Clinical Trial Results Summary
Study EN3288-902

Study Number: EN3288-902

Title of Study: Assessment of the ease with which experienced controlled-release prescription opioid abusers prepare a tamper-resistant formulation for intranasal use: comparison between OPANA® ER and oxymorphone HCl extended-release tamper-resistant tablets

Principal Investigator: Sandra Comer, PhD

Study center: New York State Psychiatric Institute, Substance Use Research Center, Department of Psychology of Columbia University

Publications (reference): Not applicable

Studied period (years):	**Phase of development:** Not applicable
Date first subject enrolled: 30 Nov 2009 Date last subject completed: 26 Jan 2010	

Objectives: The objective of the study was to assess the resistance of EN3288 to be converted into a form amenable to intranasal administration by experienced intranasal prescription opioid abusers.

Hypotheses were as follows:

1. The resulting particle size distribution of the tampered OPANA ER tablet will be smaller than that of the tampered EN3288 tablet.
2. A greater percentage of current intranasal prescription opioid abusers will be willing to snort the results of tampering with the OPANA ER tablet versus the EN3288 tablet.
3. It will take current intranasal prescription opioid abusers less time to prepare the 40 mg OPANA ER tablet into a "snortable form" than the EN3288 tablet.

Methodology: This was a study consisting of an interview and a laboratory session, both of which occurred on the same day.

Screening/Interview Session

Telephone interviews lasting approximately 10 minutes each were initially conducted to assess a subject's degree of prescription opioid use and to determine if the subject was suitable to come in for further on-site screening. Multiple interviews were conducted during the onsite screening process to enable detection of untruthfulness. Using both closed and open-ended questions, subjects were interviewed to ascertain the various ways in which they have previously tampered with prescription opioids for the purpose of abuse. In addition, drug history, general health, and medical history questionnaires were completed, and a clinical evaluation and mental status examination were performed.

Laboratory Session

After the interview session, subjects were provided with test tablets A (OPANA ER 40 mg) and B (EN3288 40 mg) in a random sequence. Subjects were not told the identity of the test tablets. Tablets were simply referred to as A or B (although the products were identified in the informed consent form). Subjects were instructed to attempt to tamper with the tablet to turn it into a form suitable for intranasal use (snorting). Subjects could use as much time as they needed to tamper with the tablets. Additional attempts of up to 3 attempts per formulation were permitted at the subject's request. Approved tools and solvents specifically requested by the subject were provided. Tablets, tools, and solvents were provided under direct, close observation by 2 staff members. After completing the task, all subjects answered study-related questions concerning their impression of the tablets.

Number of subjects (planned and analyzed): 25 subjects planned and analyzed

Criteria:

To be included into the study, subjects had to

1. Currently use prescription opioids through intranasal administration
2. Be men or women of 21 to 60 years of age
3. Be informed of the nature and risks of the study and provide written informed consent

Subjects were excluded from the study if they

1. Had any history of significant violence
2. Currently had major Axis I psychopathology, other than opioid abuse (eg, mood disorder with functional impairment, schizophrenia), which could interfere with ability to participate in the study
3. Were a significant suicide risk

Investigational product for tampering assessments, strength and, batch number: EN3288 (oxymorphone HCl extended-release tamper-resistant) 40-mg oral tablets, lot number B09056B5, were manufactured and supplied by Pharmaceutical Manufacturing Research Services, Inc. (PMRS) for Endo Pharmaceuticals Inc.

Duration of study: 1 day

Reference product for tampering assessments, strength, and batch number: The comparator product, OPANA ER (oxymorphone HCl extended-release) 40-mg oral tablets, lot number 401786NV, were manufactured by Novartis Consumer Health, Inc. for Endo Pharmaceuticals Inc. and supplied by Endo Pharmaceuticals Inc.

Criteria for evaluation: The criteria were particle size determination based on samples produced by subjects from tampering with the OPANA ER and EN3288 tablets.

Statistical methods: All statistical analyses were performed using SAS. A detailed Statistical Analysis Plan (SAP) was completed and approved before the start of the first subject.

