1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS AND RECOMMENDATIONS

Endo Pharmaceuticals has proposed oxycodone extended release (ER) and oxycodone immediate release (IR) for the management of moderate to severe pain where the use of an opioid is appropriate. The former formulation is intended for use in a chronic pain setting while the latter is recommended for acute pain. My evaluation suggests that varying evidence of efficacy exist for the proposed use of oxymorphone ER. There is statistical support of the analgesic efficacy of the drug product in the chronic low back pain population. Some support is additionally garnered from a study of postoperative pain. However, the effectiveness is not convincingly demonstrated in two studies conducted in the osteoarthritis population. Specifically, the results are sensitive to the procedure for handling missing data. The sponsor also claims that oxymorphone IR produces greater analgesic efficacy than placebo as measured by the magnitude of pain relief. The claim is substantiated via the data reviewed.

Based on my collective evaluation of NDA 21-610 and NDA 21-611, I conclude that statistical evidence supports the use of oxymorphone ER and oxymorphone IR in the management of moderate to severe pain where an opioid is appropriate.

1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

The currently proposed oxymorphone ER and oxymorphone IR tablet formulations were introduced to the Division of Anesthetic, Critical Care, and Addiction Drug 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. 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, respectively. 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 of the drug product formulations was derived from six randomized, double-blind, multicenter, and placebo-controlled trials.

Studies EN3202-15 and EN3202-25 were conducted in the osteoarthritis population. Eligible patients in the former study were randomized to oxymorphone ER 20 mg, oxymorphone ER 40 mg, OxyContin® 20 mg, or placebo. In EN3202-25, study participants were randomized to oxymorphone ER 10mg, oxymorphone ER 20 mg, oxymorphone 50 mg, or placebo. The primary endpoint in both studies was the change in arthritis pain intensity (measured via visual analog score) from baseline to the end of the respective studies. Analyses employed an analysis of covariance model with treatment

and center as main effects and baseline pain as covariate (in EN3202-15) and Tukey's modified linear trend test (in EN3202-25). In study EN3202-15, the sponsor concluded that oxymorphone ER 40 mg provided significantly greater mean pain reduction as compared to placebo. Similarly, the 40 mg and 50 mg doses of oxymorphone ER provided significantly greater pain relief as compared to placebo in EN3202-25.

In study EN3202-16, eligible individuals with chronic lower back pain were randomized to oxymorphone ER and OxyContin® for a dose titration phase. Patients who attained a fixed dose during the titration phase proceeded to an 18-day double-blind treatment phase with 1/3 of the patients re-randomized to placebo. The primary efficacy endpoint was the change in pain intensity from baseline to the end of the treatment period. The endpoint was analyzed via an ANCOVA model with factors similar to those used in previous studies. The sponsor concluded that pain intensity was significantly reduced among patients receiving oxymorphone ER as compared to patients receiving placebo.

Following discontinuation of IV opioid patient-controlled analgesia (PCA), eligible patients having undergone knee arthroplasty were randomized to oxymorphone ER 20 mg or placebo in study EN3202-12. The primary measures of efficacy included the total pain relief through 8 hours and an integrated rescue PCA and pain intensity recall score at 0–12 hours. Analyses employed ANCOVA and ANOVA models. A greater analgesic effect was achieved by the oxymorphone ER 20 mg group as compared to placebo. Moreover, oxymorphone ER 20 mg was superior to placebo as indicated by the statistically significant lower mean integrated measure.

The primary objective of Study EN3203-04 was to compare the analgesic efficacy of oxymorphone IR 10 mg, 20 mg, and 30 mg to placebo in patients with acute moderate to severe pain postoperative pain due to orthopedic surgery. The primary measure of efficacy, total pain relief over the 0–8 hour interval, was analyzed via an ANCOVA model. As further support of efficacy, this study also contained a multiple-dose phase as well as a dose response analysis of the primary endpoint. Study EN3203-05 was similar to EN3203-04; however, patients were randomized to oxymorphone IR 10 mg, oxymorphone IR 20 mg, oxycodone IR 15 mg, oxycodone IR 30 mg, or placebo. Oxymorphone IR 20 mg produced greater analgesic effects as compared to placebo in both studies. Moreover, the effect was also demonstrated in the 10 and 30 mg doses of oxymorphone IR in study EN3203-04.

1.3 PRINCIPAL FINDINGS

Recurrent concerns throughout NDA 21-610 and NDA 21-611 were the appropriateness of the analysis populations and the last observation carried forward (LOCF) strategy. In numerous studies, the intent-to-treat (ITT) population was utilized for efficacy evaluations. The population consisted of all randomized patients having at least one post-baseline measurement. An additional caveat of the defined ITT population in studies of acute pain was the exclusion of study participants who received rescue medication or withdrew within the first hour. In some studies, the analysis populations were not

consistent with the principle of intent-to-treat. Moreover, most studies utilized a last observation carried forward strategy to handle missing data. The agency previously recommended a thorough investigation of the pattern of withdrawal to offset concerns regarding the appropriateness of a LOCF strategy and subsequent conclusions. The concern regarding the missing data strategy was most evident in studies EN3202-15 and EN3202-25 where a disproportionately large number of discontinuations due to adverse events existed among participants receiving active treatments. My reanalysis of data incorporating all randomized participants and an alternative strategy for missing data resulted in conclusions that differed from those of the sponsor for studies EN3202-15 and EN3202-25.

Based on my collective evaluation of NDA 21-610 and NDA 21-611 as well as historical precedents of study requirements of approved opioids, I conclude that some statistical evidence exists to support the use of oxymorphone ER and oxymorphone IR in the management of moderate to severe pain. The strongest support is derived from study EN3202-16 for the ER formulation and studies EN3203-04 and EN3203-05 for the IR formulation.

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION AND BACKGROUND

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 sponsor, Endo Laboratories, withdrew the oral tablet formulations in 1979. The currently proposed extended release and immediate release tablet formulations were introduced to the Division of Anesthetic, Critical Care, and Addiction Drug 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 sponsor submitted NDA 21-610 and NDA 21-611 for oxymorphone extended release tablets and oxymorphone immediate release tablets, respectively. 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 is appropriate.

2.2 DATA ANALYZED AND SOURCES

Primary support of the extended release (ER) formulation is derived from four randomized, double-blind, multicenter trials, namely EN3202-12, EN3202-15, EN3202-16, and EN3202-25. Similarly, evidence for the immediate release (IR) formulation is derived from two trials, namely EN3203-04 and EN3203-05. The drug

applications were completely electronic. The study reports and data were archived in the Food and Drug Administration internal electronic document room under the network path locations \\CDESUB1\N21610\N_000\2002-12-19 and \\CDESUB1\N21611\N_000\2002-12-20. A summary of the studies is provided in Table 1. The sponsor additionally submitted three studies to provide supportive efficacy data. The studies are also provided in the table.

Table 1: Table 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	• Oxymorphone ER 20 mg (65) • Placebo (61)	• 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	• Oxymorphone ER 20 mg (116) • Oxymorphone ER 40 mg (117) • OxyContin® 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	• Oxymorphone ER (80) • OxyContin® (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	• 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
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	• 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
EN3203-05 Multicenter (9)	Double-blind, parallel group, placebo and active controlled, single dose study in patients with pain following orthopedic surgery	• 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
EN3202-17	Open-label, sequential crossover study in patients with cancer pain	• Oxymorphone ER • OxyContin® • Morphine ER	Daily pain intensity

Study Number Number of centers(n)	Study Design	Treatment Arms and Number of randomized patients at baseline (n)	Primary measure of efficacy
EN3202-18	Double-blind, crossover study in patients with cancer pain	• Oxymorphone ER • Morphine ER	Average daily pain intensity
EN3202-19	Double-blind, crossover study in patients with cancer pain	• Oxymorphone ER • OxyContin®	Average daily pain intensity

2.3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY / SAFETY

Oxymorphone extended release (ER) is proposed for "the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid therapy for an extended period of time." Efficacy has been evaluated via four studies in patients with moderate to severe pain, chronic low back pain, and post surgical pain. Oxymorphone immediate release (IR) is proposed for "the management of moderate to severe pain where the use of opioid is appropriate." Efficacy has been evaluated via two studies composed of patients with acute moderate to severe pain following orthopedic surgery.

2.3.1 STUDY DESIGNS

Due to the varying designs of the studies, the main body of my review will discuss each individual study.

2.3.1.1 Study EN3202-12

Study EN3202-12 consisted of individuals who had undergone knee arthroplasty. Prior to the day after surgery, patients received intermittent bolus doses of opioids followed by IV opioid patient-controlled analgesia (PCA). Following discontinuation of PCA, patients experiencing moderate to severe pain as measured by a categorical pain intensity scale and a visual analog scale (VAS) were randomized to oxymorphone ER 20 mg or placebo. Patients subsequently received treatment at 12 and 24 hours after the initial dose. Self-assessments of pain were recorded in patient diaries at 0.25, 0.50, 0.75, 1, and 1.5 hours and hourly thereafter through hour 8.

2.3.1.2 Study EN3202-15

Eligible patients with osteoarthritis of the knee or hip entered a 2 to 7 day washout period during which analgesic use was discontinued. Patients experiencing moderate to severe pain were randomized to oxymorphone ER 20 mg, oxymorphone ER 40 mg, OxyContin® 20 mg, or placebo. Treatment was administered every 12 hours for 4 weeks; however, patients randomized to oxymorphone ER 40 mg or OxyContin® 20 mg received half of the randomized dose during the first two weeks and the assigned doses for the treatment duration. Assessments of pain were made at weekly visits. Moreover, patients recorded pain intensity (measured via VAS) in daily diaries.

2.3.1.3 Study EN3202-16

Study EN3202-16 consisted of individuals with a confirmed diagnosis of moderate to severe, chronic lower back pain requiring opioid therapy. Following screening, eligible patients were randomized to oxymorphone ER or OxyContin® and entered a 7 to 14 day double-blind dose titration phase. Patients who attained a fixed dose during the titration phase proceeded to an 18 day double blind treatment phase. Approximately 2/3 of the subjects continued to receive the same, active study medication taken during the titration phase while the remaining 1/3 received placebo. Subjects maintained a daily dairy and recorded pain intensity and pain relief before each dose and 4 hours after the morning dose.

2.3.1.4 Study EN3202-25

Eligible patients with osteoarthritis of the knee or hip entered a 2 to 7 day washout period during which all analgesic use was discontinued. Patients experiencing moderate to severe pain were randomized to one of the following four treatment regimens: oxymorphone ER 10 mg during weeks 1 and 2, oxymorphone ER 20 mg during week 1 and oxymorphone ER 40 mg during week 2, oxymorphone ER 20 mg during week 1 and oxymorphone 50 mg during week 2, or placebo throughout study duration. Patients received study medication twice a day. Pain was assessed via the arthritis pain intensity VAS at weekly clinic visits.

2.3.1.5 Study EN3203-04

Study EN3203-04 consisted of patients with pain following total hip or knee replacement (or revision surgery provided the patients had an osteotomy). Following discontinuation of analgesic medication, eligible patients were randomized to a single dose of oxymorphone IR 10 mg, oxymorphone IR 20 mg, oxymorphone IR 30 mg, oxycodone IR 10 mg, or placebo. Assessments of pain were recorded at 0.25, 0.50, 0.75, 1.0, and 1.5 hours and hourly thereafter through hour 8. "Patients who tolerated the initial dose and requested re-medication ≥ 3 hours after the initial dose, or completed the 8 hours of assessments continued into the multiple-dose phase." During the multiple-dose phase, patients received active treatments every 4 to 6 hours as needed for 48 hours. Patients previously randomized to placebo were re-randomized to one of the four active treatments. Patients maintained a diary recording their worse daytime and nighttime pain intensities.

