

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-610

21-611

STATISTICAL REVIEW(S)



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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-610 and 21-611

Drug Name: Oxymorphone Extended Release (ER) and
Oxymorphone Immediate Release (IR)

Indication(s): Treatment of moderate to severe pain in patients requiring opioid
therapy

Applicant: Endo Pharmaceuticals

Date(s): Received 12/22/05; user fee (6 months) 06/22/06

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Biometrics Division: Division of Biometrics II

Statistical Reviewer: Dionne L. Price, Ph.D.

Concurring Reviewers: Thomas J. Permutt, Ph.D.

Medical Division: Division of Anesthesia, Analgesia, and Rheumatology Products

Clinical Team: Christina Fang, M.D,
Sharon Hertz, M.D.

Project Manager: Lisa Basham-Cruz

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Endo Pharmaceuticals has proposed oxymorphone extended release (ER) for “the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid therapy for an extended period of time.” The applicant claims that three studies conducted in the chronic low back pain population demonstrate the efficacy of the drug. In addition, the applicant believes that two studies conducted in the osteoarthritis population support the use of the drug. Based on my collective evaluation of the original NDA submission and the subsequent complete response, I conclude that there is evidence of the analgesic activity of oxymorphone ER in the chronic low back pain population. The studies have demonstrated that the drug alters the pain intensity experienced by patients with chronic low back pain when appropriately titrated. However, the effectiveness has not been demonstrated in two studies conducted in the osteoarthritis population.

The applicant has also proposed oxymorphone immediate release (IR) for “the relief of moderate to severe pain where the use of an opioid is appropriate.” The applicant’s claim of efficacy is primarily based on three studies conducted in patients having undergone orthopedic or abdominal surgery. My collective evaluation of the original NDA submission and subsequent complete response reveals statistical support for the claim. The evidence demonstrates that oxymorphone IR 20 mg provides greater pain relief compared to placebo. In addition, the applicant has demonstrated the efficacy of the drug over repeated dosing (every 4–6 hours) as measured by the time to discontinuation due to all causes.

1.2 Brief Overview of Clinical Studies

Oxymorphone ER and oxymorphone IR tablet formulations were initially introduced to the Division of Anesthesia, Analgesia, and Rheumatology Products via IND 56,919 and IND 58,602, respectively. The products were discussed at an End of Phase II meeting on 11 May 2000 and a pre-NDA meeting on 11 July 2002. During the development process, the division expressed concern regarding the appropriateness of the proposed methodologies for missing data. On 19 December 2002 and 20 December 2002, Endo Pharmaceuticals submitted NDA 21-610 and NDA 21-611 for oxymorphone ER tablets and oxymorphone IR tablets. The submissions investigated the safety and efficacy of oxymorphone (extended and immediate release) for the management of moderate to severe pain where the use of an opioid was appropriate. Primary support for the drugs was derived from six randomized, double-blind, multicenter, and placebo-controlled trials. On 15 October 2003, the division notified Endo of the approvability of the applications. Following several interactions, Endo agreed to conduct additional studies to address the deficiencies outlined in the action letters. Studies EN3202-31, EN3202-32, and EN3203-09 were submitted on 22 December 2005 as part of the complete responses.

Study EN3202-31 was a randomized, double-blind, multicenter, placebo-controlled study conducted in opioid naïve patients with chronic low back pain. Following a titration period, 205

patients were randomized to oxymorphone ER or placebo and followed for 12 weeks. The primary efficacy endpoint was the change in pain intensity from baseline to the end of the study. The endpoint was analyzed via an analysis of covariance model with factors for treatment and center and screening and baseline average pain intensity as covariates. The applicant concluded that the mean increase in pain intensity was significantly higher in patients receiving placebo compared to patients receiving oxymorphone ER. Study EN3202-32 was similar to Study EN3202-31; however, the patient population consisted of opioid-experienced patients.

Study EN3202-09 was a randomized, double-blind, multicenter, placebo-controlled, single- and multiple-dose study conducted in patients undergoing abdominal surgery. Eligible patients were randomized to oxymorphone IR 10 mg, oxymorphone IR 20 mg, oxycodone IR 15 mg, or placebo. Following an initial dose, patients assessed their pain at scheduled time points through 6 hours. Patients who completed the 6-hour single-dose phase or who requested remedication within a 4–6 hour interval entered the multiple-dose phase for the treatment duration of 48 hours. Since the applicant's objective was to assess the efficacy of the drug over repeated dosing, the primary endpoint was the time to discontinuation due to all causes over 48 hours. The applicant concluded that median time to discontinuation was longer in the treatment groups as compared to the placebo group.

1.3 Statistical Issues and Findings

In the original NDA submissions, recurrent statistical concerns were the appropriateness of the last observation carried forward strategy for handling missing data and the appropriateness of the exclusion of patients withdrawing in the first hour from the analyses. The current submissions have adequately addressed both concerns. Specifically, the designs of the two studies evaluating chronic pain minimized the number of patients discontinuing due to adverse events. Moreover, the applicant employed an imputation strategy whereby the screening, baseline, or last observations were carried forward based on the reason for discontinuation. In addition, the analysis populations throughout the current submissions included all randomized patients who received at least one dose of the study treatment.

My evaluation of the data supports the applicant's conclusions of Studies EN3202-31 and EN3202-32. I am also in agreement with the applicant's results in Study EN3203-09. These studies taken collectively with studies in the original NDA submissions provide evidence of the efficacy of oxymorphone ER (when appropriately titrated) and oxymorphone IR 20 mg.

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2. INTRODUCTION

2.1 Overview

Oxymorphone is an opioid analgesic approved in injectable (NDA 11-707) and suppository formulations (NDA 11-738). Oral tablet formulations were approved in 1959 (2 mg and 5 mg) and 1960 (10 mg) under NDA 11-737. The applicant, Endo Laboratories, withdrew the oral tablets in 1979. The proposed extended release and immediate release tablets were introduced to the Division of Anesthesia, Analgesia, and Rheumatology Products via IND 56,919 and IND 58,602, respectively. The products were discussed at an End of Phase II meeting on 11 May 2000 and a pre-NDA meeting on 11 July 2002. Additionally during the development process, Endo Pharmaceuticals submitted study protocols for division comments. The division expressed concern regarding the appropriateness of the proposed methodologies for missing data and multiplicity. On 19 December 2002 and 20 December 2002, the applicant submitted NDA 21-610 for oxymorphone extended release tablets and NDA 21-611 for oxymorphone immediate release tablets. The submissions investigated the safety and efficacy of oxymorphone for the management of moderate to severe pain where the use of an opioid was appropriate. Primary support for oxymorphone extended release was derived from four randomized, double-blind, multicenter, and placebo-controlled trials (EN3202-12, EN3202-15, EN3202-16, and EN3202-25). Support for oxymorphone IR was primarily derived from two randomized, double-blind, multicenter, and placebo-controlled trials (EN3203-04 and EN3203-05).

My completed evaluation of NDA 21-610 suggested that varying evidence of efficacy existed for the proposed use of oxymorphone ER. There was evidence of the analgesic efficacy of the drug in the chronic low back pain population. However, the effectiveness was not convincingly demonstrated in two studies conducted in the osteoarthritis population due to the sensitivity of the results to the procedure for handling missing data. Subsequently, the division notified the applicant of the approvability of oxymorphone ER and the need to address various concerns. The concerns specified in item 1 of the action letter were further discussed at a teleconference on 31 October 2003. Item 1 of the action letter and the applicant's response stated:

Action Letter Item 1

An additional adequate and well- controlled trial(s) must be performed in order to provide the following information:

- a. Efficacy over a twelve- week period in an appropriate chronic pain population in order to provide replication of the results of Study EN3202- 016. This is based on the Agency's assessment of Studies EN3202- 015 and EN3202- 025 which did not find compelling evidence of efficacy, and Study EN3202- 012 which raised safety concerns regarding the use of TRADEMARK in post-operative patients.
- b. Safety data that will address the Agency's concerns regarding TRADEMARK's effects on liver function, WBC count, and QTc interval.

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Applicant's Response:

- 1) The Agency indicates that Studies EN3202- 015 and EN3202- 025 do not provide compelling evidence of efficacy. Could you please provide more details on how the Agency came to this conclusion? More specifically,
 - What analyses did you perform to determine efficacy?
 - What population did you include in your analyses?
 - What criteria did you use to define ' compelling'?
 - Were there any non- statistical issues related to efficacy that caused concern? If so, could you please specify what they were?
- 2) What specific safety concerns were raised in Study EN3202- 012 regarding the use of oxymorphone ER in post- operative patients? In what way did these safety concerns affect the use of this study to support efficacy?
- 3) What specific concerns does the Agency have regarding oxymorphone's effects on liver function tests, WBC count, and QTc interval? Can you be more specific as to what particular data contributed to these concerns?

As a result of communications during the teleconference, the applicant submitted a general correspondence on 08 December 2003 detailing four alternative statistical approaches to the analysis of data for the two studies conducted in the osteoarthritis population. The approaches were discussed during post-action meetings that occurred on 16 March 2004 and 05 May 2004. The division concluded that evidence of analgesic activity existed; however, appropriate dosing recommendations could not be formulated from the submitted data. Thus, Endo agreed to conduct an additional study in the chronic low back pain population

My evaluation of NDA 21-611 found that oxymorphone IR produced greater analgesic efficacy than placebo as measured by the magnitude of pain relief. However, the analgesic efficacy was demonstrated in a single-dose setting only. Moreover, the division found several deficiencies in the application and subsequently notified the applicant that the application was approvable. Specifically, item 1 of the action letter stated,

Action Letter Item 1

An additional adequate and well- controlled trial is necessary in order to provide the following information:

- a. The safe and effective use of TRADEMARK in an appropriate opioid-naïve population that includes data on multiple dosing.
- b. The safe use of TRADEMARK in the postoperative setting or other appropriate clinical setting.
- c. A safe and effective dosing interval.
- d. A complete assessment of the abnormalities in liver function tests, WBC count, and QTc interval that were documented in your completed clinical studies.

Endo agreed to conduct an additional study to provide multiple-dose data. Currently, the applicant has submitted complete responses to the approvable actions for NDA 21-610 and NDA 21-611. Studies designed to address item 1 in both action letters were previously submitted as special protocols. Agreement was reached between the division and the applicant on 10 September 2004 (IR formulation) and 16 November 2004 (ER formulation). Table 1 outlines the numerous post-approval interactions between the division and the applicant.

Table 1: Timeline of Post-Action Interactions

Date	Correspondence
19 December 2002 20 December 2002	NDA 21-610 submitted by Endo Pharmaceuticals NDA 21-611 submitted by Endo Pharmaceuticals
15 October 2003	Approvable letters received by Endo
31 October 2003	Teleconference requested by Endo to receive clarification from the division on clinical and statistical issues. The division agrees to consider alternative approaches to handle missing data based on discussions occurring during the teleconference.
08 December 2003	Four alternative approaches submitted by Endo.
16 March 2004	Post-action meeting. Alternative approaches among topics of discussion. An outcome of the meeting was an agreement by the division to re-evaluate one of the proposed statistical approaches.
17 March 2004	Explanatory document pertaining to alternative statistical approaches submitted by Endo.
05 May 2004	Teleconference to discuss outcome of division's re-evaluation. Endo agrees to conduct another study with guidance from the division.
07 May 2004 – 23 August 2004	SPA and several amendments submitted for IR indication
14 May 2004 – 4 October 2004	SPA and several amendments submitted for ER indication
21 June 2004 – 10 September 2004	Division responses to SPA and amendments for IR formulation
1 July 2004 – 16 November 2004	Division responses to SPA and amendments for ER formulation
22 December 2005	Complete responses to approvable letters submitted

2.2 Data Sources

Studies EN3202-31 and EN3202-32 have been submitted as part of the complete response to the approvable letter for NDA 21-610. Similarly, Study EN3203-009 has been submitted in response to the approvable letter for NDA 21-611. The study reports and data for the electronic submissions were archived in the Food and Drug Administration internal electronic document room under the network path locations \\Cdseub1\n21610\N_000\2005-12-22 and \\Cdseub1\n21611\N_000\2005-12-22. A summary of the studies from the original NDAs and the complete responses is provided in Table 2.

Table 2: Summary of Studies

Study Number Number of centers(n)	Study Design	Treatment Arms and Number of randomized patients at baseline (n)	Primary measure of efficacy
EN3202-012 Multicenter (14)	Double-blind, parallel group, placebo-controlled, multiple-dose study in patients with post-surgical pain	<ul style="list-style-type: none"> • Oxymorphone ER 20 mg (65) • Placebo (61) 	<ul style="list-style-type: none"> • Total pain relief through 8 hours • Integrated patient - controlled analgesia and pain intensity recall score 0-12 hours
EN3202-015 Multicenter (31)	Double-blind, parallel group, placebo and active controlled, multiple-dose study in patients with osteoarthritis of the knee or hip	<ul style="list-style-type: none"> • Oxymorphone ER 20 mg (116) • Oxymorphone ER 40 mg (117) • Oxycodone ER 20 mg (120) • Placebo (119) 	Change in arthritis pain intensity from baseline to Week 3
EN3202-016 Multicenter (26)	Double-blind, parallel group, placebo and active controlled, multiple-dose study in patients with chronic low back pain	<ul style="list-style-type: none"> • Oxymorphone ER (80) • Oxycodone ER (80) • Placebo (75) 	Change in pain intensity from baseline to the end of treatment
EN3202-025 Multicenter (33)	Double-blind, parallel group, placebo, multiple-dose study in patients with moderate to severe pain due to osteoarthritis	<ul style="list-style-type: none"> • Oxymorphone ER 10 mg (95) • Oxymorphone ER 20 mg (92) • Oxymorphone ER 50 mg (91) • Placebo (91) 	Change in arthritis pain intensity from baseline to the final visit
EN3202-031 Multicenter (29)	Double-blind, parallel group, placebo controlled, multiple-dose study in opioid naïve patients with chronic low back pain	<ul style="list-style-type: none"> • Oxymorphone ER (97) • Placebo (95) 	Change in pain intensity from baseline to the end of treatment
EN3202-032 Multicenter (30)	Double-blind, parallel group, placebo controlled, multiple-dose study in opioid experienced patients with chronic low back pain	<ul style="list-style-type: none"> • Oxymorphone ER (69) • Placebo (69) 	Change in pain intensity from baseline to the end of treatment
EN3203-04 Multicenter (29)	Double-blind, parallel group, placebo and active controlled, single-dose study in patients with postsurgical pain following hip and knee replacement	<ul style="list-style-type: none"> • Oxymorphone IR 10 mg (59) • Oxymorphone IR 20 mg (59) • Oxymorphone IR 30 mg (65) • Oxycodone 10 mg (60) • Placebo (57) 	Total pain relief through 8 hours

Study Number Number of centers(n)	Study Design	Treatment Arms and Number of randomized patients at baseline (n)	Primary measure of efficacy
EN3203-05 Multicenter (9)	Double-blind, parallel group, placebo and active controlled, single-dose study in patients with pain following orthopedic surgery	<ul style="list-style-type: none"> • Oxymorphone IR 10 mg (63) • Oxymorphone IR 20 mg (67) • Oxycodone 15 mg (65) • Oxycodone 30 mg (63) • Placebo (66) 	Total pain relief through 8 hours
EN3203-09 Multicenter (21)	Double-blind, parallel group, placebo and active controlled, multiple-dose study in patients with pain following abdominal surgery	<ul style="list-style-type: none"> • Oxymorphone IR 10 mg (81) • Oxymorphone IR 20 mg (81) • Oxycodone 15 mg (83) • Placebo (85) 	Time to discontinuation due to all causes

* Bolded rows denote studies conducted as part of the complete responses.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The main body of my evaluation of efficacy will discuss each study individually.

3.1.1 Study EN3202-31

Study Design and Endpoints

Study EN3202-31 was a randomized, double-blind, placebo-controlled, multicenter study conducted in opioid-naïve patients with chronic low back pain. Initially, 326 eligible patients entered a 28-day open-label titration period and received 5 mg of oxymorphone ER every 12 hours (q12h) for the first two days. Thereafter, patients were allowed to titrate to a stable dose at increments of 5–10 mg q12h every 3–7 days. A patient’s stable or “fixed” dose was defined as the dose at which a patient tolerated the study medication and achieved adequate analgesia. Rescue medication was not allowed during the open-label titration period; therefore, any patient requiring rescue medication was discontinued. Following the titration period, approximately 205 eligible patients entered a 12-week, double-blind treatment period and were randomized to placebo or their fixed dose of oxymorphone ER. During the first four days, patients were allowed 5 mg of oxymorphone IR every 4–6 hours as supplemental rescue medication. Subsequently, rescue medication was restricted to a maximum of 5 mg of oxymorphone IR twice daily. According to the applicant, allowing unrestricted rescue during the first four days served to minimize opioid withdrawal symptoms in patients randomized to placebo. Study participants

maintained a diary and recorded daily average pain intensity. Moreover, average pain over the last 24 hours was assessed at scheduled clinic visits.

The primary measure of efficacy was the change in average pain intensity from baseline to the end of treatment. Baseline was defined as last pain assessment prior to randomization. Pain intensity was measured on a visual analog scale (VAS). Secondary efficacy outcomes included the time to early discontinuation and both patients' and physicians' global assessments of pain medication. The applicant additionally evaluated the percentage of patients experiencing at least a 30% reduction in pain.

