Study Number: EN3288-108

Title of Study: An Open-Label, Randomized, Single-Dose, Six Period, Crossover Study to Evaluate the Relative Bioavailability of EN3288 40 mg Intact and After Physical Tampering Using Various Methods Compared with OPANA® 10 mg (4 × 10 mg) in Healthy Adult Subjects

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Publications (reference): None

Studied period (years):	**Phase of development:**
Date first subject enrolled: 30 September 2009 Date last subject completed: 07 December 2009	Phase 1

Objectives: The study objective was to evaluate the relative bioavailability (rate and extent of absorption) of EN3288 40 mg, when administered intact and after physical tampering using various methods, compared with OPANA® (oxymorphone HCl) Tablets, 10 mg (4 × 10 mg), under fasted conditions. In addition the study objective was to evaluate the effect of tampering on the relative bioavailability of OPANA® ER (oxymorphone HCl) Extended-Release Tablets, 40 mg.

Methodology: This study was an open-label, randomized, 6-sequence, 6-period, crossover design. Subjects were randomly allocated to a treatment sequence, and received a single dose of EN3288, OPANA ER, or OPANA under fasted conditions in each period. Each treatment consisted of either an intact tablet or a tablet tampered utilizing 1 of 3 methods.The 6 treatment assignments were:

A EN3288 40 mg – intact tablet
B EN3288 40 mg – tablet tampered utlilzing Method 1
C EN3288 40 mg – tablet tampered utilizing Method 2
D EN3288 40 mg – tablet tampered utilizing Method 3
E OPANA ER 40 mg – tablet tampered utilizing Method 1
F OPANA 10 mg (4 × 10 mg) – intact tablets (reference product)

Each treatment period was separated by at least a 7-day washout. In total, each subject received 6 single 40 mg doses of EN3288, OPANA ER, or OPANA.

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.

To protect the subjects from potential opioid-related adverse events (AEs), the opiate antagonist naltrexone (50 mg) was administered approximately 12 and 2 hours prior to administration of EN3288, OPANA ER, and OPANA and again approximately 12 hours later in each treatment period.

End of study evaluations were conducted after the last blood collection (Day 3 of Period 6) or upon early discontinuation from the study.

Number of subjects (planned and analyzed):

Planned	30
Enrolled	35
Randomized	32
Safety Population	35 (analyzed)
Pharmacokinetic Population	29 (analyzed)

Diagnosis and main criteria for inclusion: Subjects included in the study were healthy males or females, of any race, between 18 and 45 years of age, inclusive.

Test product, dose and mode of administration, batch number: EN3288 (oxymorphone HCl extended-release tamper-resistant tablets) 40 mg, for oral administration was manufactured and supplied by Pharmaceutical Manufacturing Research Services, Inc. for Endo Pharmaceuticals Inc.: Lot B09056G. The tablet was administered intact or after tampering with 240 mL water.

Comparator product, dose and mode of administration, batch number: OPANA® ER (oxymorphone HCl) Extended-Release Tablets, 40 mg, for oral administration were manufactured by Novartis Consumer Health, Inc. for Endo Pharmaceuticals Inc. and supplied by Endo Pharmaceuticals Inc.: Lot# 401791NV. The tablet was administered after tampering with 240 mL water.

Reference therapy, dose and mode of administration, batch number: OPANA® (oxymorphone HCl) Tablets, 10 mg, for oral administration were manufactured by Novartis Consumer Health, Inc. for Endo Pharmaceuticals Inc. and supplied by Endo Pharmaceuticals Inc.: Lot 401845NV. A dose of 40 mg (4×10 mg) was administered intact, with 240 mL water.

Other product, dose and mode of administration, batch number: Naltrexone HCl 50 mg for oral administration: Lot 1170N71851 (Mallinckrodt Inc.). Commercially available naltrexone HCl 50 mg oral tablets were obtained by the pharmacy department at the clinical research facility.

Duration of treatment: Each subject was administered a total of 6 single doses of oxymorphone separated by 1 week. Three (3) doses of naltrexone were administered with each dose of EN3288, OPANA ER, and OPANA, between 12 hours prior to and 12 hours after administration. Subjects were confined from the day before until 3 days after each dose of EN3288, OPANA ER, and OPANA. Administration of study drugs occurred over a period of 37 days.

Criteria for evaluation:

Pharmacokinetics: Plasma oxymorphone and 6-hydroxy-oxymorphone (6-OH-oxymorphone) concentrations were determined over a 48-hour interval after each dose administration of EN3288, OPANA ER, and OPANA. From plasma concentrations, peak concentration (C_{max}), corresponding peak time (T_{max}), area under the concentration versus time curve (AUC_{0-t} and AUC_{0-inf}), terminal rate constant (λ_z), terminal half-life ($t_{½}$), the time plasma concentrations were above ½ C_{max} (HVD), mean residence time (MRT), C_{max}/T_{max}, and area under the first moment curve ($AUMC_{0-inf}$) were calculated for each analyte. Non-compartmental methods were used in determination of various pharmacokinetic parameters.