2.3.1.6 Study EN3202-05

The primary design of study EN3203-05 mimicked that of EN3202-04. Study 3203-05 did not contain a multiple-dose phase, and the study population consisted of patients

experiencing pain after orthopedic surgery. Moreover, patients were randomized to oxymorphone IR 10 mg, oxymorphone IR 20 mg, oxycodone IR 15 mg, oxycodone IR 30 mg, or placebo.

2.3.2 STATISTICAL METHODOLOGIES

2.3.2.1 Study EN3202-12

The primary objective of Study EN3202-12 was to investigate the analgesic efficacy of oxymorphone ER 20 mg in patients with moderate to severe postoperative pain. The study employed two evaluations of efficacy namely, a standard analgesic evaluation and a patient-controlled analgesia (PCA) opioid dose sparing evaluation. The primary measure of efficacy for the former evaluation was the total pain relief through 8 hours. The measure was defined as the area under the curve from 0 to 8 hours and was computed as the sum of the weighted assessments of pain relief. Pain relief was represented as a categorical outcome ranging from 0 (no relief) to 4 (complete relief). The primary measure of efficacy for the PCA-opioid dose sparing evaluation was the integrated rescue PCA and pain intensity recall score at 0–12 hours. Of note, the pain intensity recall score was measured on a 100 mm visual analog scale where 0 mm indicated no pain and 100mm indicated extreme pain. The integrated assessment was proposed by Silverman et al.[1] and was used as a tool to collectively assess efficacy via both pain scores and supplemental analgesic requirements. The integrated variable was computed by initially ranking individual observations for each component, namely pain intensity relief score and rescue use. The per-patient components were then expressed as percent differences from the respective mean ranks. The integrated variable was derived as the sum of the percent differences for each component (on a per-subject basis).

The efficacy endpoint, total pain relief through 8 hours, was analyzed via an analysis of covariance (ANCOVA) model with treatment and center as main effects and baseline pain intensity as a covariate. The integrated rescue PCA and the pain intensity recall variable was analyzed via an analysis of variance (ANOVA) model with treatment and center as main effects. In analyses of both efficacy endpoints, the consistency of the results across center was assessed by including a treatment-by-center interaction in the model.

Several secondary endpoints of interest included total pain relief at the 0-4, 0-6, and 0–12 hour time intervals, sum of pain intensity differences, time to rescue medication, time to meaningful pain relief, and pain relief at each assessment time point. Onset of meaningful pain relief was defined as the elapsed time from dosing to the patient's recognition of "meaningful" pain relief utilizing a stopwatch. Similarly, the time to re-medication was defined as the elapsed time from dosing to administration of rescue

[1] Silverman DG, O'Connor TZ, Brull SJ. Integrated assessment of pain scores and rescue morphine use during studies of analgesic efficacy. Anest Analg. 1993; 77; 168-70.

medication. Analysis pertaining to the onset of pain relief and time to re-medication included use of the Kaplan-Meier estimator to obtain percentiles for each treatment group and log-rank tests for treatment comparisons. Pain relief was analyzed via an ANOVA model with treatment and center as factors.

Analyses for the standard analgesic evaluation were performed on the intent-to-treat (ITT) population consisting of all randomized patients receiving the study medication and having completed 1-hour efficacy evaluation without requiring rescue medication. The ITT population for the dose sparing evaluation included all randomized patients receiving the study medication and having completed the 12-hour efficacy evaluation. A last observation carried forward (LOCF) strategy was utilized to handle missing data.

2.3.2.2 Study EN3202-15

A primary objective of Study EN3202-15 was to compare the analgesic efficacy of oxymorphone ER 40 mg to placebo in patients with moderate to severe pain due to osteoarthritis. The efficacy endpoint was the change in arthritis pain intensity from baseline to week 3. Pain intensity was assessed utilizing a VAS ranging from 0 mm (no pain) to 100 mm (extreme pain). An ANCOVA model with treatment and center as main effects and baseline pain as covariate was employed for the efficacy analysis. Each center was weighted in the model according to the number of subjects (utilizing the OM option in SAS).

A secondary objective of the study was to compare oxymorphone ER 20 mg and placebo. Secondary efficacy measures included the WOMAC osteoarthritis index pain, stiffness, and physical function subscale scores, the global assessment of osteoarthritis, and the SF-36 health survey.

Analyses were performed on the intent-to-treat (ITT) and intent-to-treat 2 (ITT2) populations. The ITT population included all randomized patients having information at the baseline and week 1 (or later) visit. The ITT2 population was characterized more broadly and included patients having at least one post-baseline assessment. The post-baseline score was retrieved from diary records for those patients withdrawing prior to the week 1 visit. A last observation carried forward strategy was utilized to handle missing data. If patients in the ITT population withdrew due to lack of treatment effect prior to week 1, the baseline observation was carried forward.

2.3.2.3 Study EN3202-16

Study EN3202-16 was an evaluation of oxymorphone ER relative to placebo in subjects with chronic low back pain. The primary efficacy endpoint was the change in pain intensity from baseline to the end of treatment (visit 6). The baseline value was defined as the last pain intensity score recorded at the end of the titration period. Pain intensity was measured using a VAS score. The endpoint was analyzed via an ANCOVA model

with treatment and center as effects and baseline pain as a covariate. Moreover, each center was weighted in the model according to the number of subjects (utilizing the OM option in SAS). The sponsor stated, "No adjustment was made for multiple comparisons. The comparison of oxycodone with placebo was made in order to verify the sensitivity of the trial." Of note, OxyContin® (the tradename) and oxycodone (the active ingredient) were used interchangeably by the sponsor throughout NDA 21-610.

Secondary measures of efficacy included (but were not limited to) the percent change in pain intensity from baseline, mean daily pain intensity, pain relief, and amount of rescue medication used. Analysis methods were described in detail and included ANCOVA and ANOVA modeling as well as the use of rank-sum test for various endpoints.

Analyses were performed on a modified ITT population consisting of all randomized patients completing the titration phase, receiving one dose of study medication, and having at least one post-baseline assessment. A LOCF strategy was utilized to handle missing data.

2.3.2.4 Study EN3202-25

The primary objective of Study EN3202-25 was to assess the analgesic efficacy dose response of oxymorphone ER 10 mg, 40 mg, 50 mg, and placebo in patients with moderate to severe pain due to osteoarthritis. The efficacy endpoint was change from baseline to the final visit in arthritis pain intensity VAS score. Tukey's modified linear trend test was employed to assess efficacy. The methodology of Tukey focused on "identifying a dose such that, when all doses (including controls) up to and including the given dose are considered together, there is no statistically trustworthy evidence of the drug's impact on the response in question."[2] The step-down procedure utilized treatments as regressors in the linear regression model. Additionally, the sponsor used an ANOVA model with factors for treatment and center. Since Tukey's trend test included considerations for multiplicity, no further adjustments for multiple comparisons were performed, according to the sponsor.

Secondary variables included changes from baseline in the WOMAC osteoarthritis pain, stiffness, and physical function subscale scores as well as global assessments of osteoarthritis. The analysis plan for the secondary measures mimicked those of the primary endpoint.

Analyses were performed on the ITT population consisting of all randomized patients receiving the study medication and having at least one post-baseline assessment of

[2] Tukey J, Ciminera J, and Heyse J. Testing the statistical certainty of response to increasing doses of a drug. *Biometrics* 1985; 41:295-301.

efficacy. Similar to other studies conducted, a LOCF strategy was utilized to handle missing data.

2.3.2.5 Study EN3203-04

The primary objective of Study EN3203-04 was to compare the analgesic efficacy of oxymorphone IR 10 mg, 20 mg, and 30 mg to placebo in patients with acute moderate to severe pain postoperative pain due to orthopedic surgery. The primary measure of efficacy, total pain relief over the 0–8 hour interval, was analyzed via an ANCOVA model similar to that of study EN3202-12. The measure was defined as the area under the pain relief curve where pain relief was represented as a categorical outcome ranging from 0 (no relief) to 4 (complete relief). An examination of the consistency of results across centers was conducted by including a treatment-by-center interaction in the model. Comparisons between the varying doses of oxymorphone and placebo were conducted using a pre-defined step-down procedure. According to the sponsor, "comparisons of oxycodone versus placebo were performed to verify the sensitivity of the study." In addition, several secondary endpoints were identified and included: total pain relief through 4 and 6 hours, sum of pain intensity difference through 4, 6, and 8 hours, time to meaningful pain relief, and time (in hours) to re-medication.

Analyses were performed on the "evaluable" patient population consisting of randomized patients receiving the study medication and completing the first hour efficacy evaluation without remedicating or vomiting. The sponsor employed a LOCF strategy to handle missing data. Moreover, analyses were repeated utilizing a baseline observation carried forward strategy.

As further support of efficacy, this study also contained a multiple-dose phase as well as a dose response analysis of the primary endpoint. The dose response analysis was performed via a regression model of total pain relief using oxymorphone IR dose as a regressor. In the multiple dose-phase, the efficacy endpoints included the worst daytime and nighttime pain and global evaluation of study medications. Only data summaries were provided for the endpoints.

2.3.2.6 Study EN3203-05

The primary objective of Study EN3203-05 was to compare the analgesic efficacy of oxymorphone IR 10 mg and 20 mg to placebo in patients with acute, moderate to severe postoperative pain due to orthopedic surgery. The analysis methodology of study EN3203-05 was very similar to that of EN3203-04. The ANCOVA model varied in that the surgery site effect was not needed due to a varying patient population. In addition, a multiple-dose phase was not conducted in study EN3203-05. A secondary objective of study EN3202-05 was to assess the relative potency of oxymorphone IR compared to

oxycodone. Parallel line assay (Reeve[3]) and regression analyses were performed to obtain estimates of relative potency.

2.3.3 SPONSOR'S RESULTS AND CONCLUSIONS

2.3.3.1 Study EN3202-12

A greater analgesic effect (as measured by total pain relief through 8 hours) was achieved by the oxymorphone ER 20 mg group as compared to placebo. Moreover, oxymorphone ER 20 mg was superior to placebo as indicated by the statistically significant lower mean integrated rescue PCA and pain intensity score among the former group. The differences in time to meaningful pain relief and time to rescue medication between active treatment and placebo were not statistically different.

2.3.3.2 Study EN3202-15

Oxymorphone ER 40 mg provided significantly greater mean pain reduction at weeks 3 and 4 as compared to placebo. The result was further supported by analysis of the ITT2 population. Although the comparisons between other active treatments in the study and placebo were not of primary focus, the sponsor noted that pain reduction did not differ among the active treatment groups and placebo for the ITT population. However, supportive analyses of the ITT2 population did yield a statistically significant difference in pain reduction among oxymorphone ER 20 mg and placebo.

2.3.3.3 Study EN3202-16

Pain intensity among patients in the oxymorphone ER group was significantly reduced as compared to patients receiving placebo. A greater reduction in pain intensity was also noted among the oxycodone group (as compared to placebo).

2.3.3.4 Study EN3202-25

In study EN3202-25, oxymorphone 40 mg and oxymorphone 50 mg provided significantly greater pain relief than placebo. There was no difference in the change in pain intensity score among the oxymorphone 10 mg and placebo groups. According to the sponsor, "Patients in the oxymorphone 10 mg group showed a clinically meaningful improvement in pain intensity; however, the absence of a statistically significant difference was due, at least in part, to the large response in the placebo group."

[3] Reeve R. Two statistical methods for estimating relative potency of bioassays, BioPharm 2000; July:54-60.