Utilizing knowledge gained from EN3202-16, the applicant determined that a sample of size 160 would be required to detect an effect size of 0.45 with 80% power. According to the applicant, "A sufficient number of patients were to be enrolled in the open-label titration period to ensure a total of 160 patients were randomized into the double-blind treatment period of the study." Twenty-nine sites enrolled patients.

Patient Disposition, Demographic and Baseline Characteristics

Descriptive demographics and baseline characteristics were summarized for the randomized patients who received at least one dose of double-blind study medication. The ages of patients ranged from 20 to 85 with a mean age of 50. In the study, 90% of patients were Caucasian, 6% were African-American, and 4% were Hispanic. Fifty-three percent of the population was female. Baseline characteristics included weight, etiology, categorical rating of chronic low back pain, and average pain intensity. A detailed table outlining the composition of the study population with respect to demographic and baseline characteristics is presented in the appendix. Demographic and baseline characteristics were similar across the treatment groups.

Of the 326 patients initially enrolled in the study, 205 patients were eligible for entry into the double-blind treatment period and were randomized. Most discontinuations during the open-label titration period were attributed to adverse events. According to the applicant, "At the end of the open-label titration period, the mean stabilized daily dose was 40 mg, ranging from 10 mg to 140 mg." One-hundred and five patients were randomized to oxymorphone ER. Fifty-three percent of the patients randomized to placebo and thirty-two percent of the patients randomized to oxymorphone ER discontinued from the double-blind treatment portion of the study. Most discontinuations were due to a lack of efficacy. Tables 2 and 3 outline the patient disposition during both phases of the study.

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Table 2: Patient Disposition during the Open-Label Titration Period – Number of patients
 Source: (adapted from Clinical Study Report EN3202-31, Table 3)

Patient Disposition	Oxymorphone ER
Entered Open-Label Titration Period	326
All Treated (Open-Label Titration Period) ^a	325
Not Treated ^b	1
Completed Open-Label Titration Period	205
Discontinued in Open –Label Titration Period ^c	120
Adverse Event	59
AE not due to opioid withdrawal	59
Opioid withdrawal- AE	0
Patient did not meet Titration-Stabilization criteria	23
Withdrew Consent	14
Lost to Follow-up	8
Investigator Opinion	5
Protocol Violation	5
Compliance with study medication is less than 80% for more than 3 days	1
Other	4
Lack of efficacy	4
Applicant request	2
Randomized and Entered Double-Blind Treatment	205

^a All patients who received at least one dose of Open-Label Titration medication.

^b Patient 031-021 was not treated according to the Drug Accountability data.

^c Reasons for discontinuation are sorted in descending order of frequency.

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Table 3: Patient Disposition during the Double-Blind Treatment Period – Number of Patients
Source: (adapted from Clinical Study Report EN3202-31, Table 4)

Patient Disposition	Oxymorphone ER	Placebo
Randomized and Entered Double-Blind Treatment Period	105	100
All Treated (Double-Blind Treatment Period) ^a	105	100
Completed Double-Blind Treatment Period	71	47
Discontinued in Double-Blind Treatment Period ^b	34	53
Lack of Efficacy	12	35
Adverse Event	9	8
AE not due to opioid withdrawal	8	6
Opioid withdrawal- AE	1	2
Withdrew Consent	7	4
Protocol Violation	3	3
Other	3	1
Compliance with study medication is less than 80% for more than 3 days	0	2
Investigator opinion	3	1
Applicant request	0	1
Lost to Follow-up	0	1
Modified Intent-to-Treat ^c	97	95

^a All patients who received at least one dose of the Double-Blind study medication.

^b Reasons for discontinuation are sorted in descending order of frequency.

^c The following patients were excluded from the Modified Intent-to-Treat (MITT) population for not having met all eligibility requirements: 001-006, 004-001, 004-002, 004-004, 004-005, 004-006, 004-007, 004-008, 004-009, 004-010, 009-008, 022-009, 030-003.

Statistical Methodologies

An analysis of covariance (ANCOVA) model with treatment and center as main effects and baseline and screening pain as covariates was employed for the primary efficacy analysis. Each center was weighted in the model according to the number of subjects (utilizing the OM option in SAS). The analyses were performed on the modified intent-to-treat (MITT) population. The MITT population consisted of randomized patients having received at least one dose of study medication. The population excluded thirteen patients that were randomized despite not having met all of the eligibility criteria.

The applicant formulated an imputation strategy that carried forward either the screening, baseline, or last observations based on the reason for discontinuation. The strategy alleviated previous concerns that potentially good scores might be assigned inappropriately. The strategy employed a worse case scenario for patients discontinuing due to adverse events and a best case scenario for patients discontinuing because of opioid withdrawal symptoms in the placebo group. Specifically, the screening pain score (prior to open-label titration period) was carried forward to

the final visit for patients who discontinued because of an adverse event. The baseline pain score (prior to randomization) was carried forward to the final visit for patients receiving placebo and discontinuing due to opioid withdrawal symptoms. The last observation carried forward strategy was used to impute missing data due to all other reasons. In addition, the applicant performed two sensitivity analyses to offset the potential bias caused by the overlap in the diagnosis of opioid withdrawal and other adverse event in the placebo group. In the first analysis, the last observation was carried forward for patients in the placebo group discontinuing due to an adverse event. In the second analysis, the baseline pain score was carried forward for patients in the placebo group discontinuing due to adverse event in the first four weeks.

Several secondary outcomes were additionally analyzed. The times to early discontinuation for lack of efficacy and for all reasons were estimated using Kaplan-Meier survival methodology. The log-rank test was employed to evaluate treatment differences. The changes from baseline to final visit in the patients' and physicians' global assessments were analyzed using rank-sum test procedures. A chi-square test was used to analyze the percentage of patients achieving a 30% reduction in average pain intensity from screening to final visit. The percent reduction at all levels was also calculated and presented graphically.

Results and conclusions

Table 4: Average Pain Intensity (VAS)

Source: (adapted from Clinical Study Report EN3202-31, Table 11)

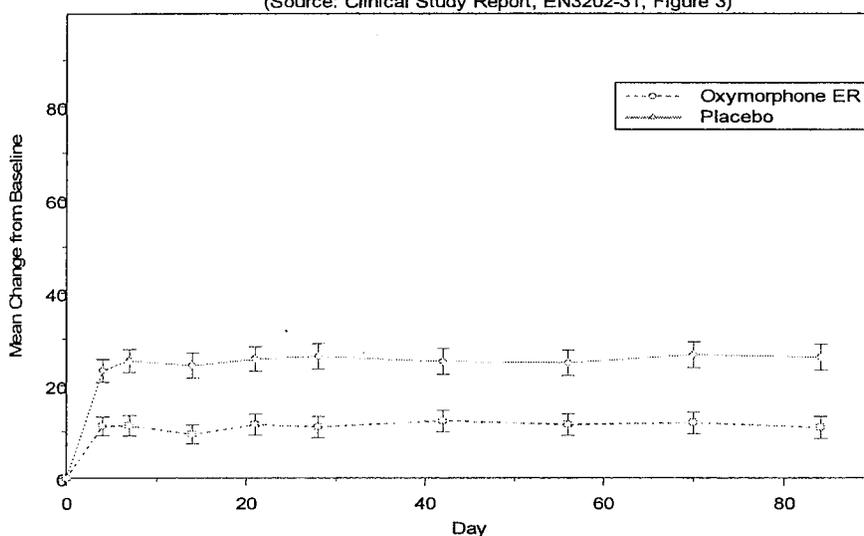
	Oxymorphone ER (N=97)	Placebo (N=95)
Baseline		
Mean (STD)	18.5 (11.2)	19.3 (11.3)
Minimum	1.0	0.0
Median	19.0	19.0
Maximum	48.0	50.0
Final Visit		
Mean (STD)	29.9 (26.2)	46.2 (27.0)
Minimum	0.0	0.0
Median	21.0	50.0
Maximum	96.0	96.0
Change from Baseline to Final Visit		
Mean	11.4 (24.4)	26.9 (27.8)
Minimum	-28.0	-38.0
Median	2.0	29.0
Maximum	76.0	82.0
LSMean ± SE	10.6 ± 2.5	27.7 ± 2.5
Treatment comparison vs. Placebo		
LS Mean Difference	-17.1	
95% CI	(-24.2,-10.0)	
p-value	<0.0001	

^aThe primary analysis used an ANCOVA model with treatment and center as effects, screening and baseline average pain intensity as covariates. The following imputation rules, for missing values, were used: Discontinued due to AE: screening value carried forward; Discontinued due to opioid withdrawal symptoms in placebo group: baseline observation carried forward; Discontinued for all other reasons: last observation carried forward; Patients who discontinued for all other reasons but without post-baseline pain score: screening observation carried forward.

The results of the applicant's primary analysis are shown in Table 4. The applicant concluded that the increase in pain intensity was larger for patients in the placebo group than in the oxymorphone ER group. Positive values across the treatment groups indicated that the pain intensity increased; however in my opinion, the increase taken in consideration with the large variability within treatment groups did not negate the overall conclusions. My evaluation of the data as well as the sensitivity analyses conducted by the applicant supported the applicant's conclusion. To further elucidate the findings, I additionally explored the mean change from baseline in average pain intensity by clinic visit (Figure 1).

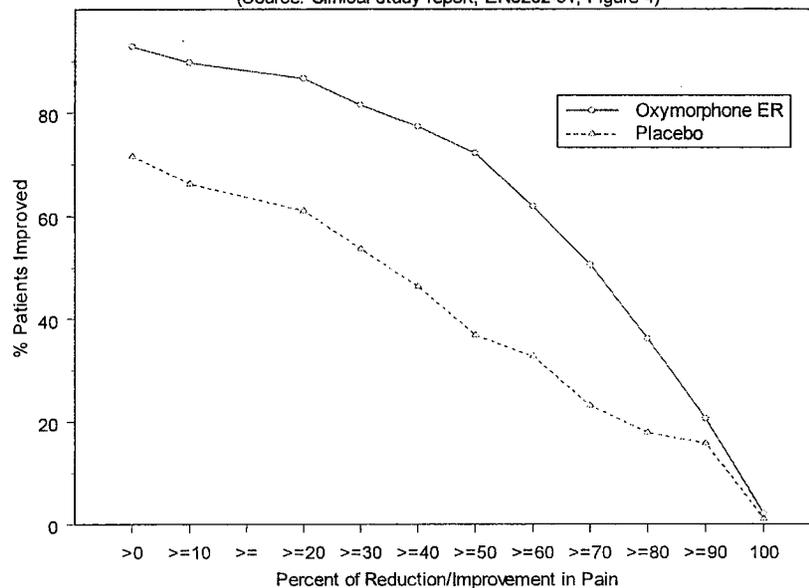
Figure 1: Mean Change from Baseline in Average Pain Intensity

(Source: Clinical Study Report, EN3202-31, Figure 3)



Other variables of interest further supported the analgesic activity of the drug. During the double-blind treatment period, a larger percentage of patients in the oxymorphone ER group rated the treatment as good, very good, or excellent compared to patients in the placebo group. A similar phenomenon occurred among physicians. Results of the global assessments of pain medication are provided in the appendix. An examination of the time to discontinuation for all reasons revealed that a smaller percentage of patients randomized to oxymorphone ER discontinued from the study at all evaluated time points as compared to patients randomized to placebo. In addition, the responder analysis provided evidence that a greater proportion of patients in the oxymorphone ER group achieved at least a 30% reduction in pain intensity than in the placebo group. Evaluations at all levels of pain improvement (≥ 10 , ≥ 20 , ≥ 30 , ≥ 40 , ≥ 50 , etc) yielded similar results (Figure 2).

Figure 2: Percent Reduction in Average Pain Intensity
 (Source: Clinical study report, EN3202-31, Figure 4)



3.1.2 Study EN3202-32

Study Design and Endpoints

Study EN3202-32 was a randomized, double-blind, placebo-controlled, multicenter study conducted in opioid-experienced patients with chronic low back pain. Initially, patients already receiving a stable dose of opioid medication entered an open-label titration period (up to 28 days). Patients received oxymorphone ER, at a dose approximately equivalent to pre-study opioid requirements, every 12 hours. Thereafter, patients were allowed to titrate to a fixed dose of oxymorphone ER. According to the applicant, the following criteria were used to establish a fixed dose.

- Patient achieved adequate pain relief (average pain intensity had to be rated ≤ 40 mm on 100-mm visual analog scale [VAS]) while receiving the same dose of study medication for 3 of 5 consecutive days immediately prior to randomization.
- Patient tolerated the dose for 3 of 5 consecutive days immediately prior to randomization.
- Patient did not require more than 2 doses of oxymorphone IR per day as a supplemental 'rescue' pain medication for 3 of 5 consecutive days immediately prior to randomization.
- Patient reached a minimum oxymorphone ER dose of 10 mg q12h (20 mg daily).

In addition, oxymorphone IR (5 mg orally every 4–6 hours, as needed) was allowed as rescue medication during the open-label titration period. Following the titration period, 143 eligible patients entered a 12-week, double-blind treatment period and were randomized to placebo or their fixed dose of oxymorphone ER. Similar to Study EN3202-31, patients were allowed 5 mg of oxymorphone IR every 4–6 hours as supplemental rescue medication during the first two

days. Subsequently, rescue medication was restricted to a maximum of 5 mg of oxymorphone IR twice daily.

The primary measure of efficacy was the change in average pain intensity from baseline to the end of treatment. Baseline was defined as last pain assessment prior to randomization. Pain intensity was measured on a visual analog scale (VAS). Secondary efficacy outcomes included the time to early discontinuation, and both patients' and physicians' global assessments of pain medication.

Using estimates from EN3202-16, the applicant determined that a sample of size 120 would be required to detect an effect size of 0.60 with 80% power. Thirty sites enrolled patients.

Patient Disposition, Demographic and Baseline Characteristics

Descriptive demographics and baseline characteristics were summarized for the randomized patients who received at least one dose of double-blind study medication. The ages of patients ranged from 21 to 73 with a mean age of 47. In the study, 87% of patients were Caucasian, and 11% were African-American. Fifty-five percent of the population was male; however, more female patients were randomized to oxymorphone ER (57%) compared to placebo (33%). Baseline characteristics included weight, etiology, categorical rating of chronic low back pain, and average pain intensity. A detailed table outlining the composition of the study population with respect to demographic and baseline characteristics is presented in the appendix.

Of the 251 patients initially enrolled in the study, 143 patients were eligible for entry into the double-blind treatment period. Most discontinuations during the open-label titration period were attributed to adverse events. According to the applicant, the stabilized daily dose ranged from 20 mg to 260 mg with a mean of 87 mg. Seventy-four percent of the patients randomized to placebo and thirty percent of the patients randomized to oxymorphone ER discontinued from during the double-blind phase. Similar to study EN3202-31, most discontinuations from the double-blind treatment period were due to a lack of efficacy. Tables 5 and 6 outline the patient disposition during both phases of the study.

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Table 5: Patient Disposition during the Open-Label Titration Period – Number of patients
 Source: (adapted from Clinical Study Report EN3202-32, Table 3)

Patient Disposition	Oxymorphone ER
Entered Open-Label Titration Period	251
All Treated (Open-Label Titration Period) ^a	250
Not Treated ^b	1
Completed Open-Label Titration Period	143
Discontinued in Open –Label Titration Period ^c	107
Adverse Event	47
AE not due to opioid withdrawal	47
Opioid withdrawal- AE	0
Patient did not meet Titration-Stabilization criteria	17
Withdrew Consent	15
Lack of efficacy	10
Lost to Follow-up	6
Investigator Opinion	6
Protocol Violation	4
Compliance with study medication is less than 80% for more than 3 days	1
Other	3
Applicant request	2
Randomized and Entered Double-Blind Treatment	143

^a All patients who received at least one dose of Open-Label Titration medication.

^b Patient 010-003 was not treated according to the drug accountability data.

^c Reasons for discontinuation are sorted in descending order of frequency.

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Table 6: Patient Disposition during the Double-Blind Treatment Period – Number of Patients
Source: (adapted from Clinical Study Report EN3202-32, Table 4)

Patient Disposition	Oxymorphone ER	Placebo
Randomized and Entered Double-Blind Treatment Period	70	73
All Treated (Double-Blind Treatment Period) ^a	70	72
Not treated ^b	0	1
Completed Double-Blind Treatment Period	49	18
Discontinued in Double-Blind Treatment Period ^c	21	54
Lack of Efficacy	8	39
Adverse Event	7	8
Opioid withdrawal- AE	0	5
AE not due to opioid withdrawal	7	3
Investigator opinion	2	2
Withdrew Consent	1	2
Protocol Violation	2	1
Used prohibited medication for more than 3 consecutive days	0	1
Compliance with study medication is less than 80% for more than 3 days	1	0
Other	1	0
Lost to Follow-up	1	1
Applicant request	0	1
All Treated Patients (Double-Blind, Efficacy) ^d	69	69

^a All randomized patients who received at least one dose of the Double-Blind study medication.

^b Patient 023-009 was randomized but not treated according to the drug accountability data.

^c Reasons for discontinuation are sorted in descending order of overall frequency.