Safety: Safety assessments included monitoring and recording of AEs from check-in to the clinical research facility on Day -1 of Period 1 through 15 days after the last dose of study medication; physical examination and routine clinical laboratory tests (hematology, serum chemistry and urinalysis) performed at screening, on Day -1 of Period 1, and on Day 3 at the end of Period 6 (or early discontinuation); and vital signs measurements conducted at screening, on Day -1 of each period, and at pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours after EN3288, OPANA ER, and OPANA administration during each period.

Statistical methods:

Pharmacokinetic Analyses: Plasma oxymorphone and 6-OH-oxymorphone concentrations were listed by time points and displayed graphically in both linear and semi-logarithmic coordinates. Descriptive statistics (mean, standard deviation, standard error, coefficient of variation, median, 25th and 75th percentiles, minimum and maximum) were computed for pertinent pharmacokinetic parameters for each treatment.

A linear mixed effects model with fixed factors for sequence, period, treatment, and a random factor for subject nested within sequence was performed on the log transformed exposure measurements (AUC_{0-inf}, AUC_{0-t}, and C_{max} of oxymorphone and its active metabolite, 6-OH-oxymorphone) for the pharmacokinetic population. The variable λ_z of each analyte was analyzed similarly to the exposure

measures except without log transformation. Only descriptive statistics were reported for the variables T_{max}, C_t, $t_{½}$, HVD, MRT, C_{max}/T_{max}, and $AUMC_{0\text{-}inf}$. The test treatment was compared to the reference treatment by calculation of the 90% confidence internal (CI) for the ratio (or difference) of the geometric least squares (LS) means.

Safety: All data collected in the study were listed by subject, treatment, date, and time. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 12). The occurrence of treatment-emergent adverse events (TEAEs) was summarized by treatment, system organ class (SOC), and preferred term. TEAEs were also summarized by severity and by treatment-related TEAEs. Descriptive statistics for vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], heart rate, and respiratory rate) were calculated for each treatment by timepoint and for change from baseline. Clinical laboratory test results were reviewed for the presence of any clinically significant result. Physical examination data were reviewed for any treatment-emergent abnormalities.

SUMMARY:

Three (3) subjects who entered the study were administered naltrexone but not randomized to receive EN3288, OPANA ER, or OPANA due to TEAEs (2 subjects) or because the study panel was filled (1 subject). Of 32 subjects randomized, 2 were discontinued due to a treatment-related TEAE (vomiting and hematemesis), and 1 was discontinued for a protocol violation. Therefore 2 additional subjects were randomized as replacement subjects, resulting in a total number of 32 subjects randomized. The mean age of the 35 subjects was 34 years; 20 (57%) were men and 15 (43%) were women; 30 (86%) were White and 5 (14%) were Black or African American.

PHARMACOKINETIC RESULTS:

Based on geometric least squares means from analysis of variance (ANOVA) oxymorphone $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ after each extended-release tablet, whether intact or after tampering, had 90% CIs within 0.80 to 1.25, when compared to $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ after OPANA 4×10 mg. C_{max} was highest after OPANA 10 mg (4×10 mg) > OPANA ER 40 mg tampered with via Method 1 > EN3288 40 mg tampered with via Method 3 > EN3288 40 mg tampered with via Method 2 > EN3288 40 mg tampered with via Method 1 = EN3288 40 mg intact. Higher C_{max} occurred earlier. The ratio C_{max}/T_{max} magnified these differences. The same ranking of tampering effects was observed for the time plasma concentrations greater than ½ C_{max}.

Comparison of tampered EN3288 40 mg to intact EN3288 40 mg showed EN3288 tampered with via Method 1 compared to EN3288 intact had 90% CIs within 0.80 to 1.25 for AUC and C_{max}. C_{max} after EN3288 was tampered with via Method 2 or Method 3 was 51% and 56% higher, respectively, than after intact EN3288.

C_{max} after EN2388 was tampered with via Method 1 was 49% lower than C_{max} after OPANA ER tampered with in the same manner.

6-OH-oxymorphone $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ after each extended-release tablet, whether intact or after tampering, had 90% CIs within 0.80 to 1.25, when compared to $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ after OPANA 10 mg (4×10 mg). C_{max} was highest after OPANA 10 mg (4×10 mg) > OPANA ER 40 mg tampered with via Method 1 > EN3288 40 mg tampered with via Method 3 > EN3288 40 mg tampered with via Method 2 > EN3288 40 mg tampered with via Method 1 > EN3288 40 mg intact. Higher C_{max} occurred earlier.

C_{max} after EN3288 was tampered with via Method 1, Method 2, or Method 3 was 17%, 102%, and 119% higher, respectively, than after intact EN3288.

C_{max} after EN3288 was tampered with via Method 1 was 59% lower than C_{max} after OPANA ER tampered with in the same manner.