2.3.3.5 Study EN3203-04

Each dose of oxymorphone IR (10, 20 and 30 mg) produced greater analgesic effects (measured by total pain relief through 8 hours) as compared to placebo. In contrast, no difference was found to exist between oxycodone IR 10 mg and placebo. In addition, the sponsor asserted that oxymorphone IR exhibited a statistically significant dose-response relationship. The time to meaningful time relief was significantly shorter for patients receiving oxymorphone IR as compared to placebo. The time to re-medication was significantly longer for patients in the oxymorphone IR 20 mg and oxymorphone IR 30 mg groups as compared to placebo. The sponsor further concluded that the analgesic efficacy in the multiple dose-phase was demonstrated. Specifically, the mean worst pain "was similar among the active treatment groups on day 1 and improved slightly on days 2-3." Moreover, the median dose intervals (averaged over three days) for all treatment groups were slightly longer than the 4–6 hour dosing recommendation.

2.3.3.6 Study EN3203-05

Oxymorphone IR 20 mg provided significantly greater pain relief as compared to placebo. Although the comparisons of oxycodone IR were not of primary interest, the sponsor further noted that oxycodone IR 15 mg and 30 mg also provided significantly greater pain relief as compared to placebo. Additionally, no significant differences existed among the oxycodone IR treatments for the primary endpoint. Due to the lack of a dose response relationship among the oxycodone groups, the sponsor stated "Analgesic modeling could not be applied and, therefore, no conclusion can be drawn regarding the relative analgesic potency of oxycodone and oxymorphone".

2.3.4 DETAILED REVIEW OF INDIVIDUAL STUDIES

2.3.4.1 Study EN3202-12

Utilizing estimates from previous studies, a sample size of 100 patients was determined to be sufficient to detect a difference of 7 in total pain relief through 8 hours between oxymorphone ER 20 mg and placebo with at least 90% power. The calculation assumed a standard deviation between 8 and 10. The study was conducted at 14 centers; however, 3 centers were pooled for analysis.

In the study, 59% of participants were female, and 87% of participants were Caucasian. The ages of subjects ranged from 33 to 85 with a mean age of 66. Baseline characteristics of interest included height and weight. Demographic and baseline characteristics did not differ between treatment arms. Detailed tables outlining the composition of the samples with respect to the demographic and baseline characteristics are presented in the appendix.

Nineteen percent of the patients randomized to oxymorphone ER 20 discontinued from the study as compared to eight percent among participants randomized to placebo.

Participants withdrew for varying reasons including insufficient therapeutic effect, adverse events, and patient or investigator request to withdraw. Of the 126 randomized patients, 104 of the subjects were included in the ITT population for the standard analgesic evaluation. One hundred and sixteen patients were included in the ITT population for the opioid dose sparing evaluation.

Tables 2-3 depict the results of the sponsor's analysis on the primary efficacy variables, total pain relief and the integrated rescue PCA and pain intensity recall score. The tables were generated via the methodology outlined in Section 2.3.2.1. Based on the results in the tables, the sponsor concluded that a greater analgesic effect (as measured by total pain relief through 8 hours) was achieved by the oxymorphone ER 20 mg group as compared to placebo. The aggregate assessment of rescue-PCA and pain intensity score further provided evidence of the analgesic effect of oxymorphone ER 20 mg. The sponsor additionally examined pain relief at each time assessment. Results are depicted in Figure 1.

Table 2: Total Pain Relief at 0–4, 0–8, 0–12 Hour Time Intervals
(as presented by the sponsor)

Treatment/ Analysis Factor	TOTPAR at 4 Hours	TOTPAR at 6 Hours	TOTPAR at 8 Hours	TOTPAR at 12 Hours
OCR 20 (N=53)	5.67 (4.00) A [4]	8.47 (6.18) A	11.26 (8.41) A	19.30 (14.70) A
Placebo (N=51)	4.33 (3.28) B [4]	6.21 (5.06) B	8.09 (6.89) B	13.72 (12.19) B
LS Mean Difference	1.77	2.89	4.01	7.07
Treatment P-value [2]	0.0110 *	0.0068 **	0.0057 **	0.0056 **
95% CI of Difference	(0.42, 3.12)	(0.82, 4.96)	(1.20, 6.83)	(2.13, 12.02)
Trt*Baseline P-value [3]	0.7114	0.8967	0.9903	0.9847
Trt*Site P-value [3]	0.6628	0.5497	0.4924	0.3166
RMS Error [2]	3.377	5.176	7.030	12.361

*, **, ***: P-value significant at level 0.05, 0.01, or 0.001 respectively.
[1] Data presented: mean (standard deviation) using LOCF.
[2] Model: TOTPAR = mu + Ti + PI(0)j + Ck + error.
[3] Model: TOTPAR = mu + Ti + PI(0)j + Ck + TPI(0)ij + TCik + error.
[4] From Fisher's protected LSD comparisons and based on model [2] LSMEANS. Treatments with the same letter are not significantly different from each other.

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Table 3: Integrated Rescue PCA and Pain Intensity Recall Scores at 0–6, 0–12, and 0–24 Hour Tim e Intervals for PCA-Opioid Dose Sparing Evaluation
(as presented by sponsor)

Time Interval Statistics	--- OCR 20 --- N=58	-- Placebo -- N=58	------ Inferential Statistics---- Source	p-value
0-6 Hours				
N	50	51	Treatment [2]	0.0004 **
Mean	-25.33	24.84	Site [2]	0.0308 *
Standard Deviation	87.669	84.246	Treatment*Site [3]	0.7567
Minimum	-184.3	-122.5		
Lower Quartile	-83.33	-31.37		
Median	-46.08	10.78		
Upper Quartile	19.61	90.20		
Maximum	194.1	168.6		
0-12 Hours				
N	**49**	**53**	**Treatment [2]**	**0.0010**
**				
Mean	**-21.00**	**19.42**	**Site [2]**	**0.0004**
**				
Standard Deviation	**89.246**	**87.979**	**Treatment*Site [3]**	**0.6954**
Minimum	**-171.8**	**-159.2**		
Lower Quartile	**-105.83**	**-39.81**		
Median	**-11.65**	**34.95**		
Upper Quartile	**39.81**	**84.47**		
Maximum	**172.8**	**188.3**		
0-24 Hours				
N	47	53	Treatment [2]	0.0024 **
Mean	-22.62	20.06	Site [2]	0.0075 **
Standard Deviation	90.184	84.164	Treatment*Site [3	0.8811
Minimum	-181.2	-172.3		
Lower Quartile	-95.05	-26.73		
Median	-20.79	18.81		
Upper Quartile	40.59	83.17		
Maximum	167.3	186.1		

*, **, ***: P-value significant at level 0.05, 0.01, or 0.001 respectively.
[1] For each time interval, the integrated scores were calculated by:
(a) Rank the averages of pain intensity recall scores and rescue PCA doses separately, and calculate the percent differences from the mean rank.
(b) Add the percent differences from mean rank for pain intensity recall score and for rescue PCA dose.
[2] From two-way analysis of variance with treatment and pooled investigational site as factors.
[3] From two-way analysis of variance with treatment, pooled investigational site, and their interaction as factors.

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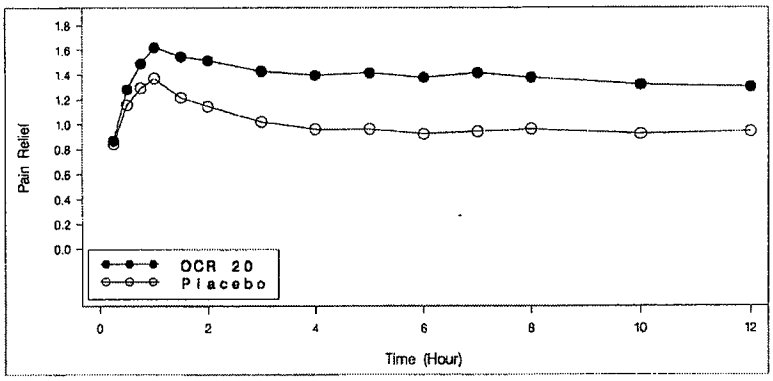
Figure 1: Pain Relief (0–12 hour) for the Standard Analgesic Evaluation



	ASSESSMENT TIME POINTS						
TREATMENT	4 HR	5 HR	6 HR	7 HR	8 HR	10 HR	12 HR
OCR 20 (N=53)	1.40 (1.13) 19 A [4]	1.42 (1.22) 16 A	1.38 (1.11) 14 A	1.42 (1.17) 13 A	1.38 (1.18) 13 A	1.32 (1.16) 9 A	1.30 (1.14) 8 A
Placebo (N=51)	0.96 (1.00) 17 B [4]	0.96 (1.06) 13 B	0.92 (0.91) 7 B	0.94 (0.93) 6 B	0.98 (0.98) 6 B	0.92 (0.91) 3 B	0.94 (0.95) 3 B
Treatment P-value [2]	0.0143 *	0.0149 *	0.0078 **	0.0077 **	0.0178 *	0.0228 *	0.0322 *
Trt*Site P-value [3]	0.4962	0.4484	0.3115	0.3212	0.3818	0.1911	0.1965
RMS Error [2]	1.007	1.041	0.949	0.980	1.001	0.992	0.995

*, **, ***: P-value significant at level 0.05, 0.01, or 0.001 respectively.
[1] Data presented: mean (standard deviation) using LOCF.
[2] Model: pr = mu + Tl + Ck + error.
[3] Model: pr = mu + Ti + Ck + TCik + error.
[4] From Fisher's protected LSD comparisons and based on model [2] LSMEANS. Treatments with the same letter are not significantly different from each other.

Individuals who received rescue medication or withdrew within the first hour were excluded from the analysis population in the standard analgesic evaluation. The sponsor stated, " Patients who received a rescue analgesic dose before one hour were not included in the standard analgesia efficacy analysis, since the analgesic activity of the study medication would have been masked by the rescue medication." Although the sponsor's argument had merit, I believe valuable information may have potentially been lost due to the exclusion of individuals who receive rescue medication or withdrew within the first hour. I reanalyzed the data utilizing an analysis population consisting of all randomized patients. Results are displayed in Table 4. Based on my evaluation, I am in agreement with the sponsor regarding the overall conclusion that a greater analgesic effect was produced by oxymorphone ER 20 mg as compared to placebo. Due to the varying definition of the ITT population, the same concern was not warranted in the opioid dose sparing evaluation.

Table 4: Total Pain Relief at 0–8 hours, All Randomized (LOCF) for the standard analgesic evaluation

	Total Pain Relief at 8 hours
OCR 20 (N=65)	9.7 (8.6)
Placebo (N=61)	6.8 (7.0)
LS Mean Difference	3.8
p-value	0.01
95% CI	(1.2, 6.4)

OCR = Oxymorphone ER
Mean values and accompanying standard deviations are shown for each treatment arm.

2.3.4.2 Study EN3202-15

Sample size calculations were performed for the efficacy measure, arthritis pain intensity VAS score collected at patient visits. Based on data from a previous study and clinical consensus (according to the sponsor), a total of 240 patients were required to detect a 15 mm mean difference between two active treatments with a standard deviation of 23.4 mm. Of note, data originating from site 2 were not included in the analyses due to a drug diversion that occurred at that site.

In the study, 61% of participants were female, and 86% were Caucasian. The ages of subjects were between 40 and 89 with a mean age of 62. Baseline characteristics of interest included weight, height, duration of disease, and index joint. Demographic and baseline characteristics did not differ between treatment arms. Detailed tables outlining the composition of the sample with respect to demographic and baseline characteristics are presented in the appendix.

Of the 491 randomized patients, 45% discontinued. The majority of participants discontinued due to adverse events with the highest percentage of participants (47%) with adverse events occurring in the oxymorphone ER 40 mg arm. However, only 5% of participants randomized to placebo discontinued due to adverse events. Similar phenomena were evident when excluding the 18 patients from site 2.

