X 10 mg Opana IR has higher Cmax compared to 40 mg tablet – Results of study # 108.**

Chewing defeats TR properties (w.r.t. Cmax)



Chewing defeats TR properties (w.r.t. Cmax)

	Comparison	Ratio	Lower 90% CI	Upper 90% CI
Cmax	B/A	2.2231	1.9427	2.544
	C/A	2.5136	2.1963	2.8769
	B/C	0.8844	0.7729	1.0121
AUC	B/A	2.223	1.9427	2.544
	C/A	2.5136	2.1963	2.8769
	B/C	0.8844	0.7729	1.0121

A: 40 mg, EN3288 Tab intact

B: 40 mg, EN3288 Tab masticated

C: 40 mg, OPANA ER Tab masticated comparator

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201655	ORIG-1	ENDO PHARMACEUTICALS INC	Oxymorphone HCl (b) (4) extended-release tablet

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SRIKANTH C NALLANI
08/24/2010

SURESH DODDAPANENI
08/24/2010

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 201-655 (000)	**Reviewer:** Sandra Suarez Sharp, Ph.D	
Division:	DAAP		
Sponsor:	ENDO Pharmaceuticals	**Team Leader:** Angelica Dorantes, Ph.D .	
Trade Name:	--	**Supervisor:** Patrick J. Marroum, Ph.D	
Generic Name:	Oxymorphone HCl (b) (4) (b) (4) ER Tablet	**Date Assigned:**	Jul 12, 2010
Indication:	relief of moderate to severe pain	**Date of Review:**	Aug 11, 2010
Formulation/strengths	ER Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	**CDER Stamp Date**	**Date of informal/Formal Consult**	**PDUFA DATE**
July 7, 2010	July 7, 2010	Jul 8, 2010	Dec 2010
Type of Submission:	Original NDA		
Type of Consult:	Dissolution method and specifications/waiver request for lower strenghts---**FILING REVIEW**		

REVIEW SUMMARY:

OPANA® (oxymorphone HCl) immediate release tablet was approved by the Agency under NDA 21-611 on June 22, 2006. The sponsor, ENDO, has developed a (b) (4) extended-release tablet for oxymorphone HCl. This New Drug Application is based on establishing bioequivalence to OPANA® ER (NDA 21-610), which was approved by FDA on June 22, 2006.

The (b) (4) formulation product is intended to be dosed twice-daily and will be available in the same dosage strengths as OPANA ER (5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg). The oxymorphone HCl (b) (4) extended-release tablet is intended to be indicated for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. It is proposed that the dosing and administration will be identical to the reference OPANA ER (oxymorphone HCl) Extended-Release Tablets.

The development program for Oxymorphone ER(b) (4) tablets consisted of the following studies:

- Two bioequivalence studies for the highest (40 mg) and lowest (5 mg) tablet strengths to the marketed product, OPANA ER (EN3288-103 and EN3288-105, respectively).
- Waiver request based on dissolution profile comparisons: The bioequivalence of intermediate tablet strengths was established by the proportional similarity of all tablet strength formulas, and the similarity of dissolution profiles.
- Food effect study: the 40 mg tablet was administered with a high fat meal (EN3288-104).
- In vivo (study EN3288-107) and vitro dose dumping effect of concurrent administration of ethanol on the oxymorphone HCl (b) (4) extended-release tablets.
- The tamper-resistant characteristics of oxymorphone HCl (b) (4) extended-release tablets were explored in in vitro tampering studies and in vivo studies EN3288-108 and EN3288-109.

All batches of oxymorphone HCl (b) (4) ER tablet and other products used in the clinical studies were

manufactured by Pharmaceutical Manufacturing Research Services (PMRS) at Horsham, PA, USA which is the commercial manufacturing site. The oxymorphone HCl (b) (4) ER tablet clinical trial formulation is the same as the to-be-marketed formulation.

The biopharmacetics review will be focused on the dissolution method and specification, the waiver request based on the dissolution profile comparisons supporting the approvability of the intermediate strengths, the in vitro alcohol interaction study, and the in vitro studies supporting the (b) (4) characteristics of the proposed drug product. The BE studies and in vivo alcohol interaction study will be review by OCP.

