CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	201-655
Drug Name:	Oxymorphone HCl-ER, (b) (4)
Study number:	EN3288-109
Applicant:	Endo Pharmaceuticals, Inc.
Date(s):	Filing Mtg: 11/04/10 PDUFA date: 01/07/11 Completion date: 12/06/10
Review Priority:	S
Biometrics Division:	DB VI
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Keywords: Crossover design; Drug abuse potential study; Self-reported endpoint; Multiple endpoints

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1. Executive Summary

Study EN3288-109 in NDA 201655 was a randomized, single-dose, double-blind, double-dummy, four-sequence, four-period, crossover study to evaluate the relative bioavailability and subjective effects of EN 3288 40 mg administered intact and after mastication compared with OPANA® ER 40 mg administered after mastication and with OPANA® 40 mg (4x10mg) administered intact in healthy nondependent recreational oral prescription opioid user experienced in mastication of extended-release opioid formulations.

There were four treatments in the study: EN 3288 40 mg – Intact, EN3288 40 mg - tablet ingested after mastication, OPANA® 40 mg IR (4x10 mg) – intact, and OPANA® ER 40 mg - tablet ingested after mastication. The comparisons of interest in this study were EN40 3288 40 after mastication versus other three treatments on the subjective abuse potential measures: Drug Liking VAS, Any Drug Effects, Good Drug Effects VAS, High VAS, Overall Drug Liking VAS, Take Drug Again VAS, ARCI MBG, Bad Effects VAS, Sick VAS and Difficulty Chewing VAS as well as Overall Chewing Experience VAS. The primary endpoint of interest in this review was Emax which was defined as the maximum response during 8 hours after dosing or the maximum of change from predose response during 8 hours after dosing if predose response is meaningful, for example, High VAS, and ARCI MBG.

A total of 41 subjects completed the study and were included in this reviewer's statistical analysis.

The reviewer's analysis showed that

- EN 3288 40 mg administered after mastication generated significantly larger drug liking, any effects, good effects, high, euphoria effect, and overall drug liking than EN3288 40 mg administered intact. There was no significant difference on Bad Effects VAS and Sick VAS in this comparison. Overall subjects wanted to administer EN 3288 40 mg after mastication more than to administer EN 3288 40 mg intact.

- EN 3288 40 mg administered after mastication produced significantly lower any effects, good effects and high than OPANA® 40 mg IR (4x10 mg) – intact and OPANA® ER 40 mg administered after mastication. However, such reduced effects were not seen for Drug Liking VAS, Overall Drug Liking VAS, Take Drug Again VAS, Bad Effects VAS and Sick VAS in these comparisons, and the least square means of the responses to EN 3288 40 mg administered after mastication on Good Effects VAS and High VAS are still considered large (72.78 ±4.18 and 76.37 ±4.12, respectively) in the unidirectional visual analog scale.

- EN 32888 40 mg was significantly more difficult to chew than OPANA® ER 40 mg. However, there was no significant difference on overall chewing experience between EN 32888 40 mg and OPANA® ER 40 mg administered after mastication. Overall, subjects disliked the chewing experience for both drugs.

2. Review Report on Study EN3288-109

2.1 Overview

2.1.1 Objectives of the study

Primary objectives

The primary objective of this study was to evaluate the relative bioavailability (rate and extent of absorption) of EN3288 40 mg when administered intact and after mastication compared with OPANA ER 40 mg (administered after mastication) and OPANA 40 mg (4×10 mg) (administered intact) under fasted conditions in healthy, nondependent, recreational oral prescription opioid users experienced in mastication of opioid formulations.

Secondary objectives

The secondary objective of this study was to evaluate the subjective effects of EN3288 40 mg administered after mastication compared with EN3288 40 mg administered intact, OPANA ER 40 mg administered after mastication, and OPANA 40 mg (4×10 mg) administered intact in healthy, nondependent, recreational oral prescription opioid users experienced in mastication of opioid formulations. In addition, this study evaluated the tamper-resistant qualities of EN3288, and explored other potential methods of oral abuse of prescription opioids as described by the recreational oral prescription opioid users.

Reviewer's comment: This review report is only for the secondary objectives of the study.

2.1.2 Study design

This was a randomized, double-blind, double-dummy, 4-sequence, 4-period, single-dose, crossover study in healthy, nondependent, recreational oral prescription opioid users experienced in mastication of opioid formulations. Each subject participated in a screening visit, a qualification phase, and a treatment phase consisting of 4 treatment periods. The washout period between two treatments in the treatment phase was at least 72 hours.

There were four treatments in the study. These treatments were

A: EN3288 40 mg – intact
B: EN3288 40 mg – tablet ingested after mastication
C: OPANA ER 40 mg – tablet ingested after mastication
D: OPANA 40 mg IR (4x10 mg) – intact (reference product)

Four treatment sequences ABCD, BCDA, CDAB, DABC, were used in the study.

Reviewer's comments: The Sponsor reported that in the treatment phase, subjects were randomized to 1 to 4 treatment sequences based on a William's design (see page 30 on EN3288-109 report). However, the design stated in Sponsor's Table 5 (on page 30 of the study report) is not a William's design.

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