Study Number: EN3288-109

Title of Study: A Randomized, Single-Dose, Double-Blind, Double-Dummy, Four-Period, Crossover Study to Evaluate the Relative Bioavailability and Subjective Effects of EN3288 40 mg Administered Intact and After Manipulation Compared With OPANA® ER 40 mg Administered After Manipulation and With OPANA® 40 mg (4 × 10 mg) Administered Intact in Healthy Non-Dependent Recreational Oral Prescription Opioid Users Experienced in Manipulation of Extended-Release Opioid Formulations

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Publications (reference): None at the time of report preparation

Studied period (years):	**Phase of development:**
Date first subject enrolled: 15 December 2009 Date last subject completed: 03 March 2010	Phase 1

Objectives:

- To evaluate the relative bioavailability (rate and extent of absorption) of EN3288 40 mg when administered intact and after manipulation compared with OPANA ER 40 mg (administered after manipulation) and OPANA 40 mg (4 × 10 mg) (administered intact) under fasted conditions in healthy non-dependent recreational oral prescription opioid users experienced in manipulation of opioid formulations
- To evaluate the subjective effects of EN3288 40 mg administered after manipulation compared with EN3288 40 mg administered intact, OPANA ER 40 mg administered after manipulation and OPANA 40 mg (4 × 10 mg) administered intact in healthy non-dependent recreational oral prescription opioid users experienced in manipulation of opioid formulations
- To evaluate the tamper-resistant qualities of EN3288 and explore other potential methods of oral abuse of prescription opioids as described by the recreational oral prescription opioid users

Methodology:

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

Within 28 days of the screening visit, the subject attended a randomized, double-blind qualification phase consisting of a 3-night confinement period in which he/she received either OPANA 30 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 OPANA 30 mg (3×10 mg). Each dose administration in the qualification phase was separated by approximately 24 hours. In addition, the tests 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. Based on the assigned treatment sequence, each subject was randomly allocated to receive a single dose of the study drug over the 4 periods. Each dose administration was given under fasted conditions and was separated by at least a 4-day washout period.

The treatments are identified as follows:

A EN3288 40 mg – intact tablet

B EN3288 40 mg – tablet ingested after manipulation

C OPANA ER 40 mg – tablet ingested after manipulation

D OPANA 40 mg (4×10 mg) – intact tablets (reference product)

The treatments were administered in a double-blind, double-dummy manner with the intact tablets (active and/or placebo) administered first followed by the manipulated tablet (EN3288, OPANA ER, or placebo).

Subjects were confined to the clinical research facility beginning on the day before dose administration (Day -1) until the morning of Day 3 (48 hours post-dose). Blood sample collections for pharmacokinetics were obtained through 48 hours post-dose in each study period.

At the end of treatment period 4, an interview session was conducted with the subject individually and in a group setting (approximately 5 subjects per group) to discuss alternate methods of oral abuse for prescription opioids.

End-of-study evaluations were conducted after the interview session on Day 3 of treatment period 4 or upon early discontinuation from the study.

Number of subjects (planned and analyzed):

Planned: Approximately 40 subjects were to be randomized to the treatment phase to ensure that at least 32 complete the study.

Analyzed: In the qualification phase, 51 subjects were exposed to 30 mg doses of OPANA immediate release formulation. Forty-three (43) qualified subjects were randomized into the treatment phase, and 41 subjects completed all 4 treatment periods of the study. The pharmacokinetic population included 31 subjects, and the pharmacodynamic population included 41 subjects.

Diagnosis and main criteria for inclusion:

Healthy male and female subjects (aged 18–55 years, inclusive), who were non-dependent recreational opioid users, were selected for enrollment. Recreational opioid use was defined as at least 5 occasions of non-medical use of opioids (eg, morphine, oxycodone, hydrocodone, hydromorphone, oxymorphone, heroin, codeine, etc.) in the past year and at least 1 use in the 12 weeks before the screening visit. Subjects also had experience with manipulation of prescription opioid products on at least 3 occasions in the past year.

Test product, dose, and mode of administration:

Treatment phase: Single oral doses of EN3288 40 mg (manufactured and supplied by Pharmaceutical Manufacturing Research Services, Inc. for Endo Pharmaceuticals Inc., Lot B09056H), intact tablet and tablet ingested after manipulation; and OPANA® ER Extended-Release Tablets 40 mg (manufactured by Novartis Consumer Health, Inc. for Endo Pharmaceuticals Inc. and supplied by Endo Pharmaceuticals Inc., NDC number 63481-693-70, Lot 401787NV), tablet ingested after manipulation.