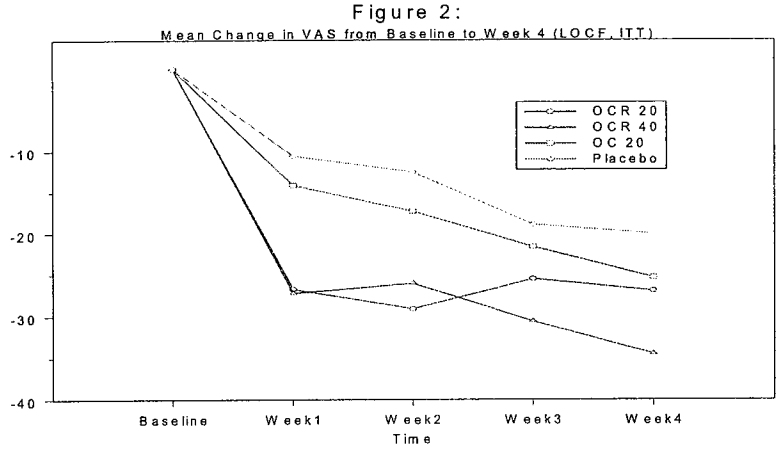
Table 5 and Figure 2 depict the results of the sponsor's analysis on the primary efficacy variable, mean change from baseline in arthritis pain intensity. The table was generated via the methodology outlined in Section 2.3.2.2.

Table 5:Mean at Baseline and LS Mean Change from Baseline in Arthritis Pain Intensity (VAS) - ITT Population Excluding Center 2 (LOCF)
(adapted from sponsor's presentation)

	Treatment	N	Mean(SE)	LSMean(SE)	LSMean Difference from Placebo	p-value	95% CI
Baseline	OCR40	75	78.7 (1.8)				
	OCR20	82	78.9 (1.9)				
	OC20	106	76.8 (1.5)				
	Placebo	113	79.3 (1.5)				
			Mean Change				
Week 3	**OCR40**	**71**	**-30.6 (3.5)**	**-29.8 (3.3)**	**-11.4**	**0.01**	**(-19.8, -3.0)**
	OCR20	78	-25.5 (3.0)	-25.3 (3.2)	-6.9	0.10	(-15.1,1.3)
	OC20	103	-21.6 (2.6)	-22.6 (2.8)	-4.2	0.28	(-11.7,3.4)
	Placebo	**111**	**-18.9 (3.1)**	**-18.4 (2.7)**			
Week 4	OCR40	71	-34.5 (3.4)	-33.7 (3.5)	-14.0	<0.01	(-22.8,-5.3)
	OCR20	78	-26.9 (3.2)	-26.6 (3.3)	-6.9	0.11	(-15.4, 1.6)
	OC20	103	-25.3 (2.8)	-26.1 (2.9)	-6.5	0.11	(-14.3, 1.4)
	Placebo	111	-20.0 (3.2)	-19.27(2.8)			

OCR = Oxymorphone ER and OC= Oxycodone
The primary efficacy variable comparison is bolded.

Figure 2:



I am not in agreement with the results due to two analysis concerns. First, the analyses were conducted on the ITT population defined as all randomized patients having information recorded at baseline and at the week 1 (or later) visit. This population excluded approximately 100 participants that dropped out prior to week 1. These participants may have withdrawn due to intolerable adverse events related to the medication. To ascertain as much information from the data as possible, the ITT2

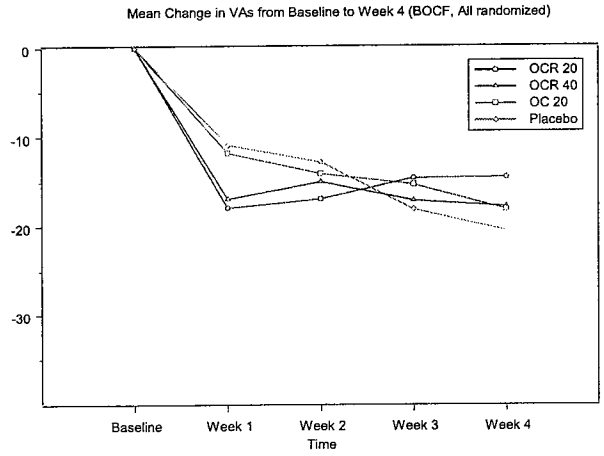
population was the more desirable analysis population. This population included all randomized patients having at least one post-baseline measurement where the post-baseline measurement was obtained from daily diary information. A second concern was the use of a LOCF strategy to handle missing data. Due to the disproportionately high numbers of patients discontinuing in the treatment arms (as compared to placebo), a LOCF strategy may have artificially inflated the effectiveness of treatment without accounting for the intolerability of the treatments. Due to my concerns, I reanalyzed the data considering all randomized patients and utilizing a baseline observation carried forward strategy to handle missing data. My results are depicted in Table 6. The results are also displayed graphically in Figure 3.

Table 6: Mean at Baseline and LS Mean Change from Baseline in Arthritis Pain Intensity (VAS) - All Randomized Population Excluding Center 2 (BOCF)

	Treatment	N	Mean(SE)	LSMean(SE)	LSMean Difference from Placebo	p-value	95% CI
Baseline	OCR40	117	78.3 (1.5)				
	OCR20	116	77.8 (1.5)				
	OC20	120	76.0 (1.5)				
	Placebo	119	79.4 (1.5)				
			Mean Change				
Week 3	**OCR40**	**117**	**-17.1 (2.5)**	**-16.9 (2.4)**	**0.7**	**0.85**	**(-6.0, 7.4)**
	OCR20	116	-14.6 (2.2)	-14.7 (2.4)	2.8	0.42	(-3.9,9.5)
	OC20	120	-15.3 (2.3)	-16.0 (2.4)	1.5	0.66	(-5.2,8.2)
	Placebo	**119**	**-18.1 (2.8)**	**-17.5 (2.4)**			
Week 4	OCR40	117	-17.8 (2.5)	-17.6 (2.5)	2.3	0.51	(-4.6,9.3)
	OCR20	116	-14.5 (2.4)	-14.6 (2.5)	5.3	0.14	(-1.7, 12.3)
	OC20	120	-18.1 (2.4)	-18.8 (2.5)	1.1	0.75	(-5.8, 8.1)
	Placebo	119	-20.5 (2.9)	-19.9 (2.5)			

OCR = Oxymorphone ER and OC= OxyContin®
The primary efficacy variable comparison is bolded.

Figure 3:



Based on my reanalysis of the data, I concluded that a statistically significant difference in mean pain reduction at Weeks 3 or 4 as compared to placebo had not been convincingly demonstrated. My results differed from those of the sponsor. Further discussion will be provided in Section 2.3.5.

2.3.4.3 Study EN3202-16

Utilizing estimates from EN3202-15, the sponsor determined that a sample of size 210 would be required to detect a treatment difference of 15 mm with a standard deviation of 31.6 with 80% power. The sample size was increased to 330 to compensate for an anticipated large number of drop-outs during the titration phase. The study was conducted at 23 sites; however, small centers were pooled as pre-specified. Of note, data originating from site 23 was not included in the analyses due to a drug diversion that occurred at that site.

In the study, 53% of participants were female, and 94% of participants were Caucasian. Individuals ranged in age from 22 to 82 with a mean age of 46. Baseline characteristics of interest included height, weight, and years with back pain. Demographic and baseline characteristics did not differ between treatment arms. Detailed tables outlining the composition of the samples with respect to the demographic and baseline characteristics are presented in the appendix.

Two hundred and thirty-five of the three hundred and thirty randomized patients entered the 18-day double-blind treatment period. Approximately 9% of patients randomized to oxymorphone ER or OxyContin® discontinued treatment while 23% of patients randomized to placebo discontinued. Most discontinuations were due to lack of efficacy.

Table 7 depicts the results of the sponsor's analysis performed on the primary efficacy variable, change from baseline to final visit in pain intensity. According to the sponsor, the average daily dose of oxymorphone was 79.4 mg.

Table 7: Change from Baseline to Final Visit in Pain Intensity (VAS Score), Assessed 4 Hours After Morning Study Medication, by Treatment
(as presented by the sponsor)

	Change in Pain Intensity (VAS, mm) from Baseline[a] to Final Visit[b]		
Statistic	Oxymorphone ER N=71	OxyContin N=75	Placebo N=67
n[c]	71	74	67
Mean	8.0	6.6	26.6
SD	24.22	25.34	25.80
Median	9.0	5.0	20.0
Min/Max	-44/85	-74/94	-32/93
LS mean difference versus placebo	-18.21	-18.55	
95% confidence interval for LS mean difference versus placebo	-25.83 to -10.58*	-26.12 to -10.98*	
P-value for LS mean difference versus placebo	0.0001*	0.0001*	

*Statistically significant difference between active treatment and placebo

[a]Baseline was defined as the last VAS pain intensity, 4 hours after study medication, recorded at the end of the titration period.

[b]If a subject discontinued early, the 4-hour VAS pain intensity from the subject's last diary record was used. If rescue medication was used after the morning dose and before the 4-hour evaluation, then the VAS recorded before rescue medication was used.

[c]If one or more subjects had missing data, then n≠N.

Of note, the positive values across treatment groups indicated that the pain intensity did increase from baseline; however, the increase taken in consideration with the large variability within treatment groups does not negate the overall conclusion.

In the design of the study, approximately 1/3 of study participants receiving oxymorphone ER or OxyContin® during the titration phase received placebo during the double-blind phase. The sponsor pooled the two differently treated placebo groups in the analysis. In correspondences dated 31 August 2000 and 14 November 2002, the agency expressed concern regarding the appropriateness of pooling the two placebo groups if the groups were not comparable. Subsequently, the sponsor compared the VAS pain intensity scores between the placebo groups. Differences were not found to exist between placebo subjects randomized to oxymorphone ER during the titration phase and placebo subjects randomized to OxyContin®. In addition, analyses of per day data for the treatment duration yielded no significant differences.

The aforementioned analysis of comparability appears reasonable. To further validate the results, I additionally analyzed the data assuming four distinct treatment groups. Based on my statistical evaluation of the study, I conclude that oxymorphone ER provides an analgesic effect as measured by reduction in pain intensity.

2.3.4.4 Study EN3202-25

A sample size of 240 was required to detect a 14 mm difference (assuming a standard deviation of 23.4 mm) between groups with 90% power. The assumptions utilized in the sample size calculation were based on findings of Bellamy et al[4,5]. The study was conducted at 33 centers; however, small centers were pooled.

Sixty-one percent of study participants were female, and ninety percent were Caucasian. The ages of subjects were between 30 and 93 with a mean age of 62. Baseline characteristics of interest included weight, height, index joint, functional class of osteoarthritis, and osteoarthritis signs and symptoms. According to the sponsor, differences in index joint at baseline were observed. Specifically the sponsor stated, "The proportion of patients who indicated a knee as the index joint was slightly higher in the oxymorphone 40 mg group (85%, 79/93 patients) and was slightly lower in the placebo group (75.8%, 69/91 patients), than in the remaining two groups (81.1% [77/95 patients] in the oxymorphone 10 mg group and 79.1% [72/91 patients] in the oxymorphone 50 mg group)." Detailed tables outlining the composition of the sample with respect to demographic and baseline characteristics are presented in the appendix.

Of the 370 randomized patients, 357 were included in the analysis population. Twelve of the randomized patients were excluded from the ITT population due to no post-baseline measurement. An additional person was excluded due to unblinding of the study medication. The rates of withdrawal among treatment groups were 62% in the oxymorphone 40 mg group, 59% in the oxymorphone 50 mg, 36% in the oxymorphone 10 mg group, and 29% in the placebo group. Most withdrawals were due to adverse events and the rate of withdrawal due to adverse events generally increased with dose.