^d The following patients were excluded from the All Treated Patients (Double-Blind, Efficacy) population due to not signing the HIPAA consent form: 007-002 (Oxymorphone ER), 022-002 (Placebo), 022-004 (Placebo), 027-002 (Placebo).

Statistical Methodologies

The methodology used in this study of opioid-experienced patients mimicked that from the study conducted in opioid-naïve patients. Specifically, an analysis of covariance model with treatment and center as main effects and screening and baseline pain as covariates was employed for the primary efficacy analysis. Each center was weighted in the model according to the number of subjects (utilizing the OM option in SAS). As in Study EN3202-31, the imputation strategy employed by the applicant carried forward either the screening, baseline, or last observations based on the reason for discontinuation. Analyses were conducted on all randomized patients having received at least one dose of study medication and having signed the HIPAA consent form.

Several secondary outcomes were additionally analyzed. The times to early discontinuation due to lack of efficacy and due to all reasons were estimated using Kaplan-Meier survival methodology. The log-rank test was employed to evaluate treatment differences. The changes from baseline to final visit in the patients' and physicians' global assessments were analyzed using rank-sum test procedures. A chi-square test was used to analyze the percentage of patients achieving a 30% reduction in average pain intensity from screening to final visit. The percent reduction at all levels was also calculated and presented graphically.

Results and conclusions

Table 7: Average Pain Intensity (VAS)
Source: (adapted from Clinical Study Report EN3202-32, Table 12)

Statistics ^a	Oxymorphone ER	Placebo
Baseline ^b		
N	68	69
Mean (STD)	23.9 (12.1)	22.2 (10.8)
Minimum	0.0	0.0
Median	23.5	23.0
Maximum	57.0	43.0
Final Visit		
N	69	69
Mean (STD)	31.3 (23.5)	54.5 (28.4)
Minimum	0.0	1.0
Median	24.0	62.0
Maximum	85.0	97.0
Change from Baseline to Final Visit		
N	68	69
Mean	7.9 (20.6)	32.4 (27.0)
Minimum	-22.0	-23.0
Median	2.0	38.0
Maximum	67.0	88.0
LSMean ± SE	8.7 ± 3.0	31.6 ± 2.9
Treatment comparison vs. Placebo		
LS Mean Difference	-23.0	
95% CI	(-31.3,-14.6)	
p-value	<0.0001	

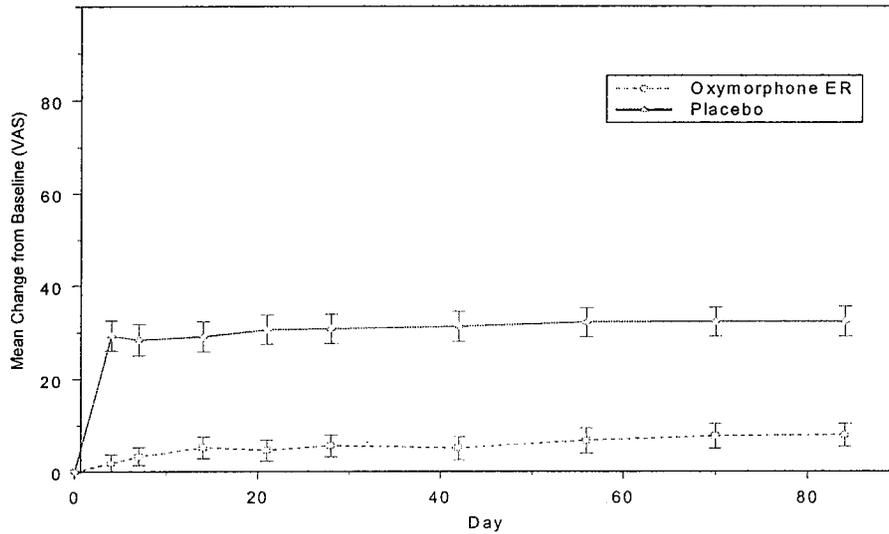
^a The primary analysis used an ANCOVA model with treatment and center as effects, screening and baseline average pain intensity as covariates. The following imputation rules, for missing values, were used: Discontinued due to AE:SOCF; Discontinued due to opioid withdrawal symptoms in placebo group: BOCF; Discontinued for all other reasons: LOCF; Patients who discontinued for all other reasons but without post-baseline pain score:SOCF.

^b Oxymorphone ER patient 009-010 has a missing CRF/Visit Baseline value. BOCF=baseline observation carried forward; LOCF=last observation carried forward; SE= standard error; SOCF= screening observation carried forward

The results of the applicant's primary analysis are shown in Table 7. The applicant concluded that the increase in pain intensity was larger for patients in the placebo group than in the oxymorphone ER group. My evaluation of the data as well as the sensitivity analyses conducted by the applicant supported the conclusion. I additionally explored the mean change from baseline in average pain intensity by clinic visit. A graphical display of the exploration is provided in Figure 3.

Figure 3: Mean Change from Baseline in Average Pain Intensity by Visit

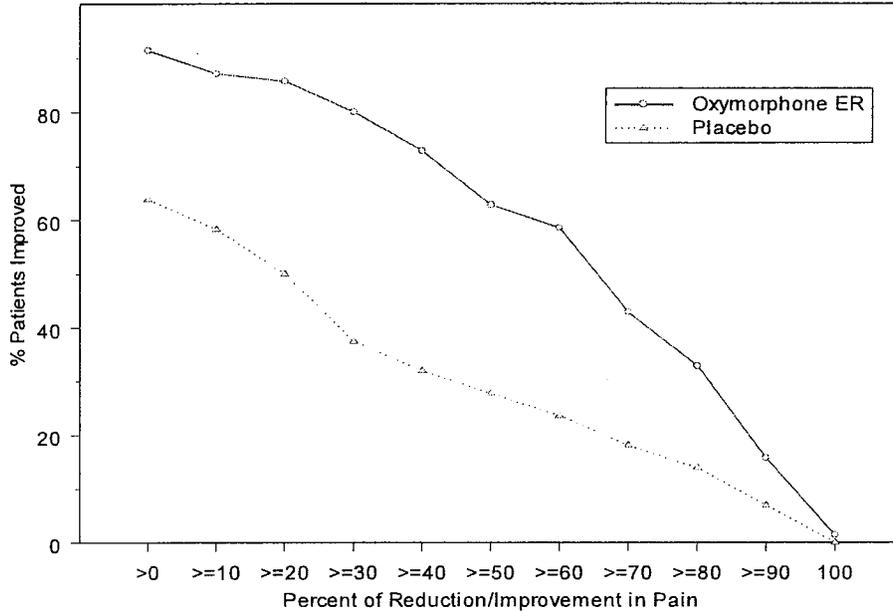
(Source: Clinical Study Report, EN3202-32, Figure 3)



Other variables of interest further supported the analgesic activity of the drug. As in Study EN3202-31, a larger percentage of patients and physicians rated oxymorphone ER as good, very good, or excellent compared to placebo. The results of the global assessments of pain medication are presented in the appendix. An examination of the time to discontinuation due to all reasons revealed that a smaller percentage of patients randomized to oxymorphone ER discontinued from the study at all evaluated time points as compared to patients randomized to placebo. The responder analysis provided evidence that a greater proportion of patients in the oxymorphone ER group achieved at least a 30% reduction in pain intensity than in the placebo group. Evaluations at all levels of pain improvement (≥ 10 , ≥ 20 , ≥ 30 , ≥ 40 , ≥ 50 , etc) yielded similar results as displayed in Figure 4.

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Figure 4: Percent Reduction in Average Pain Intensity
 (Source: Clinical Study Report EN3202-32, Figure 4)



3.1.3 Study EN3203-09

Study Design and Endpoints

Study EN3203-09 was a randomized, double-blind, placebo-controlled, single- and multiple-dose study of the efficacy and safety of oxymorphone IR conducted in opioid naïve patients. Following abdominal surgery, eligible patients received initial pain therapy via intravenous, parenteral analgesia, or intramuscular opioids. Patients who were able to take oral medication discontinued opioids up to 30 hours after surgery. Patients subsequently experiencing moderate to severe pain (as measured on a categorical scale and a 100 mm visual analog scale) were randomized to oxymorphone IR 10 mg, oxymorphone IR 20 mg, oxycodone IR 15 mg, or placebo. Following the initial dose, patients assessed their pain at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, and 6 hours. Patients who completed the 6-hour single-dose phase or who requested remediation within a 4–6 hour interval entered the multiple-dose phase. During the multiple-dose phase, patients were instructed to take their randomized doses every 4–6 hours for a total duration of approximately 48 hours. Throughout the study, any patient requiring remediation prior to 4 hours after receiving a dose was discontinued. Patient diaries were maintained and included assessments of pain relief and pain intensity as well as timing of study medication and rescue medication.

The primary measure of efficacy was the time to discontinuation for all causes during the study duration (0–48 hours). According to the applicant, “The test of efficacy in this study was to determine whether the analgesic efficacy of oxymorphone IR is maintained over repeated dosing. If the analgesic efficacy is not maintained, it is expected that patients discontinue treatment over

time.” Other variables of interest from the multiple-dose phase included the patients’ global evaluation of study medication at the end of the study, the physicians’ global evaluation, the mean current pain intensity, and the mean average pain intensity. The latter two variables were assessed using 100-mm visual analog scales prior to each dose of study medication. Specifically, patients were asked about the “pain right now” and the “average pain intensity”. Secondary variables from the single-dose phase included the sum of pain intensity differences, total pain relief, the time to first perceptible pain relief, and the time to meaningful pain relief.

A sample of size 320 was expected to detect a 20% treatment difference in drop-out rates between oxymorphone IR 10 mg and placebo with at least 80% power. Based on estimates from Study EN3203-04, the sample size was also believed to be sufficient to detect a treatment difference of 2.6 (measured on a categorical scale of 0–5) in total pain relief between the oxymorphone IR 10 mg and placebo treatments with at least 85% power, assuming a standard deviation of 5.22. The study was conducted at 21 centers.

Patient Disposition, Demographic and Baseline Characteristics

In the study, 99% of the study participants were female. Sixty-four percent of the patients were Caucasian, and 21% were African American. The ages of patients ranged from 18 to 83 with a mean age of 43. Baseline characteristics included pain intensity, incision type, and length of incision. Characteristics were similar across treatment groups. Detailed tables outlining the composition of the samples with respect to the demographic and baseline characteristics are presented in the appendix.

Only one of the 331 randomized patients was not included in the analysis population. The patient was excluded because of a failure to provide consent as outlined by the protocol. One-hundred and ninety-five patients completed the single-dose phase of the study, and 112 completed the multiple-dose phase. In the single-dose phase, the percentages of individuals discontinuing were 42%, 35%, 41%, and 47% in the oxymorphone IR 10 mg, oxymorphone IR 20 mg, oxycodone IR 10 mg, and placebo groups, respectively. Most discontinuations were due to lack of efficacy. Similarly in the multiple-dose phase, the percentages of individuals discontinuing in the oxymorphone IR 10 mg, oxymorphone IR 20 mg, oxycodone IR 10 mg, and placebo groups were 62%, 61%, 59%, and 82%, respectively. Most discontinuations were again attributed to a lack of efficacy. An overall summary of patient disposition is provided in Table 8.

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Table 8: Patient Disposition – All Randomized Patients
(Source: adapted from Clinical Study Report EN3203-09, Table 2)

	Oxymorphone IR 10mg (N=82)	Oxymorphone IR 20 mg (N=81)	Oxycodone IR 15 mg (N=83)	Placebo (N=85)	Total (N=331)
Randomized	82	81	83	85	331
All Treated Patients	82	81	83	85	331
Multiple-dose Period (0-48 Hours)					
Completed Multiple-Dose Period	31	32	34	15	112
Discontinued	51	49	49	70	219
Adverse Event	7	14	11	11	43
Withdrew Consent	9	7	4	5	25
Lack of Efficacy	34	25	33	53	145
Protocol Violation	1	1	0	1	3
Investigator Withdrew Patient	0	1	1	0	1
Other	0	1	1	0	2
Single-Dose Period (0-6 hours)					
Completed Single-Dose Period	48	53	49	45	195
Discontinued	34	28	34	40	136
Adverse Event	5	4	4	4	17
Withdrew Consent	0	1	3	1	5
Lack of Efficacy	29	21	27	35	112
Investigator Withdrew Patient	0	1	0	0	1
Other	0	1	0	0	1
Intent-to-Treat Patients	81	81	83	85	330

Statistical Methodologies

According to the applicant, the time to discontinuation was calculated using the following scheme:

For patients who discontinued due to an adverse event: first the later of the two following time points (last pain assessment, onset of first adverse event causing discontinuation) was chosen, then the earlier of that chosen time point and the termination time was used. For patients who discontinued due to lack of efficacy, the rescue time was used. For patients who discontinued due to all other causes, the earlier of the two time points (last pain assessment, termination time) was used. After the time of discontinuation was determined, the first dose time was subtracted from it to obtain the duration of time to discontinuation. For patients who completed the study, the duration was calculated as the shorter of the following two times (termination time minus first dose time, 48) and censored.

The time to discontinuation for all causes was estimated using the Kaplan-Meier method. Treatment differences were assessed using the log-rank test. Multiplicity concerns resulting from several pairwise comparisons were addressed via a step-down procedure whereby the difference

between oxymorphone IR 20 mg and placebo groups was first explored. If evidence of a difference was found, the oxymorphone IR 10 mg and placebo groups were compared.

The mean average pain and mean current pain during the multiple-dose phase were assessed via an analysis of covariance model with treatment and center as effects and baseline pain intensity as a covariate. For clarification, patients were asked to assess both their current pain and their average pain. Available pain scores were averaged for patients that discontinued early. A time-weighted average of pain scores from the single-dose phase was used for patients who discontinued prior to 6 hours. In addition, stratified rank-sum tests were employed to analyze the global evaluations of study medication. Analysis methods for outcomes from the single-dose phase mimicked methods from the multiple-dose phase. The baseline observation carried forward (BOCF) method was used to impute data for patients discontinuing due to adverse events, and the last observation carried forward (LOCF) method was used to impute data for patients discontinuing to all other reasons and for patients who received a second dose of medication prior to completion of the 6-hour assessments.

Results and Conclusions

Based on the primary analysis, the applicant concluded that patients receiving oxymorphone IR experienced a significantly longer median time to discontinuation as compared to patients receiving placebo. The applicant stated that the longer time to discontinuation among the treatment groups provided evidence of analgesia over repeated dosing. Specifically, the median times to discontinuation were 17 hours and 55 minutes, 20 hours and 15 minutes, and 4 hours and 50 minutes for patients in the oxymorphone IR 10 mg, oxymorphone IR 20 mg, and placebo groups, respectively. In addition, the oxycodone IR 15 mg group also experienced a significantly longer median time (24 hours, 5 minutes) when compared to the placebo group. Complete results are shown in Table 9. The upper bounds of some confidence intervals could not be estimated. My evaluation of the data with respect to the time to discontinuation yielded similar results to those provided by the applicant.

Table 9: Time (hours:minutes) to discontinuation due to all causes, multiple-dose period
Source: Clinical study report EN3203-009, Table 6

Statistics	Oxymorphone IR 10 mg	Oxymorphone IR 20 mg	Oxycodone IR 15 mg	Placebo
Descriptive				
N	81	81	83	85
Minimum	0:20	0:05	0:30	0:15
Maximum	48:00	48:00	48:00	48:00
Median (95% CI)*	17:55(4:30,32:35)	20:15(6:00,)	24:05(5:00,)	4:50(3:22,7:30)

* All pairwise comparisons between active treatments and placebo were significant ($p \leq 0.01$).

Moreover, the applicant concluded that the mean “current pain intensity” and the mean “average pain intensity” during the multiple-dose phase were both lower for treated patients compared to placebo patients. Averages were computed based on available data only, and the calculations of the measures did not employ an imputation strategy. Since many patients discontinued and the number of doses received varied among patients (see Table 10), the meaningfulness of the measures was not readily apparent to me. However, the medical reviewer expressed interest in

the measures as mechanisms to assess the pain trough within the population. For completeness, the applicant's findings are provided in the appendix. The results from the global evaluations are also provided in the appendix and consistently support the efficacy of oxymorphone IR 20 mg.