Duration of treatment:

Screening/qualification phase: Up to 3 weeks
Treatment phase: Approximately 4 weeks
Total duration (including washouts): Approximately 7 weeks

Reference therapy, dose, and mode of administration:

Qualification phase: Single oral doses of 30 mg OPANA® (3×10 mg, manufactured and supplied by Pharmaceutical Manufacturing Research Services, Inc. for Endo Pharmaceuticals Inc., NDC number 63481-613-70, Lot 401855NV), intact tablet; and matching placebo (manufactured and supplied by the Department of Pharmaceutical Development, Grünenthal GmbH for Endo Pharmaceuticals Inc., Lot SF030408), intact tablet.

Treatment phase: Single oral doses of 40 mg OPANA (4×10 mg), intact tablet; and matching placebo tablets ingested intact for 3 treatment arms and after manipulation for 2 treatment arms.

Criteria for evaluation:

Pharmacokinetics: Blood samples for pharmacokinetic assessment of oxymorphone and its active metabolite 6-hydroxy oxymorphone were obtained. The following parameters were measured for pharmacokinetics: C_{max} (observed peak plasma concentration), T_{max} (observed time to peak plasma concentration), C_t (the last measured plasma concentration), λ_z (terminal rate constant), $t_{½}$ (terminal half-life), AUC_{0-t} (area under the concentration time curve from time zero to last assessment), AUC_{0-inf}, half value duration, mean residence time, and C_{max}/T_{max}. Comparisons of AUC and C_{max} between the manipulated EN3288 and OPANA ER tablets versus OPANA and EN3288 (intact tablet) were made.

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

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

The following summary parameters were calculated for pupillometry: PC_{min} (apparent minimum postdose pupil diameter, PT_{min} (time to reach the apparent minimum diameter), PT25 (time to reach at least 25% reduction in pupil diameter from baseline, $PAOC_{0-2h}$ (the area over the curve to 2 hours, relative to the baseline), $PAOC_{0-8h}$, $PAOC_{0-24h}$.

The comparisons of interest were follows: treatments B vs. A, B vs. C, B vs. D, A vs. D. Other comparisons to be explored were treatments C vs. A and C vs. D.

A linear mixed effects model was fit to each endpoint. The model had treatment, period, and sequence as fixed effects, baseline (predose) measurements as a covariate where applicable, and subject nested in the sequence as a random effect. Least square means and 95% CIs for treatments and treatment differences were computed, along with the statistical significances of all treatment differences.

The E_{max} of VAS Drug Liking was used to validate the pharmacodynamic measures. A statistically significant difference between the OPANA (intact) and EN3288 (intact) treatments on means of E_{max} warranted the validity of pharmacodynamic measures.

Safety: Adverse events (AEs), concomitant medications, vital signs (blood pressure, heart rate, respiratory rate, and oxygen saturation), 12-lead electrocardiogram, clinical laboratory tests (hematology, chemistry, and urinalysis), and physical examinations.

Statistical methods:

Sample size consideration: A sample size of 32 completed subjects was determined to have greater than 80% power to detect a minimal clinically relevant difference in the bipolar Drug Liking VAS of 8 points, using an estimated standard deviation (SD) of ~11.

Assuming an intrasubject coefficient of variation (CV) of 0.22 and an expected mean ratio of 0.95, then 32 subjects would have 90% power to show that the 90% confidence intervals (CIs) of the geometric mean ratio between test and reference for AUC fall with limits of 0.8 to 1.25. Approximately 40 qualified subjects were to be enrolled in the treatment phase in order to ensure that at least 32 subjects

completed all 4 periods of the study. The variation in AUC and C_{max} increased since the drugs in some treatment periods were administered after manipulation. Assuming an intrasubject CV of 35% and an estimated geometric mean ratio of R, the 90% confidence interval for AUC and C_{max} estimates were (R/1.11, R × 1.11) with 32 subjects.

Analysis populations: The safety population consisted of all subjects who received any study treatment. The pharmacokinetic population consisted of all subjects who received all 4 treatments (A-D) and who had no major protocol violations. Data from any subject who experienced emesis at any time during the labeled dosing interval (0-12 hours) within a treatment period were not included in the pharmacokinetic analyses. In addition, any subject whose predose concentration of oxymorphone or 6-OH-oxymorphone was ≥5% of C_{max} within a treatment period was not included in the pharmacokinetic population. The pharmacodynamic population consisted of all subjects who received all 4 treatments (A-D) and who had no major protocol violations, which would exclude the subject from analysis.