The sponsor's results are depicted in Figure 4 and Table 8. The sponsor concluded that the higher doses of oxymorphone ER were "significantly superior" to placebo in reducing pain due to osteoarthritis. The conclusion was further supported by the significant linear dose-response relationship. However, no difference in pain relief was found to exist between the oxymorphone ER 10 mg and placebo groups.

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[4] Bellamy N, Carette S, Ford PM et al. Osteoarthritis Antirheumatic Drug Trials. II. Tables for calculating sample size for clinical trials. *J Rheumatol* 1992; 19: 444-50.

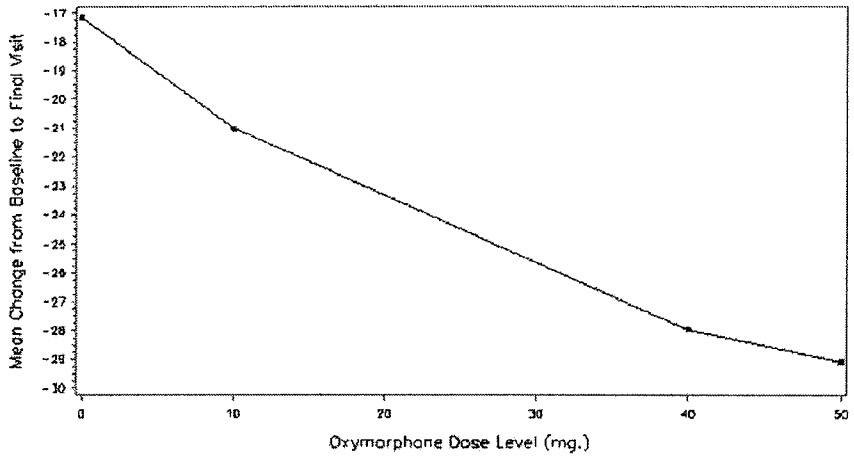
[5] Bellamy N, Carette S, Ford P and et al. Osteoarthritis Antirheumatic Drug Trilas III. Setting the delta for clinical trilas - results of a consensus development (Delphi) exercise. *J Rheumatol* 1992b;19(3):451-457.

Table 8: Change from Baseline to final visit in Arthritis Pain Intensity VAS Score - ITT Patients (as presented by the sponsor)

	Placebo (n=87)	Oxymorphone ER 10 mg (n=92)	Oxymorphone ER 40 mg (n=91)	Oxymorphone ER 50 mg (n=87)
Mean (SD)	-17.2 (29.6)	-21.0 (25.4)	-28.0 (32.0)	-29.4 (31.2)
LSMean (Std Err)	-17.0 (3.1)	-21.3 (3.0)	-28.1 (3.1)	-29.2 (3.1)
Treatment vs. Placebo LSMean Difference		-4.3	-11.1	-12.2
p-value		0.33	0.01	0.01
95% CI		(-12.8, 4.3)	(-19.7, 2.5)	(-20.9, -3.5)

LSMean=Least Squares means; SD-Standard deviation
Note: Negative change score indicates improvement

Figure 4: Mean Change from Baseline to Final visit in Arthritis Pain Intensity VAS Score (as presented by sponsor)



Stepwise trend test (regression model: change=numerical treatment dose level)

	Slope Estimate	p-value	95% Confidence Interval
Estimates with dose levels (0,10,40,50)	-0.241	0.002	(-0.391, -0.091)
Estimates with dose levels (0,10,40)	-0.260	0.013	(-0.464, -0.056)
Estimates with dose levels (0,10)	-0.386	0.350	(-1.193, 0.421)

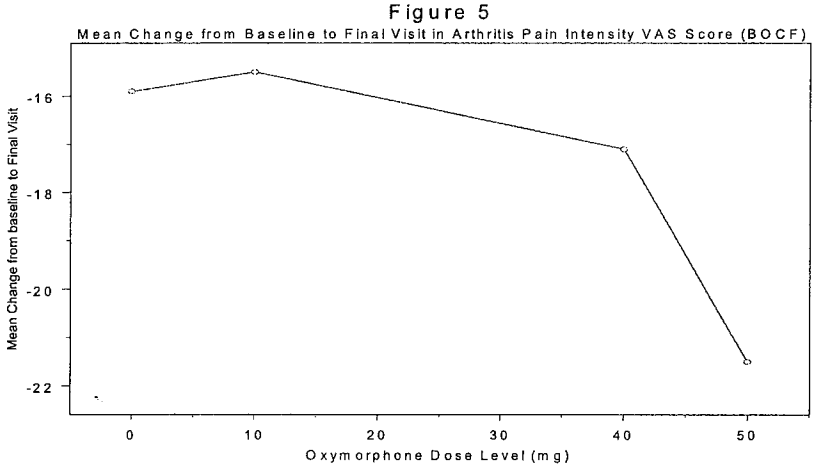
Similar to study EN3202-15, the use of a LOCF strategy to handle missing data was of concern to the review team. Due to the disproportionately high numbers of patients discontinuing in the treatment arms (as compared to placebo), a LOCF strategy may have artificially inflated the effectiveness of treatment without accounting for the intolerability of the treatments. The sponsor commented, "A sensitivity analysis was conducted which evaluated the effect of using the last observation carried forward method for handling missing data in the primary efficacy analysis. This analysis applied a standard rank transformation procedure to the primary efficacy endpoint (i.e., the change from baseline to final visit in the arthritis pain intensity VAS score) prior to performing the ANOVA."

The analysis did not alleviate the concern regarding an artificial inflation of the treatment effect; therefore, I reanalyzed the data utilizing a baseline observation carried forward strategy to handle missing data. My results are depicted in Table 9 and Figure 5. I conclude that none of the tested doses of oxymorphone ER provided significantly greater pain relief than placebo.

Table 9: Change from Baseline to final visit in Arthritis Pain Intensity VAS Score - ITT (BOCF)

	Placebo (n=87)	Oxymorphone ER 10 mg (n=92)	Oxymorphone ER 40 mg (n=91)	Oxymorphone ER 50 mg (n=87)
Mean (SD)	-15.9 (27.3)	-15.5 (24.2)	-17.1 (28.4)	-21.5 (30.8)
LSMean (Std Err)	-15.9 (2.9)	-15.9 (2.9)	-17.0 (2.9)	-21.2 (2.9)
Treatment vs. Placebo LSMean Difference		0.04	-1.1	-5.3
p-value		0.99	0.79	0.20
95% CI		(-8.0, 8.1)	(-9.2, 7.0)	(-13.5, 2.9)

Figure 5



Stepwise trend test (regression model: change = numerical treatment dose level)

	Slope	p-value	95 % Confidence Interval
Estimates with dose levels (0,10,40,50)	-0.10	0.18	(-0.26,0.05)
Estimates with dose levels (0,10,40)	-0.04	0.72	(-0.22, 0.15)
Estimates with dose levels (0, 10)	0.04	0.93	(-0.73,0.80)

2.3.4.5 Study EN3203-04

Estimates utilized in the sample size calculation were based on published literature. Specifically, a sample of size 300 was determined to be sufficient to detect a difference of 7 in total pain relief (over an 8 hour period) between the active and placebo treatments with at least 90% power. The calculation assumed a standard deviation of 10. The study

was conducted at 27 centers; however, centers were pooled due to the incompleteness of the treatment groups.

In the study, 60% of participants were female, and 85% were Caucasian. The ages of subjects ranged from 23 to 85 with a mean age of 64. Baseline characteristics captured included height, weight, and baseline pain intensity. Detailed tables outlining the composition of the samples with respect to the demographic and baseline characteristics are presented in the appendix.

Of the 300 randomized patients, 258 were included in the analysis population. In the single dose phase (of primary focus), the percentages of individuals discontinuing were 46%, 32%, 49%, 47%, and 51% in the oxymorphone IR 10 mg, oxymorphone IR 20 mg, oxymorphone IR 30 mg, oxycodone IR 10 mg, and placebo groups, respectively. Most discontinuations were due to lack of efficacy.

Table 10 depicts the results of the sponsor's analysis utilizing the methodology previously outlined in Section 2.3.2.5. The sponsor concluded that each dose of oxymorphone IR (10, 20 and 30 mg) produced greater analgesic effects (measured by total pain relief through 8 hours) as compared to placebo. In contrast, no difference was found to exist between oxycodone IR 10 mg and placebo. The conclusion was further supported by the significant dose-response relationship (as shown in the appendix).

Table 10: Summary of Total Pain Relief Scores at 0–4, 0–6, and 0–8 Hour Time Intervals (as presented by sponsor)

Treatment/Analysis Factor	TOTPAR 0-4 Hour	TOTPAR 0-6 Hour	TOTPAR 0-8 Hour
Mean (±SD)			
Oxymorphone 10 mg (N=51)	6.1 (±3.47)	8.6 (±5.44)	10.8 (±7.37)
Oxymorphone 20 mg (N=51)	7.3 (±3.49)	10.2 (±5.41)	12.6 (±7.46)
Oxymorphone 30 mg (N=57)	7.0 (±4.38)	10.1 (±6.81)	12.8 (±9.22)
Oxycodone 10 mg (N=55)	5.0 (±3.44)	6.9 (±5.01)	8.7 (±6.59)
Placebo (N=44)	4.5 (±2.93)	5.8 (±4.33)	7.1 (±5.83)
Pairwise Contrast with Placebo[a]			
Oxymorphone 10 mg			
LS Mean Difference	1.6	2.7	3.6
StdErr	0.74	1.14	1.53
P-value	0.034	0.018	0.020
95% CI of Difference	(0.1, 3.1)	(0.5, 5.0)	(0.6, 6.6)
Oxymorphone 20 mg			
LS Mean Difference	3.0	4.4	5.5
StdErr	0.75	1.15	1.54
P-value	<0.001	<0.001	<0.001
95% CI of Difference	(1.5, 4.4)	(2.1, 6.7)	(2.4, 8.5)
Oxymorphone 30 mg			
LS Mean Difference	2.5	4.1	5.5
StdErr	0.73	1.12	1.50
P-value	<0.001	<0.001	<0.001
95% CI of Difference	(1.0, 3.9)	(1.9, 6.3)	(2.5, 8.4)
Oxycodone 10 mg			
LS Mean Difference	0.5	1.0	1.5
StdErr	0.73	1.12	1.50
P-value	0.501	0.351	0.333
95% CI of Difference	(-0.9, 1.9)	(-1.2, 3.2)	(-1.5, 4.4)

[a]All pairwise comparison statistical results are between corresponding active treatments and placebo. The ANOVA model is used including main effects for treatment, center, surgical site and baseline pain stratification in the model.

The Total Pain Relief (TOTPAR) is defined as the area under the pain relief scores over the corresponding time interval. Pain Relief (Categorical) was measured on a 5-point scale: 4 = complete, 3 = a lot, 2 = moderate, 1 = a little, and 0 = none.

Numerous secondary variables were formulated and analyzed by the sponsor. My review focused on the time to re-medication, time to meaningful pain relief, and the pain relief at each time point. Variables were selected for review after discussion with review team members and evaluation of the sponsor's claim. The median time to meaningful pain relief for all study participants receiving a dose of oxymorphone IR (10, 20, and 30 mg) was approximately 1 hour and was significantly different from that of placebo patients. The median time to meaningful pain relief among oxycodone patients was 1 hour and 7 minutes and was not significantly different from placebo. The time to re-medication was significantly longer in the oxymorphone IR 20 mg and oxymorphone IR 30 mg groups (as compared to placebo). Patients re-medicated after approximately 3 hours and 42 minutes in the latter group and after 4 hours in the former. The times to re-medication were 3 hours and 4 minutes, 3 hours and 8 minutes, and 3 hours and 5 minutes in the oxymorphone 10 mg, oxycodone IR 10 mg, and placebo groups, respectively. As a final investigation of secondary endpoints, I evaluated the sponsor's depiction and analysis of

pain relief at various time points. The results are displayed in Figure 6 and Table 11. Beginning at 45 minutes and continuing through 8 hours, the oxymorphone IR 20 mg group had significantly greater pain relief as compared to the placebo group. A similar trend was noted in the oxymorphone IR 30 mg group, however, the trend was consistent after 2 hours.