Table 10: Frequency of Study Medication Doses
(Source: adapted from Clinical study report EN3203-009, Table 18)

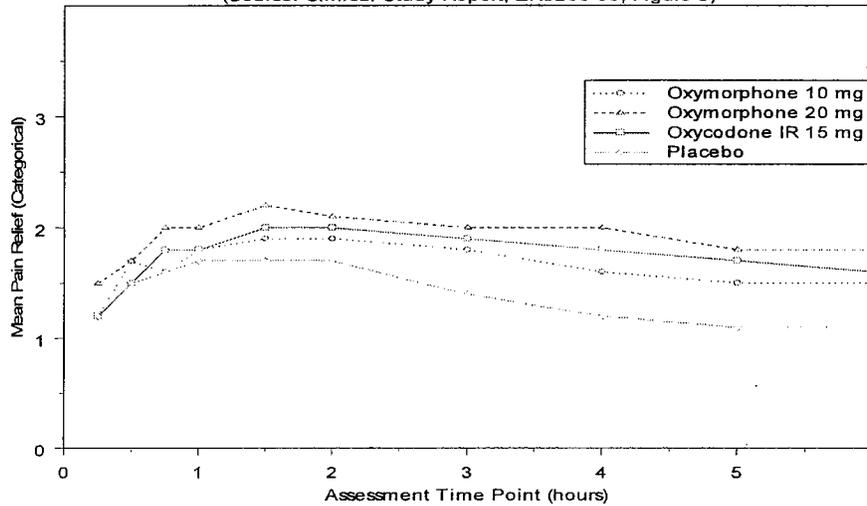
Study Medication	Oxymorphone IR 10 mg (n=82)	Oxymorphone IR 20 mg (n=81)	Oxycodone IR 15 mg (n=83)	Placebo (n=85)
Actual Number of Doses Taken				
Dose 1	82	81	83	85
Dose 2	48	53	49	45
Dose 3	43	47	46	32
Dose 4	42	44	45	22
Dose 5	41	42	44	22
Dose 6	39	35	39	18
Dose 7	32	35	37	17
Dose 8	32	33	36	15
Dose 9	31	32	34	15
Dose 10	20	20	24	9
Dose 11	14	11	16	7
Dose 12	8	5	8	4
Dose 13	4	1	2	1
Dose 14	1	0	1	0
Dose 15	1	0	1	0
Dose 16	1	0	0	0

Numerous variables were formulated and analyzed for the single-dose phase. My review focused on the total pain relief, measured on a categorical scale, since this was the variable of primary interest in the original NDA submission. The applicant's results are presented in Table 11 and further summarized in Figure 5.

Table 11: Total Pain Relief (TOTPAR, Categorical) at 0-6 Hours
(Source: reproduced from clinical study report, 3203-009, Table 11)

Statistics	Oxymorphone IR 10 mg (n=81)	Oxymorphone IR 20 mg (n=81)	Oxycodone IR 15 mg (n=83)	Placebo (n=85)
N	80	80	83	85
Mean	10.0	11.6	10.5	8.1
SD	6.7	7.1	7.2	6.0
Minimum	0.0	0.0	0.0	0.0
Median	9.8	12.2	11.2	7.6
Maximum	23.0	23.7	22.0	20.5
LS Mean	10.0	11.7	10.4	8.2
Pairwise Comparison with Placebo				
LSMean difference	1.8	3.5	2.3	
StdErr	1.0	1.0	1.0	
p-value	0.070	<0.001	0.022	
95% CI	(-0.2,3.8)	(1.6,5.5)	(0.3,4.2)	

Figure 5: Summary of Pain Relief over 0-6 Hours
 (Source: Clinical Study Report, EN3203-09, Figure 5)



The results indicated that oxymorphone IR 20 mg provided greater pain relief as compared to placebo. No difference was found between oxymorphone IR 10 mg and placebo. The results were consistent with findings from Studies EN3203-04 and EN3203-05 in the original submission. Moreover, exploration of the total pain relief measured via a visual analog scale yielded similar conclusions. The applicant additionally investigated the time to first perceptible pain relief and the time to meaningful pain relief. Neither measure differed significantly across treatment groups. The median time to first perceptible pain relief ranged from 12 to 15 minutes after dosing, and the median time to meaningful pain relief ranged from 40 to 45 minutes. At the request of the medical reviewer, Dr. Christina Fang, I additionally calculated the median time to onset of analgesia (using a definition preferred by Dr. Fang). When both meaningful relief and perceptible relief were achieved, the time to onset was computed as the minimum value. The time was censored for patients not achieving meaningful pain relief. The median time to onset of analgesia ranged from 14 minutes to 20 minutes across treatments. To further elucidate the efficacy of the drug, Dr. Fang also requested that the applicant conduct a post-hoc analysis of the time to remedication/rescue. The median time to remedication/rescue was lower in the oxymorphone IR 20 mg and oxycodone groups than in the placebo group. Specifically, the median time to remedication or rescue was 4 hours and 10 minutes in the oxymorphone IR 20 mg group and 4 hours in the placebo group. The applicant attributed the similarity in the times to the nature of the multiple-dose design. According to the applicant, "Patients were permitted to take a second dose no sooner than 4 hours after the initial dose; subsequently, patients were required to take study medication every 4–6 hours throughout the duration of the study. This may have encouraged patients, including placebo patients to stay longer."

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3.2 Evaluation of Safety

The evaluation of the safety data was conducted by Dr. Christina Fang. The reader is referred to Dr. Fang's review for information regarding the adverse event profile.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

4.1.1 Study EN3202-31

Additional analyses examined the relationship between the primary efficacy variable and patients' age, gender, and race, respectively. Specifically, analyses were conducted separately for each subgroup. The age variable was categorized utilizing the following three subgroups: ages less than 65, ages greater than or equal to 65, and ages greater than or equal to 74. Of note, the 24 patients in the category denoting age 65 or older included the 10 patients from the 74 or older category. The variable denoting race was categorized utilizing two subgroups, Caucasian and non-Caucasian. In addition, the change from baseline in pain intensity was analyzed via ANCOVA models including the subgroup variable as a covariate. Moreover, interaction terms were also added to explore the heterogeneity of the effect across subgroups. Due to the small sample sizes generated from analyses of subgroups, all analyses were considered exploratory.

Table 12 presents descriptive statistics from the subgroup analyses. The mean change in pain intensity (from baseline to the end of the study) was larger for older patients receiving oxymorphone ER compared to younger patients receiving the same treatment. In addition, the change in pain intensity was larger for females than males in the oxymorphone ER group and smaller for females than males receiving placebo. Lastly, the results suggest that the treatment difference in mean change was larger for Caucasians than among other races. Analyses adjusted for age, gender, and race supported the efficacy of the treatment.

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Table 12: Analysis of Change in Pain Intensity by Subgroups

	Oxymorphone ER	Placebo
Change from Baseline to Final Visit		
Age < 65		
n	81	87
Mean (STD)	9.4 (23.5)	26.7 (28.0)
Minimum	-28.0	-38.0
Median	0.0	28.0
Maximum	71.0	82.0
Age ≥ 65		
n	18	8
Mean	21.4 (27.2)	29.0 (27.8)
Minimum	-14	-19
Median	10.5	38.5
Maximum	76	55
Age ≥ 74		
n	7	3
Mean	33.1 (30.6)	31.3 (28.29)
Minimum	1.0	0.0
Median	25.0	39.0
Maximum	76.0	55.0
Caucasian		
n	85	86
Mean	12.9 (2.6)	28.5 (2.9)
Minimum	-26.0	-38.0
Median	3.0	30.5
Maximum	76.0	82.0
Non-Caucasian		
N	12	9
Mean	0.7 (24.1)	11.6 (35.0)
Minimum	-28.0	-30.0
Median	-3.0	-4.0
Maximum	62	74.0
Males		
N	42	46
Mean	8.4 (22.6)	30.8 (28.0)
Minimum	-26.0	-38.0
Median	1.0	38.0
Maximum	71.0	79.0
Female		
N	55	49
Mean	13.7 (25.7)	23.2 (27.5)
Minimum	-28.0	-30.0
Median	3.0	23.0
Maximum	76.0	82.0

4.1.2 Study EN3202-32

The subgroup analyses conducted in Study EN 3202-32 mimicked the analyses in Study EN3202-31 with one exception. The age variable was categorized utilizing two categories instead of three. The ages were categorized as less than 65 or greater than or equal to 65. Table 13 provides the descriptive statistics from the subgroup analyses. On average, the change in pain intensity among participants receiving oxymorphone ER was larger among younger patients compared to older patients. Additionally, the mean change in pain intensity was similar across treatment groups for both males and females. Similarly, the mean change was similar among Caucasians and non-Caucasians randomized to oxymorphone ER. As in Study EN3202-31, analyses adjusted for age, gender, and race supported the efficacy of the treatment.

Table 13: Analysis of Change in Pain Intensity by Subgroups

	Oxymorphone ER	Placebo
Change from Baseline to Final Visit		
Age < 65		
N	62	64
Mean (STD)	8.3 (20.6)	31.7 (26.4)
Minimum	-19.0	-23.0
Median	2.0	38.0
Maximum	67.0	88.0
Age ≥ 65		
N	6	5
Mean	3.8 (22.1)	41.2 (36.0)
Minimum	-22.0	-1.0
Median	1.5	60.0
Maximum	41.0	78.0
Caucasian		
N	57	61
Mean	7.9 (20.9)	34.2 (27.1)
Minimum	-19.0	-23.0
Median	1.0	40.0
Maximum	67.0	88.0
Non-Caucasian		
N	11	8
Mean	8.1 (20.0)	18.4 (22.7)
Minimum	-22.0	-2.0
Median	4.0	10.0
Maximum	52	57.0
Males		
N	30	46
Mean	9.6 (22.7)	30.5 (26.3)
Minimum	-26.0	-23.0
Median	1.0	36.0
Maximum	71.0	88.0

Table 13 continued

	Oxymorphone ER	Placebo
Female		
N	38	23
Mean	6.5 (19.0)	36.0 (28.6)
Minimum	-15.0	-6.0
Median	0.0	41.0
Maximum	59.0	83.0

4.1.3 Study EN3203-09

In Study EN3203-09, the applicant did not explore the treatment effect across subgroups. I explored the time to discontinuation due to all causes across race only. I excluded an analyses across age groups since only 7 patients were 65 years of age or older. Similarly, only 4 patients were male; therefore, a subgroup analysis by gender was not warranted.

Non-Caucasians exhibited a longer time to discontinuation across treatments compared to Caucasians. Among Caucasians, the median times to discontinuation were 10 hours and 40 minutes, 20 hours and 9 minutes, and 4 hours and 5 minutes for patients in the oxymorphone IR 10 mg, oxymorphone IR 20 mg, and placebo groups respectively. Among non-Caucasians, the median times to discontinuation were 27 hours and 30 minutes, 24 hours and 56 minutes, and 7 hours and 30 minutes for patients in the oxymorphone IR 10 mg, oxymorphone IR 20 mg, and placebo groups, respectively.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Recurrent statistical concerns throughout the original submissions for NDA 21-610 and NDA 21-611 were the appropriateness of the last observation carried forward strategy and the defined analysis populations. The missing data concern was most evident in studies whereby a disproportionately large number of discontinuations due to adverse events existed among participants receiving active treatments. The concern with the analysis populations was most apparent in the acute pain studies where study participants who received rescue medication or withdrew during the first hour were excluded from analyses. In the complete responses, the applicant adequately addressed the concerns. In studies EN3202-31 and EN3202-32, the applicant used a design whereby patients titrated to a tolerable dose prior to entering the double-blind treatment phase. An expected merit of the study design was that the number of patients discontinuing due to adverse events was diminished. However, the applicant additionally proposed an imputation strategy to further alleviate concerns. The strategy carried forward either the screening, baseline, or last observations based on the reason for discontinuation. In addition,

the analysis population in the acute pain study (EN3202-09) included all randomized patients receiving one dose of study medication.

Studies EN32020-16, EN3202-31, and EN3202-32 evaluated the change in pain intensity among patients randomized to oxymorphone ER or placebo. In all three studies, patients receiving placebo experienced a larger increase in pain intensity compared to patients receiving oxymorphone ER. Moreover, the magnitude of the change was consistent across studies. Studies EN3203-04 and EN3203-05 evaluated the total pain relief after single-dose administration in patients receiving oxymorphone IR or placebo. In both studies, patients randomized to oxymorphone IR experienced greater pain relief compared to patients randomized to placebo. Conclusions formulated from the single-dose phase of Study EN3202-09 were consistent with the previous studies. In addition, the study demonstrated a longer time to discontinuation for patients receiving oxymorphone IR (compared to placebo) in a multiple-dose setting.

5.2 Conclusions and Recommendations

Endo Pharmaceuticals proposes use of oxymorphone ER for “the relief of moderate to severe pain in patients requiring continuous, around the clock opioid therapy for an extended period of time.” Based on the collective evaluation of the original NDA submission and the subsequent complete response to the approvable action, I conclude that there is evidence of the analgesic activity of oxymorphone ER in the chronic low back pain population. The studies have shown that the drug can alter the intensity of pain experienced by patients when appropriately titrated to a fixed dose. The effectiveness of the drug was further supported by the physicians’ and patients’ positive ratings of the treatment and the lower discontinuation rates of patients receiving oxymorphone ER. Moreover, a greater proportion of patients randomized to oxymorphone ER achieved a reduction in pain intensity from baseline across a range of criteria.

The applicant also proposes use of oxymorphone IR for “the relief of moderate to severe pain where the use of an opioid is appropriate.” When compared to placebo, my evaluation of the data suggested that oxymorphone IR 20 mg provided pain relief in patients undergoing abdominal surgery or orthopedic surgery. The applicant did evaluate oxymorphone IR 10 mg and oxymorphone IR 30 mg; however, the analgesic efficacy of the doses was not replicated. In addition, the applicant investigated use of the drug in a multiple-dose setting in response to the approvable action. Specifically, patients received treatment every 4–6 hours in Study EN3203-09. In the study, the applicant evaluated the time to discontinuation due to all causes as a measure of analgesic efficacy over repeated dosing. My review found that the time to discontinuation was longer among patients receiving oxymorphone IR.

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5.2.1 Labeling – Oxymorphone ER

The applicant's draft labeling for oxymorphone ER references five clinical studies including two supportive studies conducted in patients with osteoarthritis. The studies conducted in the osteoarthritis population did not convincingly demonstrate efficacy because of the sensitivity of the results to the procedure for handling missing data; therefore, I propose that the labeling rely on the studies conducted in the chronic low back pain population only. In general, the applicant has described the study designs and presented the findings for each study. My recommendations primarily focus on the findings. The applicant repeatedly uses the phrase _____

_____. I recommend deletion of the word "_____ " from the text. I believe these deletions will not alter the interpretation. In the study conducted in opioid-naïve patients, the applicant claims, _____

_____ I suggest this sentence be placed immediately after the sentence describing the number of patients that completed the double-blind treatment period. Moreover, I also suggest the deletion of the first part of the sentence as it seems promotional in nature. A similar edit is needed in the paragraph describing the 12-week study conducted in opioid-experienced patients. The review team will need to decide on the benefit of the inclusion of the sentence stating the duration of the effect. Lastly, I do not believe the inclusion of the tables provides additional information that cannot be conveyed in the text. My suggested changes can be found in the applicant's proposed clinical trials section below. My proposed additions are italicized, and deletions are lined through.

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8 Draft Labeling

 Deliberative Process

APPENDICES

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Study EN3202-31

Demographic, Screening, and Randomization Characteristics – All Treated Patients (Double-Blind Treatment Period)
(Source: adapted from Clinical Study Report EN3202-31, Table 8)

Demographic/Statistics	Oxymorphone ER (n=105)	Placebo (n=100)
Age (yrs)		
N	105	100
Mean	51	48
STD	14	12
Median	50	48
Min, max	22, 85	20, 76
Age Group, n		
< 65	88	92
≥ 65	17	8
≥ 74	8	3
Race, n		
African American	7	5
Caucasian	93	91
Hispanic	5	4
Gender, n		
Female	59	50
Male	46	50
Stabilized Dose Level, n		
High (> 30 mg daily)	50	48
Low (≤ 30 mg daily)	55	52
Weight (pounds)		
N	105	100
Mean	195	186
STD	43	42
Median	189	180
Min, max	100, 343	110, 334
Etiology, n		
Degenerative disc disease	34	28
Herniated disc	5	3
Osteoarthritis	26	29
Spinal stenosis	8	4
Trauma	19	25
Other	38	30
Categorical Rating of Chronic Low Back Pain, n		
Moderate	81	82
Severe	24	18
Avg. Pain Intensity (VAS)		
N	105	100
Mean	70	68
STD	12	11
Median	71	69
Min, Max	45, 100	47, 93

Patient Global Assessment of Pain Medication by Visit – Modified Intent-to-Treat Population
(Source: adapted from Clinical Study Report EN3202-31, Table 13)

Visit	Patient's Global Assessment	Oxymorphone ER (N=97)	Placebo (N=95)	p-value ^a
Screening (Visit 1) ^b	Poor	39	40	0.8371
	Fair	41	43	
	Good	13	8	
	Very Good	1	0	
	Excellent	1	0	
	Total	95	91	
Baseline (Visit 5) ^c	Poor	0	0	0.3827
	Fair	1	3	
	Good	20	23	
	Very Good	46	43	
	Excellent	28	26	
	Total	95	95	
Day 28 (Visit 10) ^d	Poor	2	9	0.0098
	Fair	3	7	
	Good	23	12	
	Very Good	29	15	
	Excellent	15	6	
	Total	72	49	
Day 56 (Visit 12) ^d	Poor	3	8	0.0103
	Fair	5	3	
	Good	14	14	
	Very Good	32	13	
	Excellent	16	5	
	Total	70	43	
Final Visit	Poor	8	39	<0.0001
	Fair	9	13	
	Good	24	10	
	Very Good	34	15	
	Excellent	20	9	
	Total	95	86	

^a The p-value is from the rank-sum test, stratified by center.

^b Evaluation of pre-study medication.

^c Evaluation of Oxymorphone during the Open-Label Titration period.

^d Evaluation of Double-Blind Treatment Period medication.

