Study Number: EN3288-901

Title of Study: Assessment of the ease with which experienced controlled-release prescription opioid abusers prepare a tamper-resistant formulation for intravenous 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: 08 Dec 2009 Date last subject completed: 19 Feb 2010	

Objectives: The objective of the study was to assess the resistance of EN3288 to be converted into a form amenable to intravenous (IV) administration by experienced IV controlled-release (CR) prescription opioid abusers.

Hypotheses were as follows:

1. Current IV prescription opioid abusers will extract a smaller percentage of active drug from the EN3288 tablet than from the OPANA ER tablet.
2. It will take less time to extract drug from the OPANA ER tablet than from the EN3288 tablets.
3. Current IV prescription opioid abusers will not, if given the opportunity, choose to inject remnants (ie, gel, coating, excipients) of their extraction efforts.

Methodology: This was an outpatient 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 onsite 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 and extract active drug from it using the requested tools and/or solvents. 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 by injection
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 B09056B4, 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: Subjects manipulated the OPANA ER and EN3288 tablet for the purpose of drawing up the tablet product into a syringe for analysis. A solution that was able to be drawn into a syringe was considered an analyzable sample to determine % yield of oxymorphone extracted from a tablet.

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.

Drug yield was analyzed as the primary endpoint using a repeated measures analysis of variance (ANOVA). Independent variables included sequence, tablet and session.

Subjects' rating of willingness to inject the extract (Yes/No response) was analyzed using the Logistic regression analysis. The independent variables included sequence, tablet, and period. The actual time spent preparing tablets and the maximum time subjects would be willing to spend preparing tablets were analyzed using repeated measures ANOVA. Independent variables included sequence, tablet, and session.

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>

Of the 25 subjects enrolled in the study, a majority of subjects were white (16 subjects, 64%), male (17 subjects, 68%), and had previously used prescription opioids for pain (14 subjects, 56%). The age of subjects ranged from 23 to 55 years with the mean being 43.7 years. The subjects enrolled in the study were experienced recreational drug users of prescription opioids. The age when subjects first used prescription opioids recreationally ranged from 10 to 53 years; the mean was 28.6 years.

No subject stated that OPANA was their drug of choice. Three (3) subjects answered that they have taken OPANA recreationally. None of the subjects in the study admitted to having tampered with an OPANA tablet before.

Tools and Solvents

The most commonly used tools and solvents used by subjects in the study were Tool 1 (20 subjects, 80%), Solvent 1 (20 subjects, 80%), Tool 2 (18 subjects, 72%), Tool 3 (17 subjects, 68%), Tool 4 (14 subjects, 56%), Tool 5 (14 subjects, 56%), and Tool 6 (12 subjects, 48%). The mean number of tools and solvents used by subjects was similar between the OPANA ER and EN3288 groups (6 each).

Primary Endpoint

There was a total of 56 attempts (28 each formulation group) of tablet manipulation. For each group, 22 subjects made 1 attempt and 3 subjects made 2 attempts (25 first attempts and 3 second attempts). More attempts were analyzable from the OPANA ER group compared to the EN3288 group (7 samples from 28 [25.0%] attempts versus 6 samples from 28 [21.4%] attempts, respectively). The volume, concentration, and percent yield were similar between the 2 treatment groups. The lowest and highest yield for the OPANA ER and EN3288 groups were similar: 0.222% to 4.147% and 0.306% to 6.203%, respectively.

Secondary Endpoints

The actual time spent preparing tablets and the maximum time subjects would be willing to spend preparing tablets for abuse were similar between the OPANA ER and EN3288 groups. The mean was 8.726 vs 7.823 minutes, respectively.

A majority of subjects who worked on the OPANA ER tablet, stopped because “it turned to jelly/gummy substance/poor consistency” (17 subjects, 61%). Most subjects who worked on the EN3288 tablet stopped because “it would not break up/turn into powder/bang up” (11 subjects, 39%). Six (6) of 25 subjects (24%) stated that they had difficulty manipulating or could not manipulate the EN3288 tablet compared to no subjects for the OPANA ER tablet.

For OPANA ER and EN3288 tablets, a similar number of subjects indicated they would be willing to inject the tampered product (7 subjects from 28 attempts [25%] and 5 subjects from 28 attempts [18%], respectively).

Only a few subjects in the study were willing to inject the remnants for either the OPANA ER or EN3288 tablets (5 subjects from 28 attempts and 2 subjects from 28 attempts, respectively).

A majority of subjects (20 of 25 subjects, 80%) would be willing to pay nothing or less than OPANA ER for EN3288. The most common reason subjects gave for why they would be willing to pay nothing or less than OPANA ER for EN3288 was “cannot prepare into acceptable form that can be used IV/cannot break down/would not get high” (12 subjects) and could at least sniff less than Tablet A (OPANA ER; 2 subjects).