The dissolution method and specifications being proposed by the sponsor for Oxymorphone ER (b) (4) tablets is based on the in vitro performance of BA/BE batches and stability batches:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Acceptance criteria
Oxymorphone HCl	ER Tablet	II (paddle)	50	phosphate buffer, pH 4.5	900, 37 °C ± 0.5 °C	1 hour: (b) (4) 2 hours: (b) (4) 10 hours: NLT (b) (4)

The sponsor provided complete information in support of the approval of the proposed dissolution method and specification for oxymorphone (b) (4) ER tablets. The acceptability of the dissolution method and specifications, waiver request for intermediate strengths, in vitro alcohol interaction study, and the in vitro study to support the claim of (b) (4) characteristics of the drug will be a review issue.

RECOMMENDATION:
The ONDQA/biopharmaceutics team has reviewed NDA 201-655 (000) for filing purposes. We found this NDA filable from biopharmaceutics perspective. The following comment should be conveyed to the sponsor:

- *Since the lower strengths (5 mg to 15 mg) are not proportionally similar to the 40 mg strength, you are requested to provide dissolution profile comparisons (f2 testing) using the 5 mg strength as a reference.*

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: ADorantes, SPatwardhan, DChristodoulou, CBertha

INTRODUCTION

Oxymorphone hydrochloride (HCl) tablets are currently marketed in the United States (US), under the trade name OPANA® and are available in both an immediate-release (IR) and an extended-release (ER) dosage form. The IR form is available in dosage strengths of 5 mg and 10 mg and the ER form is available in dosage strengths of 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg. In the US, oxymorphone is a Schedule II controlled substance under the US Controlled Substances Act of 1970.

OPANA® ER (oxymorphone HCl) Extended-Release Tablets are indicated for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid therapy for an extended period of time. OPANA ER tablets incorporate the TIMERx®-N controlled-release (b) (4) to provide delivery of oxymorphone over a 12-hour dosing interval and are therefore dosed twice daily.

Endo Pharmaceuticals Inc. and its partner, Grünenthal GmbH (Aachen, Germany), have developed a (b) (4) extended-release formulation of oxymorphone HCl that according to them reduces accidental misuse (ie, breaking and/or crushing for patient convenience) and to deter certain methods of intended abuse (ie, crushing for snorting and/or injection).

Clinical Pharmacology Background

According to the sponsor, the absolute oral bioavailability of oxymorphone is approximately 10%. Steady-state levels are achieved after three days of multiple dose administration. Under both single-dose and steady state conditions, dose proportionality has been established for the 5 mg, 10 mg, 20 mg, and 40 mg tablet strengths for both peak plasma levels (Cmax) and extent of absorption (AUC)[1]. After a single oral dose of OPANA ER 40 mg, oxymorphone Cmax (mean±SD) and AUC (mean±SD) were 2.59±1.65 ng/mL and 37.90±16.20 ng*h/mL, respectively. Mean (±SD) oxymorphone half life ranged from 9.35±2.94 hours to 11.30±10.81 hours in the single dose studies.

Table 1. Mean (±SD) OPANA ER Pharmacokinetic Parameters

Regimen	Dosage	C_{max}	AUC	T ½
		(ng/mL)	(ng·hr/mL)	(hr)
Single Dose	5 mg	0.27±0.13	4.54±2.04	11.30±10.81
	10 mg	0.65±0.29	8.94±4.16	9.83±5.68
	20 mg	1.21±0.77	17.81±7.22	9.89±3.21
	40 mg	2.59±1.65	37.90±16.20	9.35±2.94
Multiple Dose[a]	5 mg	0.70±0.55	5.60±3.87	NA
	10 mg	1.24±0.56	9.77±3.52	NA
	20 mg	2.54±1.35	19.28±8.32	NA
	40 mg	4.47±1.91	36.98±13.53	NA

CHEMISTRY

Formulation

Oxymorphone hydrochloride, a semi-synthetic opioid analgesic, is supplied in 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg (b) (4) extended-release tablet strengths for oral administration. The principal mechanism of drug release of the oxymorphone HCl (b) (4) extended-release tablets is via (b) (4) The composition of the product is given in Table 3.