The primary outcome measures (ie, geometric mean diameter and geometric standard deviation) were analyzed with repeated measures analysis of variance (ANOVA). Independent variables included sequence, method, and period. In addition, 3 difference/similarity measures including mean absolute difference, mean square difference, and similarity factor, f_2, were calculated from the data to compare 2 particle size distributions of test and reference drugs.

The secondary outcome measure of the willingness to snort Tablets A and B was analyzed using logistic regression analysis. The independent variables included sequence, method, and period. The secondary endpoint of preparation time was analyzed with repeat measures ANOVA.

Two-sided *p* values were reported for each comparison of interest.

SUMMARY:

A total of 25 subjects were randomized for assessment of the investigational product. All 25 subjects completed the study. No drug was orally ingested or administered by any other route of administration to any of the participating subjects.

<u>Demography</u>

A majority of subjects in the study were black (13 subjects, 52%), male (17 subjects, 68%), and had a history of prior prescription opioid use for pain (16 subjects, 64%). The mean age of subjects was 44.1 years of age; the range was 22 to 59 years.

Tools and Solvents

The most commonly used tools and solvents used by subjects in the study for tablet manipulation were Tool 1 (23 subjects, 92%), Tool 2 (14 subjects, 56%), Tool 3 (9 subjects, 36%), Tool 4 (5 subjects, 20%), and Tool 5 (5 subjects, 20%). The mean number of tools and solvents used by subjects was similar between the OPANA ER and EN3288 groups (2 versus 3, respectively).

Primary Endpoint

Subjects made 25 attempts (25 subjects made 1 attempt) with the OPANA ER tablet and 28 attempts (22 subjects made 1 attempt and 3 subjects made 2 attempts) of manipulation with the EN3288 tablet in order to produce particles for intranasal use. No second attempts were made for the OPANA ER tablet.

More OPANA ER samples were analyzable for particle size distribution compared to the EN3288 tablets (25 analyzable samples from 25 attempts by subjects versus 8 analyzable samples from 28 attempts by subjects, respectively). Out of all the OPANA ER samples, 97.7% (by weight) of particles were smaller than 1.705 mm; out of all EN3288 samples, 8.8% (by weight) of particles were smaller than 1.705 mm.

Particles of each of the 19 (76.0%) OPANA ER samples were all ≤ 1.705 mm (ie, there was no particle > 1.705 mm in each of the 19 samples); for EN3288, there was no sample containing particles that were all ≤ 1.705 mm (ie, every EN3288 sample contains at least 1 particle > 1.705 mm).

For OPANA ER samples, weight analyzable material ranged from 78.79% to 100%. For the EN3288 samples, weight analyzable material ranged from 0.00% to 92.37%.

Of the analyzable samples, the particle size of the EN3288 samples was larger and distributed within a very narrow range compared to the OPANA ER samples.

Secondary Endpoints

Subjects manipulating the EN3288 tablet spent approximately twice as long as subjects manipulating the OPANA ER tablet (mean 5.426 versus 2.537 minutes, respectively; p=0.0005). Subjects indicated that the maximum time they would be willing to spend preparing the OPANA ER and EN3288 tablets would be 6.0 and 9.9 minutes, respectively (p=0.1497).

When subjects were asked if they would snort the particles they made, more subjects in the OPANA ER group answered “Yes” compared to the EN3288 group (24 subjects [96%] versus 3 subjects [11%], respectively). The 1 subject who would not be willing to snort the OPANA ER particles would not do so because the subject did not recognize the tablet.

When asked what they would be willing to pay for Tablet B (EN3288 tablet), all subjects in the study answered they would be willing to pay nothing or less than OPANA ER. For the subjects who were willing to pay less than OPANA ER or nothing, the most common answers were: “more effort required/too frustrating/too time consuming/too hard” (14 subjects, 56%), “cannot snort/make into a powder” (5 subjects, 20%), and “did not get enough powder” (3 subjects, 12%).

A majority of subjects in the study at least sometimes remove unwanted particles before snorting.