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Physician Global Assessment of Pain Medication by Visit – Modified Intent-to-Treat Population
(Source: adapted from Clinical Study Report EN3202-31, Table 14)

Visit	Patient's Global Assessment	Oxymorphone ER (N=97)	Placebo (N=95)	p-value ^a
Screening (Visit 1) ^b	Poor	43	45	0.8447
	Fair	42	45	
	Good	7	3	
	Very Good	2	0	
	Excellent	0	0	
	Total	94	93	
Baseline (Visit 5) ^c	Poor	0	0	0.5181
	Fair	0	2	
	Good	15	16	
	Very Good	55	50	
	Excellent	25	27	
	Total	95	95	
Day 28 (Visit 10) ^d	Poor	3	11	0.0055
	Fair	5	6	
	Good	19	10	
	Very Good	29	18	
	Excellent	16	5	
	Total	72	50	
Day 56 (Visit 12) ^d	Poor	0	6	0.0021
	Fair	3	6	
	Good	14	13	
	Very Good	35	15	
	Excellent	17	5	
	Total	69	43	
Final Visit	Poor	7	41	<0.0001
	Fair	9	14	
	Good	18	7	
	Very Good	41	14	
	Excellent	21	11	
	Total	96	87	

^a The p-value is from the rank-sum test, stratified by center.

^b Evaluation of pre-study medication.

^c Evaluation of Oxymorphone during the Open-Label Titration period.

^d Evaluation of Double-Blind Treatment Period medication.

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Study EN3202-32

Demographic, Screening, and Randomization Characteristics – All Treated Patients (Double-Blind Treatment Period)
(Source: adapted from Clinical Study Report EN3202-32, Table 8)

Demographic/Statistics	Oxymorphone ER (n=70)	Placebo (n=72)
Age (yrs)		
N	70	72
Mean	48	46
STD	12	11
Median	48	46
Min, max	21, 73	21, 70
Age Group, n		
< 65	64	67
≥ 65	6	5
≥ 74	0	0
Race, n		
African American	10	5
Caucasian	59	64
Hispanic	1	1
Pacific Islander	0	1
Other	0	1
Gender, n		
Female	40	24
Male	30	48
Stabilized Dose Level, n		
High (> 30 mg daily)	31	35
Low (≤ 30 mg daily)	39	37
Weight (pounds)		
N	69	72
Mean	201	192
STD	48	44
Median	195	198
Min, max	118, 306	95, 300
Etiology, n		
Degenerative disc disease	30	23
Herniated disc	12	17
Osteoarthritis	16	10
Spinal stenosis	2	0
Trauma	13	14
Other	15	20
Categorical Rating of Chronic Low Back Pain, n		
Moderate	49	51
Severe	21	21
Avg. Pain Intensity (VAS)		
N	70	72
Mean	67	72
STD	17	17
Median	71	74
Min, Max	22, 100	14, 100

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Patient Global Assessment of Pain Medication by Visit – Modified Intent-to-Treat Population
(Source: adapted from Clinical Study Report EN3202-32, Table 13)

Visit	Patient's Global Assessment	Oxymorphone ER (N=69)	Placebo (N=69)	p-value ^a
Screening (Visit 1) ^b	Poor	10	4	0.2145
	Fair	28	27	
	Good	23	26	
	Very Good	8	10	
	Excellent	0	2	
	Total	69	69	
Baseline (Visit 5) ^c	Poor	0	0	0.9525
	Fair	1	3	
	Good	18	13	
	Very Good	35	38	
	Excellent	14	15	
	Total	68	69	
Day 28 (Visit 10) ^d	Poor	1	4	0.1704
	Fair	3	2	
	Good	13	6	
	Very Good	22	6	
	Excellent	17	3	
	Total	56	21	
Day 56 (Visit 12) ^d	Poor	0	2	0.7393
	Fair	3	3	
	Good	17	3	
	Very Good	17	6	
	Excellent	14	4	
	Total	51	18	
Final Visit	Poor	4	40	<0.0001
	Fair	10	5	
	Good	15	7	
	Very Good	22	10	
	Excellent	18	5	
	Total	69	67	

^a The p-value is from the rank-sum test, stratified by center.

^b Evaluation of pre-study medication.

^c Evaluation of Oxymorphone during the Open-Label Titration period.

^d Evaluation of Double-Blind Treatment Period medication.

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Physician Global Assessment of Pain Medication by Visit – Modified Intent-to-Treat Population
(Source: adapted from Clinical Study Report EN3202-32, Table 14)

Visit	Patient's Global Assessment	Oxymorphone ER (N=69)	Placebo (N=69)	p-value ^a
Screening (Visit 1) ^b	Poor	13	6	0.2807
	Fair	32	30	
	Good	17	26	
	Very Good	7	6	
	Excellent	0	1	
	Total	69	69	
Baseline (Visit 5) ^c	Poor	0	0	0.3601
	Fair	0	1	
	Good	17	9	
	Very Good	32	36	
	Excellent	19	23	
	Total	68	69	
Day 28 (Visit 10) ^d	Poor	1	2	0.1160
	Fair	4	4	
	Good	9	4	
	Very Good	16	7	
	Excellent	25	4	
	Total	55	21	
Day 56 (Visit 12) ^d	Poor	0	2	0.0763
	Fair	5	4	
	Good	11	0	
	Very Good	11	8	
	Excellent	24	4	
	Total	51	18	
Final Visit	Poor	5	37	<0.0001
	Fair	6	10	
	Good	11	8	
	Very Good	23	6	
	Excellent	24	4	
	Total	69	65	

^a The p-value is from the rank-sum test, stratified by center.

^b Evaluation of pre-study medication.

^c Evaluation of Oxymorphone during the Open-Label Titration period.

^d Evaluation of Double-Blind Treatment Period medication.

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Study EN3203-09

Summary of Demographics and Baseline Characteristics – All Treated Patients
(Source: adapted from Clinical Study Report EN3203-09, Table 3)

Characteristics	Oxymorphone IR	Oxymorphone IR	Oxycodone IR	Placebo (n=85)	Total (n=331)
	10 mg (n=82)	20 mg (n=81)	15 mg (n=83)		
Age (yrs)					
N	82	81	83	85	331
Mean	43	43	43	42	43
STD	9	10	9	10	9
Minimum	21	23	18	23	18
Maximum	68	83	82	68	83
Gender, n					
Female	1	1	1	1	4
Male	81	80	82	84	327
Race, n					
Caucasian	52	57	48	58	215
African American	20	17	18	15	70
Hispanic	6	4	8	7	25
Asian	2	2	2	3	9
Hawaiian	0	0	1	0	1
Latino	0	0	1	0	1
Native American	0	0	1	0	1
Other	1	1	4	2	8
Baseline Pain Intensity (Categorical), n					
Moderate	69	74	69	73	285
Severe	13	7	14	12	46
Baseline Pain Intensity (VAS)					
N	82	81	83	85	331
Mean	62	64	65	64	64
STD	10	11	13	11	12
Minimum	50	50	50	48	48
Maximum	97	90	96	100	100

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Summary of Mean Average Pain Intensity (VAS) – Intent-to-Treat Patients – Multiple-Dose Period (0-48 hours)
(Source: Clinical Study Report, EN3203-09, Table 7)

Statistics	Oxymorphone	Oxymorphone	Oxycodone IR	Placebo (N=85)
	IR 10 mg (N=81)	IR 20 mg (N=81)	15 mg (N=83)	
n	80	80	83	85
Mean	38.9	35.2	40.2	50.5
STD	24.7	26.3	23.7	23.3
Minimum	1.0	0.0	3.9	1.6
Median	39.8	30.7	41.4	51.0
Maximum	94.2	90.3	92.6	100.0
LSMean	39.7	35.2	39.8	50.1
Pairwise Comparison with Placebo ^a				
LSMean Difference	-10.5	-15.0	-10.3	
Std Error	3.6	3.6	3.6	
P-value	0.0042	<0.0001	0.0042	
95% CI	(-17.6, -3.3)	(-22.1, -7.8)	(-17.4, -3.3)	

^aAll pairwise comparison statistical results are between corresponding active treatment and placebo. ANCOVA model is used including main effects for treatment, center and baseline pain intensity as covariate in the model.

Summary of Mean Current Pain Intensity (VAS) – Intent-to-Treat Patients – Multiple-Dose Period (0-48 hours)
(Source: Clinical Study Report, EN3203-09, Table 8)

Statistics	Oxymorphone	Oxymorphone	Oxycodone IR	Placebo (N=85)
	IR 10 mg (N=81)	IR 20 mg (N=81)	15 mg (N=83)	
n	80	80	83	85
Mean	48.8	45.0	47.5	63.3
STD	30.9	32.6	29.6	29.2
Minimum	1.0	0.0	0.0	0.0
Median	46.1	36.2	46.3	70.0
Maximum	99.0	100.0	100.0	100.0
LSMean	49.6	44.9	47.0	63.0
Pairwise Comparison with Placebo ^a				
LSMean Difference	-13.4	-18.1	-15.9	
Std Error	4.6	4.6	4.5	
P-value	0.0037	<0.0001	0.0005	
95% CI	(-22.4, -4.4)	(-27.0, -9.1)	(-24.8, -7.1)	

^aAll pairwise comparison statistical results are between corresponding active treatment and placebo. ANCOVA model is used including main effects for treatment, center and baseline pain intensity as covariate in the model.

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Patient Global Evaluation of Study Medication, Intent-to-Treat Patients
 (Source: adapted from Clinical Study Report, EN3203-09, Appendix 16.2.2, Table 12)

Statistics	Oxymorphone	Oxymorphone	Oxycodone IR	Placebo (N=85)
	IR 10 mg (N=81)	IR 20 mg (N=81)	15 mg (N=83)	
Total, n [1]	79	77	81	82
Excellent	22	25	19	11
Very Good	15	20	20	9
Good	12	7	17	17
Fair	9	9	7	18
Poor	21	16	18	27
Pairwise Comparison [2]	0.986			
Oxymorphone IR 20 mg	0.455	0.150		
Oxycodone IR 15 mg	0.018	0.005	0.122	
Placebo				

[1] Total is the number of patients with a non-missing physician global evaluation of study medication at the end of study.

[2] All pairwise comparison p-values are based on a Wilcoxon rank sum test, stratified by center.

Physician Global Evaluation of Study Medication, Intent-to-Treat Patients
 (Source: adapted from Clinical Study Report, EN3203-09, Appendix 16.2.2, Table 13)

Statistics	Oxymorphone	Oxymorphone	Oxycodone IR	Placebo (N=85)
	IR 10 mg (N=81)	IR 20 mg (N=81)	15 mg (N=83)	
Total, n	80	78	81	81
Excellent	26	32	21	17
Very Good	13	13	19	10
Good	8	5	11	12
Fair	12	12	13	20
Poor	21	16	17	22
Pairwise Comparison				
Oxymorphone IR 20 mg	0.232			
Oxycodone IR 15 mg	0.716	0.061		
Placebo	0.215	0.020	0.648	

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Food and Drug Administration

Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CARCINOGENICITY STUDIES

NDA: 21-610/21-611

Drug Name: Oxymorphone Hydrochloride Extended Release (ER) Tablets

Applicant: Endo Pharmaceuticals Inc.

Laboratory: _____

Biometrics Division: Biometrics Division 6

Statistical Reviewer: Moh-Jee Ng, M.S. (HFD-705)

Concurring Reviewers: Karl Lin, Ph.D. (HFD-705)

Medical Division: Division of Anesthetic, Analgesia, and Rheumatology Products

Pharmacologist: Mamata De, Ph.D. (HFD-170)

Keywords: NDA review, carcinogenicity

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Executive Summary

Rats received doses at 0, 2.5, 5, or 10 mg/kg/day for males, and 0, 5, 10, or 25 mg/kg/day for females. Mice received doses at 0, 10, 25, 75, or 150 mg/kg/day for both males and females.

Female rats and male mice showed both statistically significant positive dose-mortality trends and statistically differences in survival distributions. Male rats showed a statistically significant positive trend (in Cox Test), but the differences in survival distributions were not statistically significant. Female mice showed statistically significant differences in survival distributions (in Kruskal-Wallis test), but not in dose-mortality trend.

Statistical analyses of 2-year carcinogenicity studies of oxymorphone-HCL in rats and mice showed no statistically significant, positive dose-response relationships in the incidence of any tumors in either sex or in either specie, except malignant lymphoma in hemolymphoreticular tissue ($p=0.0162$) in male rats. However, the pairwise comparison in incidence rate of tumor between the control and the high-dose group ($p=0.0639$) was not statistically significant.

The high-dose rats and mice show significant reductions in mean body weight gain relative to the control group (over 42% reduction in rats and over reduction 28% in mice). It is this reviewer's opinion that, based on body weight data, the high-dose groups used in these 2-year carcinogenicity studies in rats and mice were over the maximum tolerated dose (MTD).

Introduction

The objective of this review is to evaluate the oncogenic potential of oxymorphone hydrochloride (HCl) when administered by oral gavage daily to rats and mice for two years. In rats, there were a control group (CD) and three treated groups, namely low dose (LD), medium dose (MD), and high dose (HD). The dose levels for the LD, MD, and HD groups were 2.5, 5, and 10 mg/kg/day for males, and 5, 10 and 25 mg/kg/day for females, respectively. For mice, there were a control group and four treated groups, namely low dose (LD), mid-low dose (ML), mid-high dose (MH), and high dose (HD). The dose levels for the LD, ML, MH, and HD groups were 10, 25, 75 and 150 mg/kg/day respectively. There were 100 animals in control group, and 65 animals of each sex in each treatment group for both rats and mice. The study design is summarized in Table 1.

Table 1: Overall designs of 2-year carcinogenicity study of Oxymorphone-HCL in rats and mice

Species	Rat		Mice
Strain	CD-1®(ICR)BR		CD®-1(ICR)BR
Route of Administration	Oral		Oral
Dose Unit	mg/kg/day		mg/kg/day
oxymorphom-HCL (mg/kg/day)	0 (CD)		0 (CD)
	Male	Female	10 (LD)
	2.5 (LD)	5 (LD)	25 (MD)
	5 (MD)	10 (MD)	75 (MH)
	10 (HD)	25 (HD)	150 (HD)
Number of Animals/sex/dose	100 in control group, 65/sex/dose		100 in control group 65/sex/dose
Length of Study	104 weeks		104 weeks

Reviewer's Analyses

Analyses of survival and neoplastic data were done using the programs written by Dr. Ted Guo of Division of Biostatistics II. The test for carcinogenic potential is based on the principles outlined in the Food and Drug Administration's Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceutical (May 2001).

Survival. Homogeneity and trend tests are used to examine the dose-related changes in mortality. Differences in survival distributions among the treatment groups are tested by homogeneity test. A positive trend in the proportion of deaths with respect to the dose levels is tested by trend test. Tests for homogeneity and dose-mortality trends were conducted via the Cox test¹ and the Kruskal-Wallis test². Tables A1-A4 include the numbers of animals at risk, the numbers of animals at deaths, the numbers of animals alive, the cumulative percentages of survival, and the cumulative percentages of deaths by treatment and time intervals. The time intervals used were 0-52, 53-78, 79-91, 93-103 weeks, and the terminal-sacrifice. The actual doses were used as weights. Figures 1-4 present the plots of Kaplan-Meier estimates of the survival distributions of the treatment groups. Tables B1-B4 present results of the dose-mortality trends.

Neoplastic Data. The purpose of the analysis of neoplastic data is to determine if there is a positive trend in the proportions of a selected tumor type in a selected organ/tissue with respect to the dose levels. The tumors were classified as either fatal or incidental and were analyzed using the death-rate method³, and the prevalence method, respectively. A combined test was utilized to analyze tumors classified as both fatal and incidental. Multiplicity was addressed employing a decision rule proposed in the guidance. Specifically, positive trends in incidence rates of rare and common tumors were tested at the 0.025 and 0.005 level of significance, respectively. Rare and common tumors were defined based on the tumor rate in the control group. If the tumor rate in the control group was less than 1%, the tumor was classified as rare. Otherwise, the tumor was classified as common. In all analyses, male and female data were analyzed separately for each species. Tables C1-C4 present results of the dose-tumor trends.

Lastly, to further validate results of negative studies, this reviewer evaluated the number of animals at risk in relation to the adequacy of exposure. Per the guidance document, "a 50% survival rate of the 50 initial animals in any treatment group between weeks 80-90 of a two year study may be considered as a sufficient number and adequate exposure". In addition, this reviewer examined the adequacy of the doses to see if they present a reasonable tumor challenge to the animals. This evaluation was conducted utilizing criteria outlined by Chu, Cueto, and Ward⁴. Under the criteria, a dose may be considered adequate "if there is a detachable loss in weight gain of up to 10% in a dosed group relative to the controls" and "if dosed animals show a slight increased mortality compared to the control."

¹ Cox, DR: "regression Models and Life tables" *Journal of the Royal Statistical Society, Series B*, 34, 187-220, 1972.