Figure 6: Summary of Pain Relief over 0–8 Hours
(as presented by the sponsor)

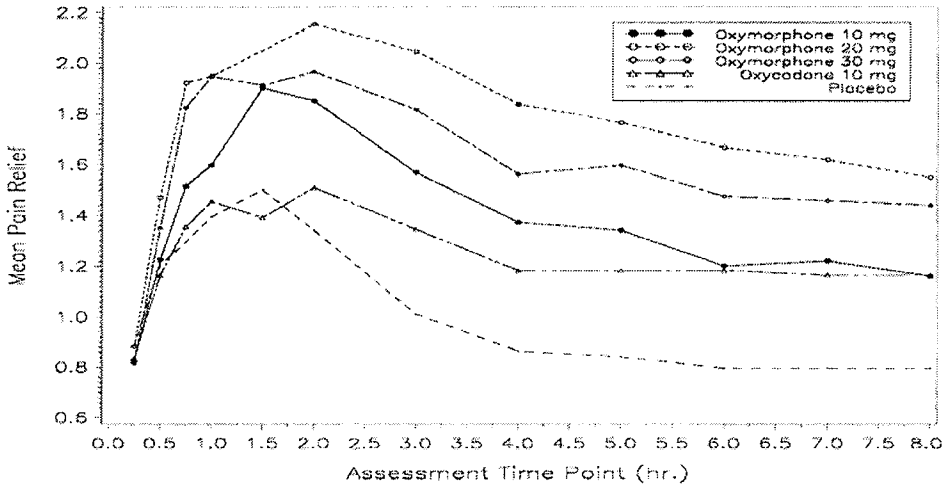


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Table 11: Summary of Pain Relief over 0–8 Hours
(as presented by the sponsor)

	Assessment Time Point											
Treatment	15 min	30 min	45 min	1 hr	1.5 hr	2 hr	3 hr	4 hr	5 hr	6 hr	7 hr	8 hr
Oxymorphone 10 mg												
n	51	50	49	50	43	38	36	23	14	12	9	3
Mean[a]	0.8	1.2	1.5	1.6	1.9	1.8	1.6	1.4	1.3	1.2	1.2	1.2
	A	A	BC	AB	AB	AB	B	BC	AB	BC	AB	AB
SD[a]	0.87	0.91	1.06	1.16	1.17	1.21	1.22	1.26	1.27	1.14	1.23	1.17
Oxymorphone 20 mg												
n	51	51	51	50	43	41	40	31	22	19	13	12
Mean[a]	0.9	1.5	1.9	1.9	2.3	2.2	2.0	1.8	1.8	1.7	1.6	1.5
	A	A	A	A	A	A	A	A	A	A	A	A
SD[a]	0.89	1.05	1.07	1.07	1.15	1.10	1.36	1.28	1.24	1.23	1.22	1.21
Oxymorphone 30 mg												
n	55	57	57	56	45	40	36	30	21	17	10	11
Mean[a]	0.8	1.4	1.8	1.9	1.9	2.0	1.8	1.6	1.6	1.5	1.5	1.4
	A	A	AB	A	AB	A	AB	AB	AB	AB	AB	A
SD[a]	0.84	1.03	1.17	1.41	1.39	1.36	1.39	1.43	1.43	1.39	1.40	1.41
Oxycodone 10 mg												
n	55	53	54	55	44	37	32	17	12	6	5	3
Mean[a]	0.8	1.2	1.4	1.5	1.4	1.5	1.3	1.2	1.2	1.2	1.2	1.2
	A	A	C	B	C	BC	BC	BC	BC	BC	BC	AB
SD[a]	0.92	1.02	1.05	1.07	1.09	1.14	1.16	1.02	1.07	1.04	1.01	1.01
Placebo												
n	43	44	41	41	36	32	27	8	1	2	1	0
Mean[a]	0.9	1.2	1.3	1.4	1.5	1.3	1.0	0.9	0.8	0.8	0.8	0.8
	A	A	C	B	BC	C	C	C	C	C	C	B
SD[a]	0.75	0.76	0.82	0.90	1.13	1.06	1.08	1.00	0.94	0.90	0.90	0.90
Treatment p-value[b]	0.987	0.441	0.004	0.024	0.001	0.001	<0.001	0.003	0.003	0.008	0.016	0.028

[a]Mean and Standard Deviation are based on extrapolated data.

[b]Based on ANOVA model including main effects for treatment, center, surgical site, and baseline pain stratification in the model.

Treatments with a common letter are not significantly different (e.g., treatments with A and AB are not significantly different).

Sample sizes (n) are not extrapolated.

Note: Some patients did not have pain relief data at all timepoints; therefore, Ns reflect the number of patients with data at each timepoint not the total N for the efficacy evaluable population.

Study EN3203-04 also included a multiple-dose phase. Only summary descriptions of the data were presented. One hundred and sixty-four patients were included in the multiple-dose phase. Dose intervals were calculated as the time span between adjacent doses per patient. The oxymorphone IR 30 mg group achieved the longest median dose interval of 9 hours and 39 minutes. All other treatment groups achieved or exceeded a dosing interval of 7 hours. Tables summarizing the worst pain score in the multiple-dose phase are in the appendix.

Individuals who received rescue medication or withdrew within the first hour were excluded from the analyses. The sponsor's rationale of exclusion mimicked that in Study EN3202-012. Again, the possibility existed that valuable information was lost due to the exclusions. The concern was conveyed to the sponsor in a correspondence dated 26 November 2002, and the sponsor submitted additional analyses of the primary endpoint including patients who re-medicated. The results support the initial analysis and are provided in the appendix. Additionally, the sponsor analyzed the data employing a baseline observation carried forward strategy to handle missing data. Due to the small number of discontinuations due to adverse events, the concern regarding the

appropriateness of a LOCF strategy was diminished. The sponsor's results of the additional analyses are consistent with previous results and are included in the appendix of this review.

2.3.4.6 Study EN3203-05

Estimates utilized in the sample size calculation were based on published literature. Specifically, a sample of size 300 was determined to be sufficient to detect a difference of 4 in total pain relief (over an 8 hour period) between the oxymorphone IR 20 mg and placebo treatment with at least 80% power. The calculation assumed a standard deviation of 7.7. The study was conducted at 9 centers throughout the United States.

In the study, 54% of participants were female, and 91% were Caucasian. The ages of subjects ranged from 23 to 86 with a mean age of 62. Baseline characteristics captured included height, weight, and baseline pain intensity. Detailed tables outlining the composition of the samples with respect to the demographic and baseline characteristics are presented in the appendix.

Of the 324 randomized patients, 302 were included in the analysis population. The percentage of individuals discontinuing were 46%, 32%, 49%, 47%, and 51% in the oxymorphone IR 10 mg, oxymorphone IR 20 mg, oxycodone IR 15 mg, oxycodone IR 30 mg, and placebo groups, respectively. The number of discontinuations due to adverse events were few across treatment groups.

Table 12 depicts the results of the sponsor's analysis utilizing the methodology previously outlined in Section 2.3.2.6. The sponsor concluded that oxymorphone IR 20 mg provided significantly greater pain relief as compared to placebo. Although the comparisons of oxycodone IR were not of primary interest, the sponsor further noted that oxycodone IR 15 mg and 30 mg also provided significantly greater pain relief as compared to placebo. Additionally, total pain relief through 8 hours did not differ among the oxycodone IR treatment arms. Due to the lack of a dose response relationship among the oxycodone IR groups, the sponsor stated "Analgesic modeling could not be applied and, therefore, no conclusion can be drawn regarding the relative analgesic potency of oxycodone and oxymorphone."

Table 12: Summary of Total Pain Relief Scores at 0–4,0–6, and 0–8 Hour Time Intervals (as presented by sponsor)

	TOTPAR		
Treatment/Analysis Factor	0-4 Hour	0-6 Hour	0-8 Hour
Mean (±SD)			
Oxymorphone IR 10 mg (N=56)	5.7 (±4.23)	7.9 (±6.21)	9.8 (±8.20)
Oxymorphone IR 20 mg (N=65)	6.8 (±4.32)	9.9 (±6.69)	12.3 (±8.74)
Oxycodone IR 15 mg (N=62)	7.5 (±4.28)	10.5 (±6.49)	12.8 (±8.55)
Oxycodone IR 30 mg (N=60)	7.3 (±4.56)	10.3 (±7.07)	12.7 (±9.38)
Placebo (N=59)	4.5 (±4.20)	6.1 (±6.07)	7.3 (±7.61)
Pairwise Contrast with Placebo[a]			
Oxymorphone IR 10 mg			
LS Mean Difference	1.2	1.7	2.2
StdErr	0.78	1.18	1.54
P-value	0.126	0.145	0.146
95% CI of Difference	(-0.3, 2.7)	(-0.6, 4.1)	(-0.8, 5.3)
Oxymorphone IR 20 mg			
LS Mean Difference	2.4	3.9	5.1
StdErr	0.75	1.14	1.48
P-value	0.002	<0.001	<0.001
95% CI of Difference	(0.9, 3.8)	(1.6, 6.1)	(2.2, 8.0)
Oxycodone IR 15 mg			
LS Mean Difference	3.0	4.3	5.3
StdErr	0.76	1.15	1.49
P-value	<0.001	<0.001	<0.001
95% CI of Difference	(1.5, 4.5)	(2.1, 6.6)	(2.4, 8.3)
Oxycodone IR 30 mg			
LS Mean Difference	2.8	4.2	5.2
StdErr	0.77	1.16	1.51
P-value	<0.001	<0.001	<0.001
95% CI of Difference	(1.3, 4.3)	(1.9, 6.4)	(2.2, 8.2)

Source: Appendix 16.2.2, Tables 4.1.1, 4.1.2, and 4.1.3

[a] All pairwise comparison statistical results are between corresponding active treatment and placebo. ANOVA model is used including main effects for treatment, center, and baseline pain stratification in the model.

Notes: The Total Pain Relief (TOTPAR) is defined as the area under the pain relief (Categorical) scores over corresponding time interval.

Pain Relief (Categorical) is measured in five point scale: 4 = complete, 3 = a lot, 2 = some, 1 = a little, and 0 = none.

Similar to EN3202-04, numerous secondary variables were formulated and analyzed by the sponsor. I again focused on the time to re-medication, time to meaningful pain relief, and the pain relief at each time point. The median time to meaningful pain relief for all study participants receiving active treatments was approximately 1 hour and was significantly different from the time of 8 hours among placebo patients. In addition, the time to re-medication was significantly longer in the active treatment groups as compared to placebo. The time to rescue medication ranged from 3 hours and 34 minutes to 4 hours

and 53 minutes among the active treatments. Patients re-medicated after approximately 2 hours in the placebo group. To gain further insight into the pain relief over time, the mean pain relief at each assessment time point was plotted and depicted in Table 13. Beginning at 1 hour and continuing throughout 8 hours, the study participants randomized to oxymorphone IR 20 mg experienced significantly more pain relief than study participants randomized to placebo. Similar trends were noted in participants randomized to oxycodone IR 15 mg and oxycodone IR 30 mg.