Within subject variability was 12.6% for oxymorphone $AUC_{0\text{-}t}$ and 31.6% for oxymorphone C_{max}; 14.0% for 6-OH-oxymorphone $AUC_{0\text{-}t}$ and 30.6% for 6-OH-oxymorphone C_{max}.

Plasma Pharmacokinetics of Oxymorphone after Single Oral Doses of Intact and Tampered EN3288 40mg, Tampered OPANA ER 40 mg, and Intact OPANA 10 mg (4×10 mg) Tablets Administered to Fasted Healthy Subjects – Arithmetic Mean±SD (%CV) (N=29)

Treatment	**A**	**B**	**C**	**D**	**E**	**F**
Drug Product	**EN3288 40 mg**	**EN3288 40 mg**	**EN3288 40 mg**	**EN3288 40 mg**	**OPANA ER 40 mg**	**OPANA 10 mg (4×10 mg)**
Tampering Method	**Intact tablet**	**Method 1**	**Method 2**	**Method 3**	**Method 1**	**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)[a]	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±3.99984 (38.5)	9.1±2.847 (31.2)	4.3±2.411 (56.4)	3.5±2.475 (70.6)	2.6±0.148 (56.9)	1.7±1.443 (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)

[a] Median (range)

Plasma Pharmacokinetics of 6-Hydroxy-Oxymorphone after Single Oral Doses of Intact and Tampered EN3288 40mg, Tampered OPANA ER 40 mg, and Intact OPANA 10 mg (4×10 mg) Tablets Administered to Fasted Healthy Subjects – Arithmetic Mean±SD (%CV) (N=29)

Treatment	A	B	C	D	E	F
Drug Product	EN3288 40 mg	EN3288 40 mg	EN3288 40 mg	EN3288 40 mg	OPANA ER 40 mg	OPANA 10 mg (4×10 mg)
Tampering Method	Intact tablet	Method 1	Method 2	Method 3	Method 1	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)[a]	44.51±22.353 (50.2)	45.34±19.791 (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)[b]	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)[a]	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)[a]	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±5.4312 (52.4)	8.0±3.280 (41.2)	3.0±1.203 (39.9)	2.1±0.995 (47.2)	1.5±0.645 (41.9)	1.4±1.863 (130)
MRT (h)	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)	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)

[a] N=27 for EN3288 40 mg, intact tablet; N=28 for EN3288 40 mg, tampered with via Method 1; N=27 for EN3288 40 mg tampered with via Method 2; N=26 for EN3288 40 mg tampered with via Method 3; N=25 for OPANA ER 40 mg tampered with via Method 1; N=24 for OPANA 10 mg (4×10 mg), intact tablets.

[b] Median (range)

SAFETY RESULTS:

There were no serious adverse events (SAEs) or deaths reported during the study. Four (4; 11%) of 35 subjects were discontinued due to a TEAE. Overall, at least 1 treatment-related TEAE occurred in 6 of 35 (17%) subjects in this study. At least 1 treatment-related TEAE occurred in 2 of 35 (6%) subjects administered naltrexone 50 mg only, in 1 of 29 (3%) subjects after EN3288 40 mg tampered with utilizing Method 2, in 2 of 30 (7%) subjects after EN3288 40 mg tampered with utilizing Method 3, and in 1 of 30 (3%) subjects after OPANA 10 mg (4×10 mg) administered as intact tablets. No treatment-related TEAE occurred in 29 subjects administered EN3288 40 mg as intact tablets or as tablets tampered with utilizing Method 1 or in 30 subjects administered OPANA ER 40 mg tampered with utilizing Method 1.

The TEAEs related to naltrexone 50 mg were nausea, vomiting, and dizziness (1 case each). The TEAEs related to EN3288 40 mg tampered with utilizing Method 2 were nausea and regurgitation (1 case each). TEAEs related to EN3288 40 mg, tampered with utilizing Method 3, were nausea, vomiting, abdominal pain, and dizziness (1 case each). The TEAEs related to OPANA 10 mg (4×10 mg) administered as intact

tablets were nausea, vomiting, abdominal pain, and hematemesis (1 case each). Treatment-related TEAEs resulted in study discontinuation for 4 subjects: dizziness and vomiting after naltrexone 50 mg; vomiting after EN3288 40 mg, tampered with Method 3; and hematemesis after OPANA 10 mg (4×10 mg) administered as intact tablets. All treatment-related TEAEs were mild or moderate in intensity; none was serious, and all resolved. Six (6) treatment-related TEAEs (in 2 subjects) required treatment.

Changes in vital signs were small and there were no clinically significant trends. There was 1 clinically significant change in physical examination findings; 1 subject was discharged with mild epigastric tenderness to deep palpation. There were no clinically significant changes in clinical laboratory test results.

Most treatment-related TEAEs had been identified in labeling of naltrexone, OPANA ER, or OPANA. The exception was hematemesis, which was experienced after administration of OPANA 10 mg (4×10 mg) as intact tablets. There were no new implications from the safety evaluation for the intended uses of extended-release EN3288 tablets.