[1] Drugs at the FDA

Table 2. Composition of 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg Oxymorphone Hydrochloride [redacted] Extended-Release Tablets (%w/w basis)

Ingredient (%w/w)	5 mg	7.5 mg	10 mg	15 mg	20 mg	30 mg	40 mg	Function
Oxymorphone hydrochloride	2.33	3.49	4.65	6.98	9.30	13.95	18.60	Drug Substance
Polyethylene oxide (PEO) [redacted]	[redacted]							
Hypromellose [redacted] (HPMC) [redacted]								
Polyethylene glycol [redacted] (PEG)a								
α-tocopherol [redacted]								
Citric acid, anhydrous								

Table 3. Oxymorphone HCl [redacted] ER Tablet (EN3288), OPANA ER and OPANA IR Batches Used in Clinical Trials Listed by Study Number

Study Number	Product	Strength	Lot Number
EN3288-103	EN3288	40 mg	B09056B1
	OPANA ER	40 mg	401569NV
EN3288-104	EN3288	40 mg	B09056B2
	OPANA ER	40 mg	401569NV
EN3288-105	EN3288	5 mg	B09051B1
	OPANA ER	5 mg	401557NV
EN3288-107	EN3288	40 mg	B09056B3
EN3288-108	EN3288	40 mg	B09056G
	OPANA ER	40 mg	401791NV
	OPANA IR	10 mg	401845NV
EN3288-109	EN3288	40 mg	B09056H
	OPANA ER	40 mg	401787NV
	OPANA IR	10 mg	401855NV

Reviewer's Comments

(b) (4)

the ratio of PEO to total weight of the dosage form is within the limits defined by the SUPAC-MR guidance up to and including Level II (≤ 10%) for the bracket 40 mg, 30 mg, and 15 mg and the bracket for 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg). The sponsor conducted two BE studies (comparing the 40 mg and 5 mg strengths to their respective references) which are sufficient to link all the strengths using dissolution profile comparisons.

Proposed Dissolution Method and Specifications

The following table summarizes the proposed dissolution method and specification for Oxymorphone ER (b) (4) Tablets:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Acceptance criteria
Oxymorphone HCl	ER Tablet	II (paddle)	50	phosphate buffer, pH 4.5	900, 37 °C ± 0.5 °C	1 hour: (b) (4) 2 hours: (b) (4) 10 hours: NLT (b) (4)

It is noted that this dissolution method is the same as that approved for oxymorphone HC ER tablets[2] and it is also approved for Opana ER Tablets.

Mean dissolution results for oxymorphone HCl (b) (4) extended-release tablet batches (EN3288) used in human clinical trials are summarized in Table 4. The mean dissolution profiles are represented in Figure 1 and Figure 2 for the 40 mg and 5 mg tablets, respectively.

Table 4. Mean Dissolution Profiles of Oxymorphone HCl (b) (4) Extended-Release Tablet Batches Used in Clinical Trials

Batch Number	Strength	Mean Percent of Labeled Amount Dissolved by Hour[a]								
		0	0.5	1	2	4	8	10	12	14
B09056 (n=12)	40 mg	0	(b) (4)							
B09051 (n=12)	5 mg	0								

a In-vitro dissolution testing for the EN3288, 5 mg and 40 mg tablets was performed by (b) (4)

[2] FDA dissolution method database online

Figure 1. Dissolution Profiles of EN3288 40 mg Tablets and OPANA ER 40 mg Tablets Used in Bioequivalence Studies EN3288-103 and EN3288-104

Figure 2. Dissolution Profiles of EN3288 5 mg Tablets and OPANA ER 5 mg Tablets Used in Bioequivalence Study EN3288-105.

Dissolution Profiles of All Seven Strengths of Oxymorphone Hydrochloride (b) (4) Extended-Release Tablets

The dissolution profiles of all 7 strengths of oxymorphone hydrochloride (b) (4) extended-release tablets in the pH 4.5 medium (the primary method) are shown in Figure 3. It seems, according to the sponsor, that the f2 values provided in Table 5 demonstrate that all 7 strengths of oxymorphone hydrochloride (b) (4) extended-release tablets exhibit similar dissolution profiles.

Figure 3. Dissolution Profiles of All Seven Strengths of Oxymorphone Hydrochloride (b) (4) (b) (4) Extended-Release Tablets in pH 4.5 Medium (N=12).