² Gehan, EA: "A Generalized Wilcoxon Test for Comparing K Samples Subject to Unequal Patterns of Censorship" *Biometrika*, 52, 203-223, 1965

³ Peto, R, MC Pike, NE Day, RG Gray, PN Lee, S Parish, J Peto, S Richards, and J Wahrendorf: "Guidelines for Simple Sensitive Significance Tests for Carcinogenic Effects in Long-Term Animal Experiments" *In Long-term and Short-term Screening Assays for Carcinogens: A critical Appraisal*, World Health Organization 1980

⁴ Chu C, C Cueto, and JM Ward: "Factors in the evaluation of 200 National Cancer Institute Carcinogen Bioassays" *Journal of Toxicology and Environmental Health*, 8, 251-280,

Analysis of the Rat Data

Analysis of survival data. The dose-mortality trend was statistically significant using the Cox test ($p=0.0226$), however, no statistically significant using the Kruskal-Wallis test ($p=0.0859$) for males. The dose-mortality trend was statistically significant using the Cox test ($p=0.0007$) and the Kruskal-Wallis test ($p=0.0014$) for females (see appendix Tables B1-B2). Table 2 summarizes the accumulative survivals of the study. The respective accumulative survival rates at the end of the treatment for the CD, LD, MD, and HD group were 38, 43, 48, and 60% in the males, and 30, 34, 40 and 57% in the females, respectively. Figures 1 and 2 (see appendix) present the survival curves as a function of time for males and females. Each group had at least 22 rats surviving to the scheduled sacrifice at week 104 (see Table 3). Sufficient numbers of rats survived the treatment to the end of the study to provide a strong evidence of adequate exposure of the drug to the animals.

Table 2: Accumulative Survival (%) presented for Rats

Sex oxymorphone-HCL (mg/kg/day)	Male				Female			
	CD 0	LD 2.5	MD 5	HD 10	CD 0	LD 5	MD 10	HD 25
Weeks 0 - 52	96	88	92	91	95	97	95	97
53 - 78	85	79	75	79	68	83	75	89
79 - 91	63	65	62	72	49	54	57	68
92 -103	38	43	48	60	30	34	40	57

Table 3: Numbers of Rats Survived the Treatment at Week 104

Oxymorphone-HCL (dose group)	CD	LD	MD	HD
Sex				
Male	38	28	31	39
Female	30	22	26	37

Analysis of neoplastic data: Table 4 lists the result of significant dose-tumor trend test for male rats. The statistical significance for the positive trend test was tested at 0.025 and 0.005 significance levels for common and rare tumors, respectively. The statistical significance for the pairwise differences was tested at 0.01 and 0.05 for common and rare tumors, respectively. Tables C1-C2 (see appendix) list the incidence rates of tumors with p-values in testing positive dose-tumor trends. There is a statistically significant positive trend in the incidence of malignant lymphoma in hemolymphoreticular tissue ($p=0.0162$) in male rats. However, no statistically significant difference was detected in pairwise comparison when the control group compared with the HD group ($p=0.0639$) in this tumor type.

Table 4: Results of significant dose-tumor trend Tests for Male Rats

Tumor oxymorphon-HCL (mg/kg/day)	CD 0 mg/kg/day	LD 2.5 mg/kg/day	MD 5 mg/kg/day	HD 10 mg/kg/day	P-values [†]
Number of animals examined	100	65	65	65	
Hemolymphoreticular Tissue/Malignant lymphoma	1	0	0	4 0.0639 [‡]	0.0162*

Source data: dataset received on 3/22/2006, analysis data R1M56919

[†]: p-value presents for dose groups CD, LD, MD and HD trend.

[‡]: p-value presents pairwise comparison between the high dose and the control group.

*: Bold areas show statistical significance at 0.025 level.

Table 5 provides an additional statistical analysis in combining difference types of tumors site. No statistically significant result was found in any of the tumor combinations.

Table 5: Results of Trend Tests in Combining Tumors for Rats

Organ/Tumor oxymorphone-HCL (mg/kg/day)	CD 0 mg/kg/day	LD 2.5 mg/kg/day	MD 5 mg/kg/day	HD 10 mg/kg/day	P-values [†]
Male					
Liver/ adenoma & carcinoma hepatocellular	5	2	0	1	0.9602
Pancreas/carcinoma & adenoma: islet cell	19	13	8	8	0.9108
Pituitary/adenoma & carcinoma: Pars distalis	65	30	34	23	0.9995
Pituitary/adenoma & carcinoma: Pars distalis & adenoma: pars intermedia	65	30	34	24	0.9992
Thyroid/adenoma & carcinoma: C-cell	17	11	3	8	0.9459
Thyroid/adenoma & carcinoma: Follicular cell	6	2	2	3	0.6887
Skin miscellaneous/papilloma & carcinoma: squamous cell	2	4	2	4	0.4262
Adrenal/adenoma & carcinoma: cortical	4	2	3	2	0.7262
Whole bodies/carcinoma: squamous cell	1	2	0	4	0.1366
Female					
Pancreas/carcinoma & adenoma: islet cell	8	3	4	1	0.9844
Subcutaneous Tissue/ fibrosarcoma & fibroma	6	1	1	3	0.7150
Uterus/sarcoma & polyp: Endometrial stromal	6	4	7	9	0.1185
Pituitary/ adenoma & carcinoma: Pars distalis	83	52	52	46	0.9997
Thyroid/ adenoma & carcinoma: Follicular cell	1	0	0	1	0.5419
Adrenal/ adenoma & carcinoma: cortical	11	3	2	2	0.9775
Mammary gland/ adenoma & fibroadenoma	49	29	26	22	0.9737
Whole bodies/carcinoma: squamous cell	0	2	2	3	0.0604
Whole bodies/Leiomyoma	0	0	0	3	0.1052

[†]: p-values present for dose groups CD, LD, MD and HD trends.

Table 6 summarizes the survival data for the HD group at weeks 52, 91, and the end of the study. More than 50% of the male and female rats were alive at the end of week 91. This suggests a sufficient number of animals with adequate exposure.

Table 6: Survival data for the High Doses of Male and Female Rats

Sex	End of 52 Weeks	End of 91 Weeks	End of Study at Week 103
Male	91%	72%	60%
Female	97%	68%	57%

To evaluate adequacy of dose levels used, a summary of the body weight data was generated and displayed in Table 7. The HD male and female rats had 42% and 45% reduction in mean weight gain relative to the control group, respectively. The body weight data suggest that the high doses (10 mg/kg/day for males and 25 mg/kg/day for females) used in the rat study were over the maximum tolerated dose (MTD)⁴.

Table 7: Mean Body Weight (%) for Rats

	Dose Groups	Mean Body Weight (grams)		Mean Body Weight Gain (MBWG)	% Differences in MBWG
		Beginning Study (week 1)	End of Study (week 104)		
Male	0 mg/kg/day	291.2	770.0	478.8	
	2.5 mg/kg/day	302.1	697.9	395.8	-17
	5 mg/kg/day	305.6	649.9	344.3	-28
	10 mg/kg/day	299.3	578.1	278.8	-42
Female	0 mg/kg/day	210.3	501.0	290.7	
	5 mg/kg/day	204.2	455.8	251.6	-13
	10 mg/kg/day	204.5	385.2	180.7	-38
	25 mg/kg/day	201.5	360.1	158.6	-45

Source: Adapted from ENDO Study No. EN3202-381-02, text tables 4 & 5, pages 99-114

Conclusion of the Rat Study

In the 2-year study, rats received oxymorphone-HCL doses at 0, 2.5, 5, or 10 mg/kg/day for males, 0, 5, 10, or 25 mg/kg/day for females. The dose-mortality trend was statistically significant using the Cox test ($p=0.0226$), but, no statistically significant using the Kruskal-Wallis test ($p=0.0859$) for males. The dose-mortality trend was statistically significant using the Cox test ($p=0.0007$) and the Kruskal-Wallis test ($p=0.0014$) for females. The respective accumulative survival rates at the end of the treatment for the CD, LD, MD, and HD group were 38, 43, 48, and 60% in the males, and 30, 34, 40 and 57% in the females, respectively. Each group had at least 22 rats surviving to the scheduled sacrifice at week 104. A sufficient number of rats survived long enough to be at risk of late developing tumors. There was a statistically significant trend in the incidence of malignant lymphoma in hemolymphoreticular tissue ($p=0.0162$) in male rats. However, there was no statistically significant difference in this tumor type in the pairwise comparison when the control group with the HD group ($p=0.0639$). The HD male and female rats showed significant reduction in mean body weight gain relative to the control group (42% and 45%, respectively). The body weight data suggested that the high doses (10 mg/kg/day for males and 25 mg/kg/day for females) used in the rat study were over the maximum tolerated dose (MTD)⁴.

Analysis of the Mice Data

Analysis of survival data. The dose-mortality trend was statistically significant in male mice using the Cox test ($p=0.0018$) and the Kruskal-Wallis test ($p=0.0026$). However, the trend was not statistically significant in female mice using the Cox test ($p=0.5353$) and the Kruskal-Wallis test ($p=0.4985$) (see appendix Tables B3-B4). Table 8 summarizes the accumulative survivals of the study. The respective accumulative survival rates at the end of the treatment for the CD, LD, ML, MH and HD group were 50, 63, 65, 42, and 37 % in males, and 38, 57, 52, 55, and 46% in females, respectively. Each group had at least 24 mice surviving to the scheduled sacrifice at week 104 (see Table 9). Sufficient numbers of mice survived the treatment to the end of the study. Figures 3 and 4 (see appendix) present the survival curves as a function of time for males and females.

Table 8: Accumulative Survival (%) presented for Mice

Sex	Male					Female				
	CD 0	LD 10	ML 25	MH 75	HD 150	CD 0	LD 10	ML 25	MH 75	HD 150
oxymorphone-HCL (mg/kg/day)										
Weeks 0 - 52	96	99	94	92	92	97	97	94	91	92
53 - 78	73	86	88	80	69	76	85	86	.	79
79 - 91	62	75	79	57	54	54	71	80	77	71
92 - 103	50	63	65	42	37	38	57	52	55	46

Table 9: Numbers of Mice Survived the Treatment at Week 104

oxymorphone-HCL (mg/kg/day)	CD 0	LD 10	ML 25	MH 75	HD 150
Sex					
Male	50	41	42	27	24
Female	38	37	34	36	30

Analysis of neoplastic data: The statistical significance for the positive trend test was tested at 0.025 and 0.005 significance levels for common and rare tumors, respectively. The statistical significance for the pairwise differences was tested at 0.01 and 0.05 for common and rare tumors, respectively. No significantly positive dose-response relationships in incidence for any tumor types were detected in either sex. Tables C3-C4 (see appendix) list the incidence rates of tumors with p-values in testing positive linear dose-tumor trends.

Table 10 provides an additional statistical analysis in combining tumors different types of site. No statistically significant result was found in any of the tumor combinations.

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Table 10: Results of Trend Tests in Combining Tumors for Mice

Organ/Tumor oxymorphone-HCL (mg/kg/day)	CD 0 mg/kg/day	LD 10 mg/kg/day	ML 25 mg/kg/day	MH 75 mg/kg/day	HD 10 mg/kg/day	P- values [†]
Male						
Lung/carcinoma & adenoma Alveolar/bronchiolar	25	13	12	13	5	0.9830
Liver/ hemangiosarcoma & hemangioma	6	1	1	1	4	0.2364
Liver/adenoma & carcinoma hepatocellular	31	6	8	5	5	0.9952
Kidney/ carcinoma & adenoma tubular cell	1	0	0	1	0	0.4786
Adrenal/adenoma & carcinoma cortical	1	1	2	0	0	0.8090
Adrenal/benign & malignant pheochromocytoma	3	0	0	0	0	1.0000
Spleen/hemangiosarcoma & hemangioma	2	3	0	0	0	0.9357
Female						
Lung/carcinoma & adenoma: Alveolar/bronchiolar	13	13	8	12	4	0.9565
Liver/ adenoma & carcinoma: Hepatocellular	2	1	0	0	1	0.6041
Liver/hemangiosarcoma & hemangioma	1	1	1	0	0	0.9090
Uterus/Polyp & sarcoma: Endometrial stromal	6	8	4	0	1	0.9964
Uterus/Leiomyosarcoma Leiomyoma	2	0	0	0	0	0.9010
Spleen/ hemangiosarcoma & hemangioma	1	2	1	1	1	0.5312
Lymph node mesenteric/ Hemangioma & hemangiosarcoma	1	1	0	0	0	0.9502

[†]: p-values present for dose groups CD, LD, ML, MH and HD trends.

Table 11 summarizes the survival data for the HD groups at weeks 52, 91, and the end of the study. The survival rates at week 91 for male and females in the HD group were 32% and 78%, respectively. More than 50% of the HD male and female mice were alive at the end of week 91 suggesting sufficient number of animals with adequate exposure.

Table 11: Survival data for the High Doses of Male and Female Mice

Sex	End of 52 Weeks	End of 91 Weeks	End of Study at week 103
Male	92%	54%	37%
Female	92%	71%	46%

To evaluate adequacy of doses used, a summary of the body weight data was generated and displayed in Table 12. The HD males and females had 28% and 29% reduction in mean body weight gain to the control group, respectively. The body weight data suggest that the HD used in the mouse study was over the MTD.

Table 12: Mean Body Weight (%) for Mice

Sex	Dose Groups	Mean Body Weight (grams)		Mean Body Weight Gain (MBWG)	% Differences in MBWG
		Beginning Study (week 1)	End of Study (week 104)		
Male	0 mg/kg/day	30.76	38.71	7.95	
	10 mg/kg/day	29.80	37.81	8.01	1
	25 mg/kg/day	29.97	35.22	5.25	-34
	75 mg/kg/day	30.22	35.87	5.65	-29
	150 mg/kg/day	30.16	35.89	5.73	-28
Female	0 mg/kg/day	23.77	36.23	12.46	
	10 mg/kg/day	22.76	32.82	10.06	-19
	25 mg/kg/day	22.49	31.37	8.88	-29
	75 mg/kg/day	23.19	31.53	8.34	-33
	150 mg/kg/day	22.19	31.02	8.83	-29

Source: Adapted from [redacted] Projct No. 77070, text table 4, page 88-104

Conclusion of the Mouse Study

In the 2-year study, mice received oxymorphone-HCL dosed at 0, 10, 25, 75, or 150 mg/kg/day. The dose-mortality trend was statistically significant in male mice using the Cox test ($p=0.0018$) and the Kruskal-Wallis test ($p=0.0026$). However, the trend was not statistically significant in female mice using the Cox test ($p=0.5353$) and the Kruskal-Wallis test ($p=0.4985$). The respective accumulative survival rates at the end of the treatment for the CD, LD, ML, MH and HD group were 50, 63, 65, 42, and 37 % in males, and 38, 57, 52, 55, and 46% in females, respectively. Each group had at least 24 mice surviving to the scheduled sacrifice at week 104. Sufficient numbers of mice survived the treatment to the end of the study. No significant positive dose-reponse relationships in tumor incidence rate for any tumor types were detected in either sex. The HD male and female mice show significant reductions in mean body weight gain (42% and 45% reductions in mean weight gain relative to the control group, respectively). The body weight data suggested that the high doses used in the mouse study was over MTD.

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Appendices

Table A1: Analysis of Mortality Data for Male Rats by Treatment and Time

	Analysis of Mortality	No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CONTROL 0 mg/kg/day	0-52	100	4	96	96.0	4.0
	53-78	96	11	85	85.0	15.0
	79-91	85	22	63	63.0	37.0
	92-103	63	25	38	38.0	62.0
	TERMINAL SACRIFICE	38	38	0		
LOW 2.5 Mg/kg/day	0-52	65	8	57	87.7	12.3
	53-78	57	6	51	78.5	21.5
	79-91	51	9	42	64.6	35.4
	92-103	42	14	28	43.1	56.9
	TERMINAL SACRIFICE	28	28	0		
MED 5 mg/kg/day	0-52	65	5	60	92.3	7.7
	53-78	60	11	49	75.4	24.6
	79-91	49	9	40	61.5	38.5
	92-103	40	9	31	47.7	52.3
	TERMINAL SACRIFICE	31	31	0		
HIGH 10 mg/kg/day	0-52	65	6	59	90.8	9.2
	53-78	59	8	51	78.5	21.5
	79-91	51	4	47	72.3	27.7
	92-103	47	8	39	60.0	40.0
	TERMINAL SACRIFICE	39	39	0		

Source data: dataset received on 3/22/2006, analysis data R1M56919

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Table A2: Analysis of Mortality Data for Female Rats by Treatment and Time

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CONTROL 0 mg/kg/day	0-52	100	5	95	95.0	5.0
	53-78	95	27	68	68.0	32.0
	79-91	68	19	49	49.0	51.0
	92-103	49	19	30	30.0	70.0
	TERMINAL SACRIFICE	30	30	0		
LOW 5 Mg/kg/day	0-52	65	2	63	96.9	3.1
	53-78	63	9	54	83.1	16.9
	79-91	54	19	35	53.8	46.2
	92-103	35	13	22	33.8	66.2
	TERMINAL SACRIFICE	22	22	0		
MED 10 mg/kg/day	0-52	65	3	62	95.4	4.6
	53-78	62	13	49	75.4	24.6
	79-91	49	12	37	56.9	43.1
	92-103	37	11	26	40.0	60.0
	TERMINAL SACRIFICE	26	26	0		
HIGH 25 mg/kg/day	0-52	65	2	63	96.9	3.1
	53-78	63	5	58	89.2	10.8
	79-91	58	14	44	67.7	32.3
	92-103	44	7	37	56.9	43.1
	TERMINAL SACRIFICE	37	37	0		

Source data: dataset received on 3/22/2006, analysis data R1F56919

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Table A3: Analysis of Mortality Data for Male Mice by Treatment and Time