Table 13: Summary of Pain relief Over 0–8 Hours
(as presented by sponsor)

	Assessment Time Point										
Treatment	15 min	30 min	45 min	1 hr	2 hr	3 hr	4hr	5 hr	6 hr	7 hr	8 hr
Oxymorphone IR 10 mg											
n	54	55	55	54	41	33	25	18	12	8	7[a]
Mean[b]	0.9 AB	1.4 A	1.7 AB	1.7 AB	1.8 BC	1.5 B	1.4 B	1.3 BC	1.3 AB	1.3 AB	1.2 AB
SD[b]	1.01	1.09	1.23	1.31	1.32	1.37	1.33	1.38	1.37	1.40	1.36
Oxymorphone IR 20 mg											
n	63	62	63	63	47	40	34	29	23	18	16
Mean[b]	0.7 B	1.3 A	1.7 AB	1.9 A	2.0 AB	2.0 A	2.0 A	1.9 A	1.7 A	1.6 A	1.6 A
SD[b]	0.86	1.18	1.31	1.27	1.30	1.36	1.40	1.40	1.36	1.34	1.29
Oxycodone IR 15 mg											
n	62	62	61	61	52	44	33	29	19	13	10[a]
Mean[b]	0.8 AB	1.3 A	1.8 AB	2.1 A	2.3 A	2.1 A	2.0 A	1.7 AB	1.6 A	1.6 A	1.6 A
SD[b]	0.91	1.15	1.25	1.31	1.31	1.37	1.37	1.43	1.43	1.43	1.44
Oxycodone IR 30 mg											
n	60	60	59	60	48	38	36	26	20	17	12
Mean[b]	0.9 AB	1.5 A	2.0 A	2.1 A	2.2 AB	2.2 A	2.0 A	1.7 AB	1.6 A	1.5 A	1.5 A
SD[b]	1.09	1.13	1.30	1.30	1.44	1.44	1.51	1.39	1.38	1.35	1.32
Placebo											
n	59	58	59	59	34	20	15	11	9	5	3[a]
Mean[b]	1.1 A	1.3 A	1.4 B	1.3 B	1.3 C	1.2 B	1.1 B	1.0 C	1.0 B	0.9 B	0.9 B
SD[b]	0.98	1.09	1.14	1.28	1.41	1.32	1.25	1.22	1.27	1.12	1.15
Treatment p-value[c]	0.211	0.889	0.137	0.003	<0.001	<0.001	<0.001	0.002	0.022	0.010	0.018

[a]The following explains the discrepancy between the Hour 8 summary in this table and total number of patients who completed the Hour 8 evaluation in Table 1:

- 105-001 (Oxymorphone IR 10 mg) completed 8-Hour evaluation but was excluded from efficacy-evaluable population due to protocol violation (c.f. SAP).
- 303-093 (Oxycodone IR 15 mg) provided all 8-Hour primary efficacy data (efficacy evaluable) but was recorded as discontinued due to protocol violation (the only one in the trial).
- 302-100 (placebo) was recorded as completed 8-Hour study but only provided up to 6-hour primary efficacy data including rescue.

[b]Mean and Standard Deviation are based on extrapolated data.
[c]Based on ANOVA model including main effects for treatment, center, and baseline pain stratification in the model.

Treatments with a common letter are not significantly different (e.g., treatments with A and AB are not significantly different).
Sample sizes (n) are not extrapolated.

Concerns regarding the definition of the analysis population and the strategy for handling missing data mimicked those presented in EN3203-04. The sponsor reanalyzed the data utilizing the same definition and strategies of EN3203-04. The results are consistent with initial findings and are included in the appendix of the review.

2.3.4.7 Studies EN3203-018 and EN3202-019

The sponsor additionally submitted two randomized, double-blind, multicenter, crossover studies as supportive evidence. The studies were similar in design with the only variation in the treatment arms. In study EN3202-18, the primary objective of the study was to compare the efficacy of oxymorphone ER and morphine ER utilizing an equivalence (non-inferiority) model. The primary objective of study EN3202-19 differed from study EN3202-18 in that the treatments of interest were oxymorphone ER and OxyContin®. Study participants received morphine ER or OxyContin® (respectively for EN3202-18 and EN3202-19) until a stable dose had been achieved for 3 days. Individuals achieving pain control (via a stable dose) were randomized to a sequence of oxymorphone ER for a week followed by active control for a week or a sequence of active control for a week followed by oxymorphone ER. Analgesic efficacy was evaluated by using the 24-hour average pain intensity rating from the final visit of each treatment period. The analysis for both studies utilized a mixed effects model with treatment, sequence, and period as fixed effects and subject as a random effect. Both studies failed to show equivalence of oxymorphone ER and the active control.

2.3.5 STATISTICAL REVIEWER'S FINDINGS

Recurrent concerns throughout NDA 21-610 and NDA 21-611 were the appropriateness of the analysis populations and the last observation carried forward strategy. In numerous studies, the ITT population was utilized for efficacy evaluations. The population consisted of all randomized patients having at least one post-baseline measurement. An additional caveat of the defined ITT population in some studies of acute pain was the exclusion of study participants who received rescue medication or withdrew within the first hour. Specifically in study EN3202-15, the first efficacy assessment occurred one week after the baseline assessment. The possibility of differential withdrawal as a result of treatment assignment existed during that first week; therefore, exclusion of patients may have had an impact on overall results. The same concern also existed in studies EN3202-12, EN3203-04, and EN3203-05. Patients who re-medicated or withdrew within the first hour were excluded. Again, the re-medication or withdrawal may have been related to treatment assignment. In the absence of a clinical justification for the exclusion of patients from the ITT populations, I reanalyzed the data utilizing analyses populations consistent with the principle of ITT.

In several correspondences, the agency recommended the sponsor thoroughly investigate the pattern of treatment withdrawal among patients included in analysis. Specifically the agency commented,

> When considering missing data, the pattern of withdrawal should be thoroughly investigated. For example, the possibility exists that patients discontinue due to intolerable side effects. The last record of such a discontinued patient may consist of a high score apparently suggesting treatment effectiveness at the time of withdrawal; however, the dose required for effectiveness may also have caused intolerable side

> effects. Since the pattern of withdrawal is treatment related, conclusions formulated based on a last observation carried forward analysis could be misleading. To offset potentially misleading conclusions, the sensitivity of results of the analysis to the procedure utilized for handling missing data should be investigated.

The concern regarding the last observation carried forward strategy was most evident in studies EN3202-15 and EN3202-25 where a disproportionately large number of discontinuations due to adverse events existed among individuals receiving active treatments. I utilized an alternative strategy imputing subject-specific baseline values (indicating no change). A successful demonstration of efficacy while utilizing a baseline carried forward procedure would provide assurance that the conclusions of efficacy are not dependent on the method of handling missing data.

A final concern was that of multiplicity. In several of the studies multiple comparisons arose from the statistical testing of numerous pairwise comparisons. In studies EN3202-25, EN3203-04, and EN3203-05, the sponsor utilized step-down procedures to offset concerns regarding multiple comparisons. In studies EN3202-15 and EN3202-16, the sponsor pre-specifies respective primary hypotheses each involving one comparison of interest.

2.4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Analyses were performed with respect to gender and age for EN3202-15, EN3202-16, and EN3202-25. Due to the varying study designs, the sponsor did not pool data for the subgroup analyses. The measure of efficacy for the three studies was the change from baseline in pain intensity. Terms for gender, age, and treatment by subgroup factor were respectively added to the analysis of covariance models utilized in the primary analyses. Age was categorized into two groups, age below 65 and ages greater than or equal to 65.

No significant age or gender effects were found to exist in studies EN3202-15 or EN3202-25. In study EN3202-16, an age effect did exist. However the sponsor stated, "This effect is artificial because of a skewed sample size; the number of oxymorphone ER patients in the less than 65 age category was 67, whereas, for the greater than or equal to 65 age category the number was 4." Moreover, a significant treatment by center interaction existed in EN3202-16. Examination of the change in pain intensity among males and females within treatment groups yielded a smaller reduction in pain intensity among males as compared to females within the oxymorphone ER group. In contrast, a larger reduction among males as compared to females was evident within the OxyContin® group. The sponsor stated, "A possible explanation for these diverse findings is the large inter-individual variability among patients that is further magnified in a subpopulation analysis such as this."

As an additional subgroup examination, the sponsor considered opioid-experienced and opioid-naïve patients in studies EN3202-15 and EN3202-25. Differences between the two groups of patients did not exist for the primary outcome.

The sponsor did not perform subgroup analyses for study EN3202-12. My analysis found a statistically significant gender effect. Specifically, females experienced greater total pain relief as compared to males.

In studies EN3203-04 and EN3203-05, the sponsor presented descriptive statistics for the primary efficacy outcome by age group and gender where data was combined for both studies. The sponsor did not perform any formal statistical test. I additionally performed separate analyses with respect to gender and age for the studies. The primary outcome was the total pain relief as previously defined. Terms for gender, age, and treatment by subgroup factor were respectively added to the analysis of covariance models utilized in the primary analyses. Age was categorized into two groups, age below 65 and ages greater than or equal to 65.

No age or gender effects existed in EN3202-04. An age effect did exist in EN3202-05. Specifically, older study participants experienced greater pain relief as compared to younger study participants.

Overall, I am in general agreement with the sponsor's findings pertaining to the subgroups. The sponsor did not propose any efficacy claims for any subgroup of patients. Furthermore, the results were consistent and lend support to the primary findings.

2.5 CONCLUSIONS AND RECOMMENDATIONS

The sponsor claims that oxymorphone ER provides relief of moderate to severe pain in patients requiring continuous opioid therapy for an extended time. Varying evidence of efficacy exists for oxymorphone ER. Specifically, there is statistical support favoring the analgesic efficacy of oxymorphone ER as compared to placebo in the chronic low back pain population. However, the proposed drug product does not convincingly demonstrate effectiveness in the osteoarthritis population.

Study EN3202-16, a randomized, double-blind, and placebo-controlled study of approximately 330 patients with chronic lower back pain, provides the strongest support of efficacy. The design of the study is desirable in that a population believed to have consistent chronic pain is utilized, and participants are titrated to a stabilized dose. Such a design may be more indicative of a practical setting. Moreover, the analgesic difference shown between OxyContin® and placebo (implying an internal measure of assay sensitivity) strengthen the effectiveness of the drug. Study EN3202-12 additionally provides some supportive evidence of effectiveness. According to the sponsor, EN3202-15 and EN3202-25 both demonstrate effectiveness of OxyContin®. However, the effectiveness was questionable due to the lack of consistency of results when varying statistical methods were applied.

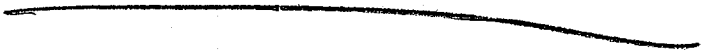
The sponsor also claims that oxymorphone IR produces greater efficacy than placebo as measured by the magnitude of pain relief. The evidence taken collectively from studies

EN3203-04 and EN3203-05 indicates statistical support favoring oxymorphone IR for pain relief. Additional claims are made regarding the onset of analgesia and the dosing interval derived from the multiple dose-phase of the former study. The evidence suggests that the median time to meaningful pain relief is approximately one hour. Moreover, the median dose interval for the oxymorphone IR 30 mg group is 9.5 hours. All other active treatment groups achieve or exceed a dosing interval of 7 hours.

Based on my collective evaluation of NDA 21-610 and NDA 21-611 as well as historical precedents of study requirements of approved opioids, I conclude that statistical evidence exists to support the use of oxymorphone ER and oxymorphone IR in the management of moderate to severe pain where an opioid is appropriate.

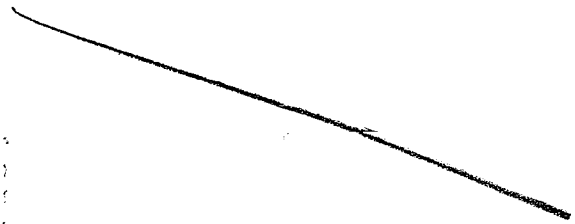
2.6 LABELLING

The sponsor's draft labeling for oxymorphone ER refers to six clinical studies including two supportive studies in patients with chronic cancer pain. Due to the varying evidence of efficacy, I propose that the labeling rely on study EN3202-16. Specifically, I suggest utilization of the following portion of the proposed labeling:



Recommended doses will need to be determined by the review team in collaboration with the sponsor.