Table 5. Similarity Factor (f2) of the Dissolution Profiles of All Seven Strengths of Oxymorphone Hydrochloride (b) (4) ER Tablets in pH 4.5 Medium

Reference Product versus Test Product	Similarity factor (f2)
40 mg (Lot B09056) versus 5 mg (Lot B09051)	68.5
40 mg (Lot B09056) versus 5 mg (Lot B09052)	71.3
40 mg (Lot B09056) versus 5 mg (Lot B09053)	67.8
40 mg (Lot B09056) versus 7.5 mg (Lot B09142)	70.9
40 mg (Lot B09056) versus 10 mg (Lot B09054)	77.3
40 mg (Lot B09056) versus 15 mg (Lot B09143)	91.2
40 mg (Lot B09056) versus 20 mg (Lot B09055)	83.7
40 mg (Lot B09056) versus 30 mg (Lot B09144)	97.6
40 mg (Lot B09056) versus 40 mg (Lot B09057)	90.6
40 mg (Lot B09056) versus 40 mg (Lot B09058)	88.1

Reviewer's Comments

Since the lower strengths (5 mg to 15 mg) are not proportionally similar to the 40 mg strength, the sponsor will be requested to provide similarity factors using the 5 mg strength as a reference.

Dissolution profiles, using the FDA published method but in 3 different media (pH 1.2, 4.5, and 6.8), were generated on oxymorphone hydrochloride (b) (4) extended-release tablets 5 mg (Figure 4), 20 mg (Figure 5), and 40 mg strengths (Figure 6). Similarity factor (f2) values depicted in Table 6 demonstrate that dissolution profiles are similar in pH 1.2, 4.5, and 6.8 media for the 5 mg, 20 mg, and 40 mg strengths.

Figure 4. Dissolution Profiles of 5 mg Oxymorphone Hydrochloride (b) (4) Extended-Release Tablets in pH 1.2, 4.5, and 6.8 Media (N=12)

Figure 5. Dissolution Profiles of 20 mg Oxymorphone Hydrochloride (b) (4) Extended-Release Tablets in pH 1.2, 4.5, and 6.8 Media (N=12).

Figure 6. Dissolution Profiles of 40 mg Oxymorphone Hydrochloride (b) (4) Extended-Release Tablets in pH 1.2, 4.5, and 6.8 Media (N=12).

Table 6. Similarity Factor (f2) of the Dissolution Profiles of Oxymorphone Hydrochloride [redacted] Extended-Release Tablets, 5 mg, 20 mg, and 40 mg, in pH 1.2, 4.5, and 6.8 Media

Reference Product versus Test Product	Similarity factor (f2)
5 mg (Lot HLTU37), pH 4.5 versus pH 1.2	76.8
5 mg (Lot HLTU37), pH 4.5 versus pH 6.8	84.6
20 mg (Lot B09055), pH 4.5 versus pH 1.2	68.2
20 mg (Lot B09055), pH 4.5 versus pH 6.8	89.5
40 mg (Lot HLTX61), pH 4.5 versus pH 1.2	68.8
40 mg (Lot HLTX61), pH 4.5 versus pH 6.8	95.6
40 mg (Lot HLTX61) versus 5 mg (Lot HLTU37) in pH 1.2	66.3
40 mg (Lot HLTX61) versus 20 mg (Lot B09055) in pH 1.2	82.8
40 mg (Lot HLTX61) versus 5 mg (Lot HLTU37) in pH 4.5	60.0
40 mg (Lot HLTX61) versus 20 mg (Lot B09055) in pH 4.5	85.3
40 mg (Lot HLTX61) versus 5 mg (Lot HLTU37) in pH 6.8	66.6
40 mg (Lot HLTX61) versus 20 mg (Lot B09055) in pH 6.8	76.1

Comparison of dissolution profiles between the oxymorphone hydrochloride [redacted] ER tablets and the OPANA ER tablets were conducted using the FDA published dissolution method. According to the sponsor, the similarity factor (f2) values demonstrate that the dissolution profiles of the oxymorphone hydrochloride [redacted] extended-release tablets are similar to those of respective OPANA ER tablets (Table 7).