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CONTROL 0 mg/kg/day	0-50	100	4	96	96.0	4.0
	51-78	96	23	73	73.0	27.0
	79-91	73	11	62	62.0	38.0
	92-103	62	12	50	50.0	50.0
	TERMINAL SACRIFICE	50	50	0		
LOW 10 Mg/kg/day	0-50	65	1	64	98.5	1.5
	51-78	64	8	56	86.2	13.8
	79-91	56	7	49	75.4	24.6
	92-103	49	8	41	63.1	36.9
	TERMINAL SACRIFICE	41	41	0		
MID-LOW 25 mg/kg/day	0-50	65	4	61	93.8	6.2
	51-78	61	4	57	87.7	12.3
	79-91	57	6	51	78.5	21.5
	92-103	51	9	42	64.6	35.4
	TERMINAL SACRIFICE	42	42	0		
MID-HIGH 75 mg/kg/day	0-50	65	5	60	92.3	7.7
	51-78	60	8	52	80.0	20.0
	79-91	52	15	37	56.9	43.1
	92-103	37	10	27	41.5	58.5
	TERMINAL SACRIFICE	27	27	0		
HIGH 150 mg/kg/day	0-50	65	5	60	92.3	7.7
	51-78	60	15	45	69.2	30.8
	79-91	45	10	35	53.8	46.2
	92-103	35	11	24	36.9	63.1
	TERMINAL SACRIFICE	24	24	0		

Source data: dataset received on 3/22/2006, analysis data M1M56919

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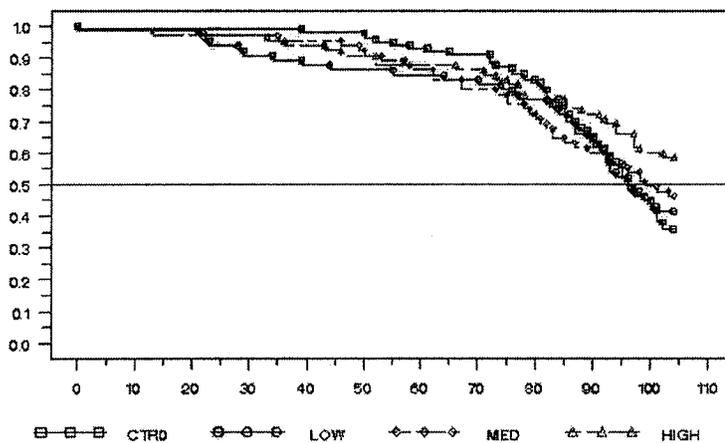
Table A4: Analysis of Mortality Data for Female Mice by Treatment and Time

	Analysis of Mortality	No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CONTROL 0 mg/kg/day	0-52	100	3	97	97.0	3.0
	53-78	97	21	76	76.0	24.0
	79-91	76	22	54	54.0	46.0
	92-103	54	16	38	38.0	62.0
	TERMINAL SACRIFICE	38	38	0		
LOW 10 Mg/kg/day	0-52	65	2	63	96.9	3.1
	53-78	63	8	55	84.6	15.4
	79-91	55	9	46	70.8	29.2
	92-103	46	9	37	56.9	43.1
	TERMINAL SACRIFICE	37	37	0		
MID-LOW 25 mg/kg/day	0-52	65	4	61	93.8	6.2
	53-78	61	5	56	86.2	13.8
	79-91	56	4	52	80.0	20.0
	92-103	52	18	34	52.3	47.7
	TERMINAL SACRIFICE	34	34	0		
MID-HIGH 75 mg/kg/day	53-78	65	6	59	90.8	9.2
	79-91	59	9	50	76.9	23.1
	92-103	50	14	36	55.4	44.6
	TERMINAL SACRIFICE	36	36	0		
	HIGH 150 mg/kg/day	0-52	65	5	60	92.3
53-78		60	9	51	78.5	21.5
79-91		51	5	46	70.8	29.2
92-103		46	16	30	46.2	53.8
TERMINAL SACRIFICE		30	30	0		

Source data: dataset received on 3/22/2006, analysis data M1F56919

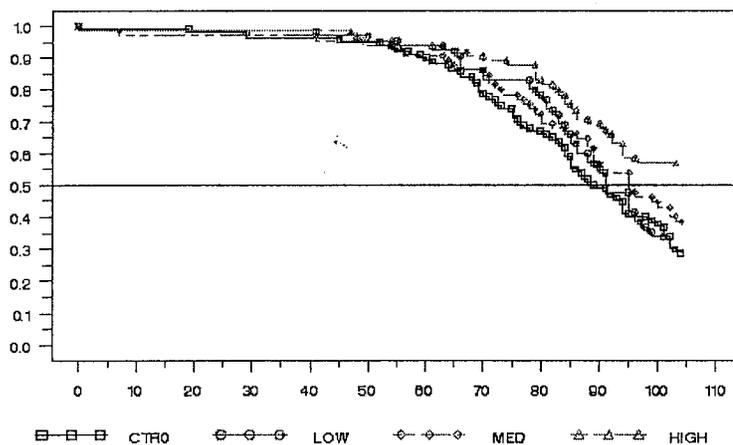
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Figure 1: Kaplan-Meier Survival Curve of the 2-year Oral Carcinogenicity Study of Oxymorphone in Male Rats



Source data: dataset received on 3/22/2006, analysis data R1M56919

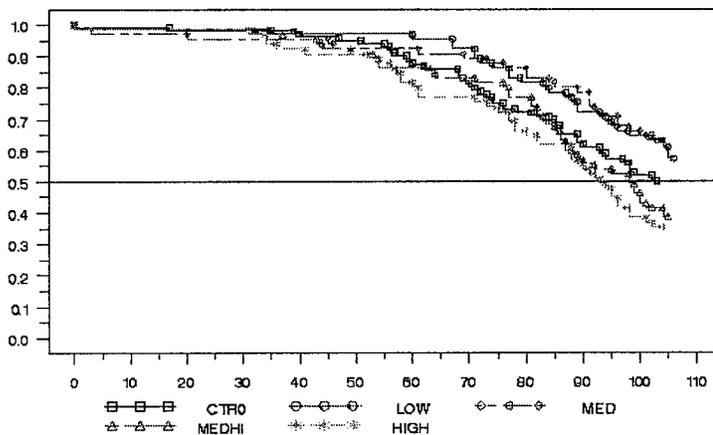
Figure 2: Kaplan-Meier Survival Curve of the 2-year Oral Carcinogenicity Study of Oxymorphone in Female Rats



Source data: dataset received on 3/22/2006, analysis data R1F56919

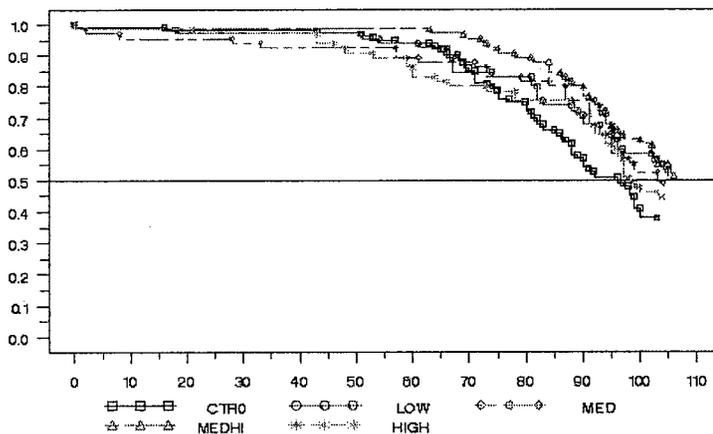
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Figure 3: Kaplan-Meier Survival Curve of the 2-year Oral Carcinogenicity Study of Oxymorphone in Male Mice



Source data: dataset received on 3/22/2006, analysis data M1M56919

Figure 4: Kaplan-Meier Survival Curve of the 2-year Oral Carcinogenicity Study of Oxymorphone in Female Mice



Source data: dataset received on 3/22/2006, analysis data M1F56919

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Table B1: Analysis of Dose-Mortality Trend for Male Rats

Time-Adjusted Trend Test	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Dose-Mortality Trend	5.1999	0.0226	2.9505	0.0859
Homogeneity	5.4417	0.1422	3.7020	0.2955

Bold areas showed statistically significant at 0.05 level.

Table B2: Analysis of Dose-Mortality Trend for Female Rats

Time-Adjusted Trend Test	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Dose-Mortality Trend	11.5696	0.0007	10.2368	0.0014
Homogeneity	11.6603	0.0086	10.5351	0.0145

Bold areas showed statistically significant at 0.05 level.

Table B3: Analysis of Dose-Mortality Trend for Male Mice

Time-Adjusted Trend Test	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Dose-Mortality Trend	9.7190	0.0018	9.0793	0.0026
Homogeneity	16.7397	0.0022	16.3605	0.0026

Bold areas showed statistically significant at 0.05 level.

Table B4: Analysis of Dose-Mortality Trend for Female Mice

Time-Adjusted Trend Test	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Dose-Mortality Trend	0.3844	0.5353	0.4582	0.4985
Homogeneity	9.2075	0.0561	9.8314	0.0434

Bold areas showed statistically significant at 0.05 level.

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Table C1: Report on Test for Positive Dose-Tumor Trends in Male Rats

Organ Name	Tumor Name	CTRO	LOW	MED	HIGH	P-Value
BRAIN	Malignant oligodendroglioma	0	1	0	0	0.6552
BRAIN	Malignant astrocytoma	1	2	0	2	0.3607
HEART	Benign schwannoma: endocardial	1	0	1	1	0.3003
LUNG	Carcinoma: squamous cell	0	0	0	1	0.2218
RECTUM	Adenoma	1	0	0	0	1.0000
STOMACH	Fibrosarcoma	0	0	0	1	0.2868
STOMACH	Papilloma: squamous cell	1	0	0	0	1.0000
COLON	Adenocarcinoma	0	1	0	0	0.6720
LIVER	Lipoma	1	0	0	0	1.0000
LIVER	Adenoma: hepatocellular	4	1	0	1	0.9200
LIVER	Carcinoma: hepatocellular	1	1	0	0	0.8753
PANCREAS	Carcinoma: islet cell	10	7	2	4	0.8646
PANCREAS	Adenoma: islet cell	9	7	6	4	0.8054
PANCREAS	Adenoma: acinar cell	0	0	1	0	0.2955
KIDNEY	Carcinoma: tubular cell	1	0	0	0	1.0000
KIDNEY	Adenoma: tubular cell	0	0	0	2	0.0410
URINARY BLADDER	Carcinoma: transitional cell	0	1	0	0	0.7206
TESTIS	Adenoma: interstitial cell	3	1	0	3	0.4242
PROSTATE	Adenocarcinoma	0	1	0	0	0.6886
PROSTATE	Adenoma	0	0	0	1	0.2868
SUBCUTANEOUS TISSU	Lipoma	2	3	0	1	0.5220
SUBCUTANEOUS TISSU	Fibrosarcoma	8	3	2	2	0.7427
SUBCUTANEOUS TISSU	Osteosarcoma	1	0	0	0	1.0000
SUBCUTANEOUS TISSU	Fibroma	6	2	3	4	0.1103
SUBCUTANEOUS TISSU	Malignant schwannoma	0	0	1	1	0.0725
SUBCUTANEOUS TISSU	Sarcoma (not otherwise specifi	0	1	0	0	0.5143
SUBCUTANEOUS TISSU	Chondrosarcoma	0	0	1	0	0.4444
PITUITARY	Adenoma: pars distalis	64	30	33	23	0.9994
PITUITARY	Carcinoma: pars distalis	1	0	1	0	0.7227
PITUITARY	Adenoma: pars intermedia	0	0	0	1	0.2868
THYROID	Carcinoma: C-cell	8	2	0	0	0.9985
THYROID	Adenoma: C-cell	10	9	3	8	0.6060
THYROID	Adenoma: follicular cell	6	2	1	3	0.7093
THYROID	Carcinoma: follicular cell	0	1	1	0	0.5563
PARATHYROID GLAND	Adenoma	4	1	0	1	0.9142
ADRENAL	Adenoma: cortical	4	2	2	2	0.7488
ADRENAL	Benign pheochromocytoma	17	9	13	15	0.1161
ADRENAL	Carcinoma: cortical	0	0	1	0	0.5147
ADRENAL	Malignant pheochromocytoma	0	1	0	1	0.3314
HEMOLYMPHORETICULAR TISSUE	Histiocytic sarcoma	2	1	3	4	0.1099
HEMOLYMPHORETICULAR TISSUE	Malignant lymphoma	1	0	0	4	0.0162 (⚠)
HEMOLYMPHORETICULAR TISSUE	Leukemia: granulocytic	1	0	0	0	1.0000
LYMPH NODE MESENTERIC	Hemangiosarcoma	0	1	1	0	0.6368
MAMMARY GLAND	Adenocarcinoma	0	1	0	1	0.2347
MAMMARY GLAND	Fibroadenoma	0	1	2	0	0.3692
MAMMARY GLAND	Adenoma	1	0	0	0	1.0000

SKIN MISCELLANEOUS	Keratoacanthoma	2	2	1	2	0.6354
SKIN MISCELLANEOUS	Papilloma: squamous cell	1	2	2	1	0.6944
SKIN MISCELLANEOUS	Carcinoma: squamous cell	1	2	0	3	0.2608
SKIN MISCELLANEOUS	Trichoepithelioma	2	0	0	0	1.0000
SKIN MISCELLANEOUS	Plasmacytoma	0	1	0	0	0.8571
SKIN MISCELLANEOUS	Adenoma: basal cell	0	2	0	0	0.7603
MUSCLE SKELETAL MI	Rhabdomyosarcoma	0	0	1	0	0.6667
FAT	Lipoma	2	1	1	0	0.9638
FAT	Hemangiosarcoma	1	0	0	0	1.0000
ABDOMEN	Osteosarcoma	2	0	0	0	0.9684
ABDOMEN	Fibrosarcoma	1	0	0	0	1.0000
ABDOMEN	Sarcoma (not otherwise specifi	0	1	0	0	0.7500
ABDOMEN	Hemangiosarcoma	0	1	0	0	0.5000

Source data: dataset received on 3/22/2006, analysis data R1M56919

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Table C2: Report on Test for Positive Dose-Tumor Trends in Female Rats

Organ Name	Tumor Name	CTR	LOW	MED	HIGH	P-Value
BRAIN	Malignant oligodendroglioma	1	0	0	0	1.0000
BRAIN	Malignant astrocytoma	0	0	1	0	0.5478
LUNG	Carcinoma: squamous cell	0	0	0	1	0.2187
CECUM	Leiomyoma	0	0	0	1	0.3217
LIVER	Adenoma: hepatocellular	6	0	3	2	0.7939
LIVER	Carcinoma: metastasis	1	0	0	0	1.0000
LIVER	Hemangiosarcoma	1	0	0	0	1.0000
PANCREAS	Carcinoma: islet cell	4	2	2	1	0.8801
PANCREAS	Adenoma: islet cell	4	1	2	0	0.9824
KIDNEY	Hemangioma	0	1	0	0	0.7391
SUBCUTANEOUS TISSUE	Lipoma	2	2	0	0	0.9732
SUBCUTANEOUS TISSUE	Fibrosarcoma	4	1	1	3	0.4873
SUBCUTANEOUS TISSUE	Fibroma	2	0	0	0	1.0000
SUBCUTANEOUS TISSUE	Hemangiosarcoma	0	1	0	0	0.7500
SUBCUTANEOUS TISSUE	Sarcoma (not otherwise specifi	0	1	0	1	0.3509
OVARY	Cystadenocarcinoma	1	0	0	0	1.0000
OVARY	Malignant granulosa-theca cell	0	1	0	1	0.2109
UTERUS	Sarcoma: endometrial stromal	1	3	2	0	0.8402
UTERUS	Polyp: endometrial stromal	5	1	5	9	0.0328
UTERUS	Benign granular cell tumor	2	0	0	1	0.5612
UTERUS	Fibrosarcoma	0	0	0	1	0.1400
UTERUS	Leiomyoma	0	0	0	1	0.3217
UTERUS	Carcinoma: squamous cell	0	0	0	1	0.3217
UTERUS	Adenoma: endometrial	1	0	0	0	1.0000
VAGINA	Polyp	1	0	0	0	1.0000
VAGINA	Benign granular cell tumor	0	2	1	0	0.7239
VAGINA	Leiomyoma	0	0	0	1	0.3246
VAGINA	Sarcoma: stromal	1	0	0	0	1.0000
PITUITARY	Adenoma: pars distalis	78	45	49	46	0.9945
PITUITARY	Carcinoma: pars distalis	5	7	3	0	0.9851
PITUITARY	Malignant schwannoma	0	0	1	0	0.4433
THYROID	Carcinoma: C-cell	2	2	1	1	0.8024
THYROID	Adenoma: C-cell	7	7	8	6	0.4993
THYROID	Adenoma: follicular cell	1	0	0	0	1.0000
THYROID	Carcinoma: follicular cell	0	0	0	1	0.3217
PARATHYROID GLAND	Adenoma	0	1	0	1	0.2122
ADRENAL	Adenoma: cortical	10	2	2	1	0.9918
ADRENAL	Benign pheochromocytoma	1	1	5	4	0.0713
ADRENAL	Carcinoma: cortical	2	1	0	1	0.7686
HEMOLYMPHORETICULAR TISSUE	Histiocytic sarcoma	1	0	0	0	1.0000
HEMOLYMPHORETICULAR TISSUE	Malignant lymphoma	2	1	1	2	0.4020
HEMOLYMPHORETICULAR TISSUE	Mast cell tumor	0	1	0	0	0.7391
THYMUS	Malignant thymoma	0	0	1	0	0.5377
SALIVARY GLAND MANDIBUL	Adenocarcinoma	1	0	0	0	1.0000
MAMMARY GLAND	Adenocarcinoma	24	23	25	17	0.7197
MAMMARY GLAND	Fibroadenoma	44	28	21	21	0.9554
MAMMARY GLAND	Adenoma	6	1	9	2	0.7146
SKIN MISCELLANEOUS	Keratoacanthoma	0	0	1	0	0.6949
SKIN MISCELLANEOUS	Carcinoma: squamous cell	0	2	2	1	0.6325