Pharmacokinetic analysis: All pharmacokinetic results (concentrations and pharmacokinetic variables) were summarized by treatment (A, B, C, and D) using appropriate descriptive statistics. The details of the λ_z estimation (used number of points, used time interval and R^2) were listed. Log-transformation (natural log) of exposure measurements ($AUC_{0-\infty}$, AUC_{0-t}, and C_{max} of oxymorphone and its active metabolite, 6-OH-oxymorphone) were performed prior to analysis. A linear mixed effects model with fixed factors for sequence, period, treatment, and a random factor for subject nested within sequence were performed on the log-transformed exposure measurements for the pharmacokinetic population. The results (difference of least squares means, CIs for the difference between A and D, B and D, C and D, B and A, C and A, and between B and C) were antilogged after analyses. The geometric mean ratios (A/D, B/D, C/D, B/A, C/A, and B/C) for AUC_{0-inf}, AUC_{0-t}, and C_{max} were calculated by the antilog of the least squares mean difference of the log transformed values. A 90% CI for the ratios was constructed as the antilog of the confidence limits of the least squares mean differences. The parameter λ_z of oxymorphone and its active metabolite, 6-OH-oxymorphone, was analyzed similarly to the exposure measures except without log-transformation. Only descriptive statistics were performed for the variables T_{max}, C_t, $t_{½}$, HVD, MRT, and C_{max}/T_{max}.

Pharmacodynamic analysis: PD variables for each treatment period were derived from the pharmacodynamic assessments. In the calculation, actual sample times (hours, relative to the corresponding drug administration time) were used instead of planned time points. For each treatment period in the treatment phase, the time the subject swallowed the intact tablets was considered time zero. Each PD measures at each time during treatment phase will be summarized by treatment (A, B, C, and D) using appropriate statistics. The derived pharmacodynamic variables were summarized by treatment for qualification phase (if applicable) and treatment phase, respectively. All the assessments and the derived variables data were presented in the individual listings as well. A linear mixed effects model was fit to each endpoint with treatment, period, and sequence as fixed effects, baseline (predose) measurements as a covariate where applicable, and subject nested in the sequence as a random effect. The endpoints were derived pharmacodynamic variables E_{max}, AUE_{0-t} for VAS and ARCI, PC_{min}, $PAOC_{0-t}$ for Pupillometry, the scores of VAS Overall Drug Liking, Taken Drug Again, Manipulation Experience and Price Value Assessment Questionnaires.

Safety analysis: The frequency of AEs was tabulated using the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class (SOC) and preferred terms, and treatment. The maximum intensity and frequency of AEs was summarized by treatment. Serious adverse events (SAEs) and AEs resulting in discontinuation were summarized separately. Vital sign and ECG measurements and clinical laboratory tests were summarized using descriptive statistics or frequency distribution, as appropriate. Individual laboratory test results that were outside the normal range for that test were flagged as high (H) or low (L), as appropriate.

Interview session analysis: The responses from the interview session questions were summarized.

SUMMARY:

In the qualification phase, 51 subjects were exposed to 30 mg doses of OPANA immediate release formulation. Of these, 43 (84%) subjects completed the qualification phase and were randomized to the treatment phase, 6 (12%) could not discriminate between active treatment and placebo, 1 had an SAE (tachycardia) while receiving placebo, and 1 discontinued because of subject decision. A total of 43 subjects were randomized to the treatment phase. Of those, 41 (95%) subjects completed the study; 2 (5%) were discontinued due to 2 AEs of vomiting (for both of these subjects, the first vomiting AE was during treatment with OPANA ER manipulated and the second AE was during treatment with OPANA 4×10 mg intact).

PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS:

The pharmacokinetic results can be summarized as follows:

- Mean oxymorphone concentrations increased most rapidly after treatment D (OPANA 4×10 mg intact) to a maximum of 7.15 ± 3.84 ng/mL at 0.5 hours after dosing; to short plateaus from 0.5 to 1.0 hours of 4.7 ng/mL after treatment C (OPANA ER manipulated) and 4.0 ng/mL after treatment B (EN3288 manipulated). These mean concentrations contrast strongly with the lower rise to a mean value of 1.6 ng/mL at 1.5 hours after treatment A (EN3288 intact). The mean concentrations after treatment A reached maxima of 1.8 ng/mL at 5 hours after the dose. Exponential decay of oxymorphone concentrations was evident from 12 hours after dosing. Results for 6-OH-oxymorphone were similar.
- Despite manipulation of the TRF formulation EN3288 and OPANA ER, both formulations retained some of their extended-release character compared to the immediate-release formulation, as demonstrated by the time course of plasma concentrations versus time. Mean C_{max} was distributed over a 4-fold range and, along with T_{max}, provided a tool for evaluation of the extent of the effects of manipulation upon the character of the 4 formulations. These effects can be ranked where mean C_{max} was greatest and median T_{max} observed was the shortest after the immediate release formulation (intact OPANA 4×10 mg) < OPANA ER 40 mg manipulated < EN3288 40 mg manipulated < EN3288 40 mg intact. These observations are supported by similar observations for 6-OH-oxymorphone plasma pharmacokinetics.
- The effect of manipulation upon the 2 ER formulations was compared. Oxymorphone CIs for AUC_{0-t} and AUC_{0-inf} were within the equivalence limits (0.80, 1.25). The C_{max} ratio was 0.88 for manipulated EN3288 compared with manipulated OPANA ER, and the CIs for oxymorphone were not within the equivalence limits (0.77, 1.01). 6-OH-oxymorphone C_{max} expressed a similar effect, with a C_{max} ratio of 0.90. Oxymorphone median T_{max} was longer after treatment B (EN3288 manipulated; 0.90 hours) compared with treatment C (OPANA ER manipulated; 0.69 hours).

The pharmacodynamic results can be summarized as follows:

- The evaluation of pharmacodynamic assessment was valid as E_{max} for VAS Drug Liking (both 'At This Moment' and 'Overall') was significantly different between the OPANA 4×10 mg intact and EN3288 intact treatments.
- On measures of positive and balance effects, EN3288 manipulated induced numerically lower E_{max} and AUE_{0-2h} than OPANA ER manipulated and OPANA 4×10 mg intact, however, the difference was statistically significant only on some of the "at the moment" assessments (VAS Good Effects, VAS High, and VAS Drug Liking [AUE_{0-2} only]). The difference was not significant on any of the "end of the day" measures.
- On measures of positive and balanced effects, administration of EN3288 intact was associated with significantly lower positive effects than administration of EN3288 manipulated, OPANA ER manipulated, and OPANA 4×10 mg intact.

- On measures of positive and balanced effects, the median time to reach E_{max} was within 2 hours postdose for all treatments.
- On the measure of negative effects, all treatments were associated with similar level of unpleasant responses and no consistent differentiation between treatments was noted.
- Administration of all treatments was associated with decreased pupil diameter, with EN3288 intact inducing the smallest maximum change from pre-dose in comparison to the remaining treatments.
- Manipulating EN3288 was more difficult than manipulating OPANA ER or placebo. The overall manipulation experience for EN3288 and OPANA ER was disliked compared to placebo but there was no significant difference between these treatments.
- On individual interview questionnaires, oxycodone had the highest rate of abuse, with subjects clearly preferring that over morphine, codeine, oxymorphone, or other prescription opioids.
- The majority of subjects abuse oxycodone by swallowing (intact and after manipulation) as major routes methods of abuse, however, the preferred route is swallowing whole.

SAFETY RESULTS:

- There were no deaths and no significant AEs in the treatment phase of the study. There was 1 SAE of moderate tachycardia with placebo during the qualification phase; this subject was discontinued from the study. Two (2) subjects were discontinued in the treatment phase due to treatment-emergent AEs (TEAEs) for vomiting after taking both OPANA ER and OPANA 4×10 mg intact treatments.
- The highest incidence of TEAEs was observed following OPANA 4×10 mg (88%; 38/43), followed by OPANA ER 40 mg manipulated (79%; 34/43), EN3288 40 mg tablet manipulated (62%; 26/42), and EN3288 40 mg intact tablet (37%; 15/41). The incidence of TEAEs following placebo was 12% (6/51).
- The following were the most common TEAEs overall and occurred in generally increasing numbers from treatment A to treatment D: pruritis, nausea, vomiting, headache, somnolence, and dizziness. Reported TEAEs were consistent with expected effects of oxymorphone administration.
- Most subjects had TEAEs that were mild or moderate in intensity. One (1) subject experienced a severe TEAE (pruritis).
- The majority of subjects experienced TEAEs that were considered probably or possibly related to the study drugs.
- Changes in vital signs were small and there were no clinically significant trends. There was 1 clinically meaningful change in physical examination findings; 1 subject was discharged with phlebitis/cellulitis of the right forearm which was treated with vancomycin and linezolid and was resolved. There were no clinically meaningful changes in clinically laboratory test results.