Table 7. Similarity Factor (f2) of the Dissolution Profiles Between OPANA® ER Tablets and Oxymorphone Hydrochloride [redacted] Extended-Release Tablets [redacted] in pH 4.5 Medium (N=12 unless noted)

Reference Product versus Test Product	Similarity factor (f2)
5 mg, OPANA ER (Lot 63481-907[a], 400816NV[b], 401397 NV[a]) versus [redacted] (Lot B09051)	81.0
5 mg, OPANA ER (Lot 63481-907[a], 400816NV[b], 401397 NV[a]) versus [redacted] (Lot B09052)	78.3
5 mg, OPANA ER (Lot 63481-907[a], 400816NV[b], 401397 NV[a]) versus [redacted] (Lot B09053)	81.7
7.5 mg, OPANA ER (Lot 401033NV[b]) versus [redacted] (Lot B09142)	71.5
10 mg, OPANA ER (Lot 400835NV[b], 400879NV[b]) versus [redacted] (Lot B09054)	73.1
15 mg, OPANA ER (Lot 401155NV[b]) versus [redacted] Lot B09143)	72.9
20 mg, OPANA ER (Lot 400934NV[b], 400943NV[b]) versus [redacted] (Lot B09055)	67.5
30 mg, OPANA ER (Lot 401447NV[b]) versus [redacted] (Lot B09144)	70.2
40 mg, OPANA ER (Lot 400914NV[b], 400935NV[b]) versus [redacted] (Lot B09056)	65.9
40 mg, OPANA ER (Lot 400914NV[b], 400935NV[b]) versus [redacted] (Lot B09057)	66.4
40 mg, OPANA ER (Lot 400914NV[b], 400935NV[b]) versus [redacted] Lot B09058)	64.4

[a] N=3
[b] N=6

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Dissolution of Tablets After Tampering

According to the sponsor, numerous in vitro studies were conducted to demonstrate the TR characteristics of this formulation by evaluation of changes in the rate of release of the drug from the drug product if it is misused either intentionally or unintentionally. The sponsor states that the in vitro studies evaluated the extractability of the drug from the formulation under the effects of pH, temperature, alcohol concentration, solvent volume and polarity, at various exposure times in combination with agitation on disruption or destruction of the drug product (b) (4) The destruction of the drug product (b) (4) also included increasing the total surface area of the tablet from intact to being "crushed", (b) (4) or cut up into pieces. The in vitro dissolution results for tablets manipulated to increase surface area are presented (Figure 8) since the tablets administered in the in vivo study were manipulated in a similar manner.

In vitro dissolution testing of intact and tampered oxymorphone HCl (b) (4) extended release tablets, 40 mg (GRT6008 (b) (4), Lots HLT61-1 and CTX73) was performed using USP <711> Apparatus 2, at 50 rpm, in 900 mL of pH 4.5 phosphate buffer at 37°C. Dissolution results were reported over 120 minutes (2 hours).

Figure 8. Dissolution Profiles of Oxymorphone HCl (b) (4) Extended- Release Tablets (40 mg) Intact and Tampered with in Various Ways, Compared to Tampered OPANA ER (USP <711> Apparatus 2 at 50 rpm; 900 mL pH 4.5 Phosphate Buffer at 37°C; GRT6008 (b) (4) = Oxymorphone HCl (b) (4) Extended-Release Tablets, EN3288)

Reviewer's Comments

According to the sponsor, a typical IR profile is observed for OPANA ER tablets, 40 mg after tampering (b) (4) *In comparison, the sponsor states that the ER property of oxymorphone HCl* (b) (4) *ER tablets is still maintained to various degrees, depending on the surface area exposed. However, this conclusion is based on the results of one tablet. In addition, it is shown in Figure 8 that after one hour the % dissolved difference is about* (b) (4) *Therefore, the TR characteristics of the drug are inconclusive from biopharmaceutics perspective.*

Reviewer's Conclusion

The sponsor provided complete information in support of the approval of the proposed dissolution method and specification. The acceptability of the dissolution method and specifications, waiver request for intermediate strengths, in vitro alcohol interaction study, and the in vitro study to support the (b) (4) characteristics of the drug will be a review issue.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201655	ORIG-1	ENDO PHARMACEUTICALS INC	Oxymorphone HCl (b) (4) extended-release tablet

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/s/

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08/19/2010

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08/20/2010