Source data: dataset received on 3/22/2006, analysis data R1F56919

Table C3: Report on Test for Positive Dose-Tumor Trends in Male Mice

Organ Name	Tumor Name	CTR	LOW	MED	MEDHI	HIGH	P-Value
LUNG	Carcinoma: alveolar/bronchiola	12	6	2	2	1	0.9836
LUNG	Adenoma: alveolar/bronchiolar	14	9	10	11	4	0.8649
STOMACH	Adenoma	1	0	0	0	0	1.0000
CECUM	Fibroma	0	1	0	0	0	0.7283
LIVER	Hemangiosarcoma	5	1	0	1	2	0.5847
LIVER	Adenoma: hepatocellular	18	3	6	4	5	0.7995
LIVER	Carcinoma: hepatocellular	13	4	2	1	1	0.9935
LIVER	Cholangiocarcinoma	0	1	0	0	0	0.7318
LIVER	Hemangioma	1	0	1	0	2	0.0679
PANCREAS	Carcinoma: islet cell	0	1	0	0	0	0.7253
KIDNEY	Hemangiosarcoma	1	0	0	0	0	1.0000
KIDNEY	Carcinoma: tubular cell	1	0	0	0	0	1.0000
KIDNEY	Adenoma: tubular cell	0	0	0	1	0	0.2772
URINARY BLADDER	Submucosal mesenchymal tumor	0	1	2	1	1	0.2433
TESTIS	Adenoma: interstitial cell	1	3	1	3	0	0.6322
TESTIS	Adenoma: rete testis	1	0	0	0	0	1.0000
EPIDIDYMIS	Interstitial (Leydig) cell ade	0	0	1	0	0	0.6000
SUBCUTANEOUS TISSUE	Myxoma	0	0	1	0	0	0.8000
ADRENAL	Benign pheochromocytoma	1	0	0	0	0	1.0000
ADRENAL	Adenoma: cortical	1	1	1	0	0	0.8307
ADRENAL	Malignant pheochromocytoma	2	0	0	0	0	1.0000
ADRENAL	Carcinoma: cortical	0	0	1	0	0	0.5054
HEMOLYMPHORETICULAR TISSUE	Malignant lymphoma	9	3	7	5	1	0.9163
HEMOLYMPHORETICULAR TISSUE	Histiocytic sarcoma	1	2	0	1	0	0.7949
SPLEEN	Hemangiosarcoma	2	1	0	0	0	0.9002
SPLEEN	Hemangioma	0	2	0	0	0	0.8033
BONE MARROW	Hemangioma	1	0	0	0	0	1.0000
LYMPH NODE	Hemangiosarcoma	0	1	0	0	0	0.7778
LYMPH NODE MESENTERIC	Hemangioma	0	1	0	0	0	0.7268
HARDERIAN GLAND	Adenoma	9	4	9	1	1	0.9905
TAIL	Fibrosarcoma	1	0	1	0	0	0.7273
JEJUNUM	Adenoma	0	1	0	0	0	0.7283
	Hemangiosarcoma	5	2	0	1	2	0.8836

Source data: dataset received on 3/22/2006, analysis data M1M56919

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Table C4: Report on Test for Positive Dose-Tumor Trends in Female Mice

Organ Name	Tumor Name	CTR	LOW	MED	MEDHI	HIGH	P-Value
LUNG	Carcinoma: alveolar/bronchiola	6	7	2	3	1	0.9698
LUNG	Adenoma: alveolar/bronchiolar	7	6	6	9	3	0.7040
LUNG	Sarcoma: metastasis	0	1	0	0	0	0.7829
CECUM	Sarcoma (not otherwise specifi	0	0	0	0	1	0.1837
CECUM	Fibroma	0	0	1	0	0	0.5714
LIVER	Hemangiosarcoma	1	0	1	0	0	0.8591
LIVER	Adenoma: hepatocellular	1	1	0	0	1	0.4219
LIVER	Carcinoma: hepatocellular	1	0	0	0	0	1.0000
LIVER	Hemangioma	0	1	0	0	0	0.7829
PANCREAS	Adenoma: islet cell	1	0	0	0	0	1.0000
URINARY BLADDER	Submucosal mesenchymal tumor	0	0	1	4	1	0.1151
SUBCUTANEOUS TISSUE	Fibrosarcoma	0	1	1	0	0	0.6556
SUBCUTANEOUS TISSUE	Myxoma	1	0	0	0	0	1.0000
SUBCUTANEOUS TISSUE	Lymphangioma	0	0	0	0	1	0.2500
SUBCUTANEOUS TISSUE	Keratoacanthoma	1	0	0	0	0	1.0000
OVARY	Cystadenocarcinoma	1	0	0	1	0	0.6193
OVARY	Cystadenoma	0	3	1	1	0	0.8072
OVARY	Benign granulosa-theca cell tu	3	0	0	0	0	1.0000
OVARY	Adenoma: tubulostromal	0	0	1	0	0	0.5714
OVARY	Benign luteoma	0	0	1	0	0	0.5714
UTERUS	Polyp: endometrial stromal	4	5	3	0	1	0.9840
UTERUS	Fibrosarcoma	1	1	0	0	0	0.9441
UTERUS	Sarcoma: endometrial stromal	2	3	1	0	0	0.9669
UTERUS	Sarcoma (not otherwise specifi	1	0	0	0	0	1.0000
UTERUS	Leiomyosarcoma	1	0	0	0	0	1.0000
UTERUS	Hemangioma	2	1	1	0	0	0.9664
UTERUS	Leiomyoma	1	0	0	0	0	1.0000
UTERUS	Carcinoma: squamous cell	2	0	0	0	0	1.0000
UTERUS	Fibroma	1	0	0	0	0	1.0000
UTERUS	Adenoma: endometrial	1	0	0	0	0	1.0000
UTERUS	Adenocarcinoma: endometrial	0	0	1	0	0	0.5714
UTERUS	Deciduoma	0	1	0	0	0	0.7829
PITUITARY	Adenoma: pars distalis	10	2	3	1	0	0.9983
PITUITARY	Adenoma: pars intermedia	0	0	0	0	1	0.1714
THYROID	Adenoma: follicular cell	1	0	0	0	0	1.0000
ADRENAL	Benign pheochromocytoma	0	0	1	0	0	0.5714
ADRENAL	Adenoma: cortical	1	1	0	0	0	0.9538
HEMOLYMPHORETICULAR TISSUE	Malignant lymphoma	13	8	11	10	12	0.2161
HEMOLYMPHORETICULAR TISSUE	Histiocytic sarcoma	12	7	2	0	2	0.9957
SPLEEN	Hemangiosarcoma	1	0	1	0	1	0.4075
SPLEEN	Hemangioma	0	2	0	1	0	0.6247
LYMPH NODE MESENTERIC	Hemangiosarcoma	1	0	0	0	0	1.0000
LYMPH NODE MESENTERIC	Hemangioma	0	1	0	0	0	0.7791
HARDERIAN GLAND	Adenoma	5	4	2	1	1	0.9445
MAMMARY GLAND	Adenocarcinoma	2	2	3	5	3	0.1693
SKIN	Carcinoma: squamous cell	0	1	0	0	0	0.7174
SKIN	Carcinoma: basal cell	0	0	0	2	0	0.3814
SKIN MISCELLANEOUS	Carcinoma: squamous cell	1	0	0	1	0	0.7908
SKIN MISCELLANEOUS	Carcinoma: basal cell	2	0	0	0	1	0.6625

MUSCLE SKELETAL	Hemangiosarcoma	0	0	0	0	1	0.2174
BONE MISCELLANEOUS	Osteosarcoma	0	0	0	0	1	0.6667
DUODENUM	Adenoma	1	0	0	0	0	1.0000
	Hemangiosarcoma	1	0	1	0	1	0.4670

Source data: dataset received on 3/22/2006, analysis data M1F56919

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Statistical Review and Evaluation

STABILITY STUDIES

NDA: 21-611

Name of drug: Oxymorphone immediate release tablets

Sponsor: Endo Pharmaceuticals

Indication: Treatment of moderate to severe pain in patients requiring opioid therapy

Documents reviewed: \\CDESUB1\N21611\N_000\2003-07-17\cmc

Project manager: Lisa Basham-Cruz

Chemistry reviewer: Dominic Chiapperino, Ph.D.

Dates: NDA Received 12/20/02; user fee (10 months) 10/20/03;

Statistical reviewer: Dionne L. Price, Ph.D.

Secondary reviewer: Karl Lin, Ph.D.

Biometrics division director: S. Edward Nevius, Ph.D.

Keywords: NDA review, stability

1 INTRODUCTION

Endo Pharmaceuticals has submitted data for three batches of Oxymorphone immediate release 5 mg and 10 mg. Each batch is tested through 6 months at 40°C/75% RH and through 24 months at 25°C/60% RH. Batches are packaged in _____ bottles and _____ bottles. The sponsor has proposed expiration dating of _____ months.

2 STATISTICAL REVIEW AND EVALUATION

Assay data and _____ (the major degradation product) data were reported. The sponsor evaluated the data via a linear regression model. The sponsor provided the following description of the planned analysis:

Analysis was done by using SAS/PROC GLM, including non-valued placeholder data to generate confidence levels of prediction at monthly intervals for all lots. In effect, this method creates an interval for every study, with the slopes estimated according to the selected model. At each month, the 'most extreme' interval bound is found, and the composite 'most extreme' boundary is indicated on the displayed figures to demonstrate the performance of the product.

Results are depicted in the sponsor's graphs below.

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The sponsor's analyses appeared to pool the data from different strengths and containers. Since certain assumptions of homogeneity were not justified, the pooling of the data may have been inappropriate. Therefore, I additionally analyzed the stability data utilizing the FDA tool, e-review for stability analysis. For the data provided, I assumed the degradation pattern was explained via a linear relationship. The e-review tool initially tested the "batch poolability". Thus, the underlying algorithm fitted linear regression models to the batches (per package and dose) and applied tests for equality of slopes and/or intercepts. Batches were pooled for analysis only if neither the slopes nor the intercepts were significantly different at the level of α . The degradation pattern arising from dissimilar batches was described via models with separate intercepts and slopes or via models with separate intercepts and common slopes. The expiration date for pooled batches of oxymorphone immediate release (IR), based on oxymorphone potency, was determined by the intersection of the 95% lower confidence bound and the lower specification limit. The expiration date for batches with common slope and separate intercept was the minimum of the three intersections. Dating of the primary degradation product, based on α was determined by the intersection of the 95% upper confidence bound and the specification limit of α . My results are depicted in the tables below:

Table 1: Expiry Dating: oxymorphone ER potency

Assay	Selected Model	Expiration Date
5 mg (bottle)	Common slope and separate intercepts	
5 mg (bottle)	Common slope and intercept	
5 mg (blister)	Common slope and intercept	
10 mg (bottle)	Common slope and separate intercepts	
10 mg (bottle)	Common slope and separate intercepts	
10 mg (blister)	Common slope and separate intercepts	

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3 CONCLUSIONS AND RECOMMENDATIONS

Endo Pharmaceuticals submits stability data for 24 months. Evaluation of the data suggests that the 24-month data are within the specifications and support extrapolation to 30 months. The sponsor requests a 30-month expiry dating period; however, the request assumes the degradation pattern will continue throughout a prolonged period of time.

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Statistical Review and Evaluation

STABILITY STUDIES

NDA: 21-610
Name of drug: Oxymorphone extended release tablets
Sponsor: Endo Pharmaceuticals
Indication: Treatment of moderate to severe pain in patients requiring opioid therapy
Documents reviewed: \\CDESUB1\N21610\N_000\2003-07-17\cmc
Project manager: Lisa Basham-Cruz
Chemistry reviewer: Jila Boal, Ph.D.
Dates: NDA Received 12/19/02; user fee (10 months) 10/19/03;
Statistical reviewer: Dionne L. Price, Ph.D.
Secondary reviewer: Karl Lin, Ph.D.
Biometrics division director: S. Edward Nevius, Ph.D.

Keywords: NDA review, stability

1 INTRODUCTION

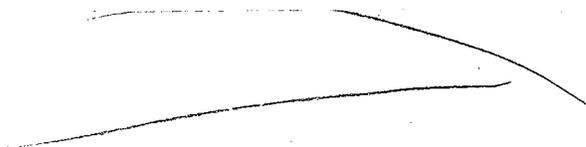
Endo Pharmaceuticals has submitted data for three batches of Oxymorphone extended release 5 mg, 10 mg, 20 mg, and 40 mg, respectively. Each batch is tested through 6 months at 40°C/75% RH and through 24 months at 25°C/60% RH. Of note, only 18 months of data are reported for two of the 5 mg batches. Batches are packaged in bottles and bottles. The sponsor has proposed expiration dating of 36 months.

2 STATISTICAL REVIEW AND EVALUATION

Assays were reported for Oxymorphone extended release (ER) only. The sponsor evaluated the data via a linear regression model. The sponsor provided the following description of the planned analysis:

Analysis was done by using SAS/PROC GLM, including non-valued placeholder data to generate confidence levels of prediction at monthly intervals for all lots. In effect, this method creates an interval for every study, with the slopes estimated according to the selected model. At each month, the 'most extreme' interval bound is found, and the composite 'most extreme' boundary is indicated on the displayed figures to demonstrate the performance of the product.

Results are depicted in the sponsor's graph below. The sponsor concluded that the assay would remain within the specification through 36 months.



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The sponsor's analysis appeared to pool the data from different strengths and containers. Since certain assumptions of homogeneity were not justified, the pooling of the data may have been inappropriate. Therefore, I additionally analyzed the stability data utilizing the FDA tool, e-review for stability analysis. For the data provided, I assumed the degradation of oxymorphone ER was explained via a linear relationship. The e-review tool initially tested the "batch poolability". Thus, the underlying algorithm fitted linear regression models to the batches (per package and dose) and applied tests for equality of slopes and/or intercepts. Batches were pooled for analysis only if neither the slopes nor the intercepts were significantly different at the level of α . The degradation pattern of oxymorphone ER arising from dissimilar batches was described via models with separate intercepts and slopes or via models with separate intercepts and common slopes. The expiration date for pooled batches was determined by the intersection of the 95% lower confidence bound and the lower specification limit. The expiration date for batches with common slope and separate intercept was the minimum of the three intersections. My results are depicted in the table below:

Assay	Selected Model	Expiration Date
5 mg (bottle)	Common slope and separate intercepts	
5 mg (bottle)	Common slope and separate intercepts	
5 mg (blister)	Common slope and separate intercepts	
10 mg (bottle)	Common slope and intercept	
10 mg (bottle)	Common slope and intercept	
10 mg (blister)	Common slope and intercept	
20 mg (bottle)	Common slope and intercept	
20 mg (bottle)	Common slope and separate intercepts	
20 mg (blister)	Common slope and intercept	
40 mg (bottle)	Common slope and intercept	
40 mg (bottle)	Common slope and intercepts	
40 mg (blister)	Common slope and separate intercepts	

3 CONCLUSIONS AND RECOMMENDATIONS

Endo Pharmaceuticals submits stability data for 24 months. Evaluation of the data suggests that the 24-month data are within the specifications and support extrapolation to 36 months. The sponsor requests a 36-month expiry dating period; however, the request assumes the degradation pattern will continue throughout a prolonged period of time. An extension beyond 36 months may be requested in the future when data are available to support a longer expiry-dating period. Twenty-four-month stability data are provided for one 5 mg batch; therefore, the data support extrapolation to twenty-four months for the 5 mg dose.

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Statistical Review and Evaluation CLINICAL STUDIES

NDA: 21-610 and 21-611
Name of drug: Oxymorphone Extended Release (ER) and
Oxymorphone Immediate Release (IR)
Applicant: Endo Pharmaceuticals
Indication: Treatment of moderate to severe pain in patients requiring
opioid therapy
Documents reviewed: \\CDESUB1\N21610\N_000\2002-12-19\clinstat
\\CDESUB1\N21611\N_000\2002-12-20\clinstat
Project manager: Lisa Basham-Cruz
Clinical reviewer: Shaun Comfort, M.D.
Dates: Received 12/19/02; user fee (10 months) 10/19/03;
Received 12/20/02; user fee (10 months) 10/20/03
Statistical reviewer: Dionne L. Price, Ph.D.
Statistics team leader: Thomas Permutt, Ph.D.
Biometrics division director: S. Edward Nevius, Ph.D.

Keywords: NDA review, clinical studies

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