The proposed draft labeling for oxymorphone IR reads as follows:



Of note, study EN3203-04 evaluated the analgesic efficacy of the 10, 20, and 30 mg doses of TRADEMARK while study EN3203-05 evaluated the efficacy of the 10 and 20 mg doses of TRADEMARK. Moreover, the effectiveness of the 10 mg dose was not replicated in both studies.

2.7 APPENDIX

2.7.1 EN3202-12

	OCR 20	Placebo	p-value
Age (years)			0.3122[a]
N	65	61	
Mean	65.0	66.6	
Standard Deviation	8.27	8.84	
Range	39 - 85	33 - 80	
Age Category N (%)			
< 65 years	30 (46.2%)	19 (31.1%)	0.1080[b]
≥ 65 years	35 (53.8%)	42 (68.9%)	
Sex N (%)			0.5335[b]
Female	40 (61.5%)	34 (55.7%)	
Male	25 (38.5%)	27 (44.3%)	
Race N (%)			0.6004[b]
Black	8 (12.3%)	7 (11.5%)	
Caucasian	56 (86.2%)	54 (88.5%)	
Hispanic	1 (1.5%)	0 (0.0%)	
Weight (kg)			0.7782[a]
N	65	61	
Mean	92.18	92.69	
Standard Deviation	22.578	18.017	
Range	58.2 - 194.1	59.0 - 147.7	
Height (cm)			0.6835[a]
N	64	61	
Mean	168.56	169.36	
Standard Deviation	11.491	9.764	
Range	145.2 - 192.0	152.4 - 185.5	

Data source: Appendix 16.2.2 Table 2 and Listings 3.1 and 3.3.
[a] P-value from 2-way ANOVA with treatment and pooled investigational centers as factors.
[b] P-value from CMH test adjusted for pooled investigational centers.

2.7.2 EN3202-15

		OCR 40 (N=121)	OCR 20 (N=119)	OC 20 (N=125)	Placebo (N=124)
Age (years)	Mean ± SE	61.4 ± 1.0	63.4 ± 0.91	62.7 ± 1.0	61.7 ± 1.0
[n (%)]	< 65	74 (61.2)	62 (52.1)	66 (52.8)	72 (58.1)
	≥ 65	47 (38.8)	57 (47.9)	59 (47.2)	52 (41.9)
Sex	Female	78 (64.5)	66 (55.5)	72 (57.6)	81 (65.3)
	Male	43 (35.5)	53 (44.5)	53 (42.4)	43 (34.7)
Race	Caucasian	106 (87.6)	97 (81.5)	112 (89.6)	107 (86.3)
[n (%)]	Black	11 (9.1)	19 (16.0)	9 (7.2)	12 (9.7)
	Hispanic	3 (2.5)	1 (0.8)	4 (3.2)	4 (3.2)
	Asian	0	1 (0.8)	0	0
	Other	1 (0.8)	1 (0.8)	0	1 (0.8)
Weight (kg)	Mean ± SD	96.7 ± 27.4	94.6 ± 23.3	94.7 ± 22.5	93.1 ± 22.3
Height (cm)	Mean ± SD	167 ± 12.1	170 ± 10.8	168 ± 10.8	168 ± 8.9
Duration of Disease (years)	Mean ± SD	9.2 ± 8.1	9.1 ± 7.9	9.8 ± 9.6	10.3 ± 8.4
[n (%)]	< 5 years	44 (36.4)	34 (28.6)	41 (32.8)	27 (21.8)
	≥ 5 years	77 (63.6)	85 (71.4)	84 (67.2)	96 (77.4)
	Missing	0	0	0	1 (0.8)
Index Joint	Knee	94 (77.7)	92 (77.3)	94 (75.2)	93 (75.0)
[n (%)]	Hip	27 (22.3)	27 (22.7)	31 (25.0)	31 (25.0)

Data source: Appendix 15.3 Table 2.
OCR = Oxymorphone CR and OC = OxyContin

2.7.3 EN3202-16

Table 8. Demographic and Baseline Characteristics by Treatment, Safety Population

Characteristic	Oxymorphone ER N=110	OxyContin N=111	Placebo N=108	P-value[a]
Age (years)				0.3758
n	110	111	108	
Mean	45.5	46.2	47.5	
SD	10.45	11.05	10.10	
Median	44.0	45.0	47.0	
Min/Max	26/82	22/76	26/79	
Sex n (%)				0.6046
Male	56 (50.9)	63 (56.8)	55 (50.9)	
Female	54 (49.1)	48 (43.2)	53 (49.1)	
Race n (%)				0.6548
Caucasian	104 (94.5)	101 (91.0)	103 (95.4)	
Black	4 (3.6)	4 (3.6)	3 (2.8)	
Hispanic	2 (1.8)	5 (4.5)	2 (1.9)	
Asian	0 (0.0)	0 (0.0)	0 (0.0)	
Other	0 (0.0)	1 (0.9)	0 (0.0)	
Weight (kg)				0.7224
n	110	111	108	
Mean	83.3	84.0	81.8	
SD	21.13	19.49	19.95	
Median	80.2	81.8	77.3	
Min/Max	48/149	45/140	45/135	
Height (cm)				0.5976
n	110	111	108	
Mean	172.2	172.1	170.9	
SD	9.94	10.38	10.57	
Median	174.0	172.7	171.5	
Min/Max	147/196	142/196	147/196	
Years with back pain				0.8201
n	110	111	108	
Mean	8.3	7.7	8.0	
SD	6.84	8.16	7.06	
Median	6.2	5.0	5.6	
Min/Max	0/32	0/53	0/32	

Data Source: Appendix 16.3.2, Table 1; Appendix 16.5, Listing 3.1

[a]The p-values for age, weight, height, and years with back pain were determined by ANOVA; the p-values for sex and race were determined by a chi-square test.

2.7.3 EN3202-16

Table 8. Demographic and Baseline Characteristics by Treatment, Safety Population

Characteristic	Oxymorphone ER N=110	OxyContin N=111	Placebo N=108	P-value[a]
Age (years)				0.3758
n	110	111	108	
Mean	45.5	46.2	47.5	
SD	10.45	11.05	10.10	
Median	44.0	45.0	47.0	
Min/Max	26/82	22/76	26/79	
Sex n (%)				0.6046
Male	56 (50.9)	63 (56.8)	55 (50.9)	
Female	54 (49.1)	48 (43.2)	53 (49.1)	
Race n (%)				0.6548
Caucasian	104 (94.5)	101 (91.0)	103 (95.4)	
Black	4 (3.6)	4 (3.6)	3 (2.8)	
Hispanic	2 (1.8)	5 (4.5)	2 (1.9)	
Asian	0 (0.0)	0 (0.0)	0 (0.0)	
Other	0 (0.0)	1 (0.9)	0 (0.0)	
Weight (kg)				0.7224
n	110	111	108	
Mean	83.3	84.0	81.8	
SD	21.13	19.49	19.95	
Median	80.2	81.8	77.3	
Min/Max	48/149	45/140	45/135	
Height (cm)				0.5976
n	110	111	108	
Mean	172.2	172.1	170.9	
SD	9.94	10.38	10.57	
Median	174.0	172.7	171.5	
Min/Max	147/196	142/196	147/196	
Years with back pain				0.8201
n	110	111	108	
Mean	8.3	7.7	8.0	
SD	6.84	8.16	7.06	
Median	6.2	5.0	5.6	
Min/Max	0/32	0/53	0/32	

Data Source: Appendix 16.3.2, Table 1; Appendix 16.5, Listing 3.1

[a]The p-values for age, weight, height, and years with back pain were determined by ANOVA; the p-values for sex and race were determined by a chi-square test.

2.7.4 EN3202-25

	Placebo (N=91)	Oxymorphone 10 mg (N=95)	Oxymorphone 40 mg (N=93)	Oxymorphone 50 mg (N=91)
Age (yrs.)				
N	91	95	93	91
MEAN	60	63	62	62
STD	11.15	10.87	11.51	11.42
MIN	36	30	34	38
MAX	93	84	85	85
Sex - N (%)				
MALE	39 (42.9)	30 (31.6)	35 (37.6)	42 (46.2)
FEMALE	52 (57.1)	65 (68.4)	58 (62.4)	49 (53.8)
Race - N (%)				
CAUCASIAN	81 (89.0)	82 (86.3)	87 (93.5)	83 (91.2)
BLACK	8 (8.8)	9 (9.5)	6 (6.5)	6 (6.6)
HISPANIC	0	1 (1.1)	0	0
OTHER	2 (2.2)	3 (3.2)	0	2 (2.2)
Height (in.)				
N	91	95	92	91
MEAN	66.5	65.9	66.2	66.9
STD	3.83	3.74	4.76	4.00
MIN	59.0	57.0	54.0	59.0
MAX	78.0	74.0	78.0	76.0
Weight (lb.)				
N	91	95	92	91
MEAN	220.2	209.0	209.2	207.3
STD	55.62	50.01	52.07	48.90
MIN	114.0	116.0	104.0	110.0
MAX	425.0	360.0	350.0	353.0

Data Source: Appendix 16.2.2, Table 2.1

Final

2.7.5 EN3203-04

	Oxymorphone 10 mg (N=59)	Oxymorphone 20 mg (N=59)	Oxymorphone 30 mg (N=65)	Oxycodone 10 mg (N=60)	Placebo (N=57)
Age (yrs.)					
N	59	59	65	60	57
MEAN	63.9	66.5	61.5	62.8	62.4
STD	11.03	9.97	11.57	12.11	9.33
MIN	36	36	23	35	39
MAX	85	83	85	81	80
Sex - N (%)					
MALE	20 (33.9)	20 (33.9)	31 (47.7)	23 (38.3)	25 (43.9)
FEMALE	39 (66.1)	39 (66.1)	34 (52.3)	37 (61.7)	32 (56.1)
Race - N (%)					
CAUCASIAN	52 (88.1)	50 (84.7)	55 (84.6)	51 (85.0)	48 (84.2)
BLACK	5 (8.5)	7 (11.9)	6 (9.2)	8 (13.3)	5 (8.8)
HISPANIC	1 (1.7)	2 (3.4)	3 (4.6)	1 (1.7)	3 (5.3)
ASIAN	0	0	1 (1.5)	0	0
OTHER	1 (1.7)	0	0	0	1 (1.8)
Height (in.)					
N	59	58	65	60	57
MEAN	66.4	65.9	67.0	66.8	66.8
STD	4.11	3.79	3.74	4.44	4.08
MIN	58.0	60.0	60.0	60.0	57.0
MAX	75.0	77.0	77.0	78.0	74.0
Weight (lb.)					
N	59	59	65	60	57
MEAN	205.8	199.2	207.8	199.5	207.6
STD	49.81	53.37	44.89	37.66	41.64
MIN	114.0	113.0	116.0	138.0	137.0
MAX	311.0	450.0	320.0	325.0	367.0
Baseline Pain Intensity (Categorical)					
Mild	0	1 (1.7)	0	0	0
Moderate	44 (74.6)	38 (64.4)	48 (73.8)	49 (81.7)	41 (71.9)
Severe	15 (25.4)	20 (33.9)	17 (26.2)	11 (18.3)	16 (28.1)

Data Source: Appendix 16.4, LISTING 1.2 and LISTING 9

Note: Patient 07-005 (oxymorphone IR 20 mg) is excluded from the summary of height due to a data entry error of 675 inches.

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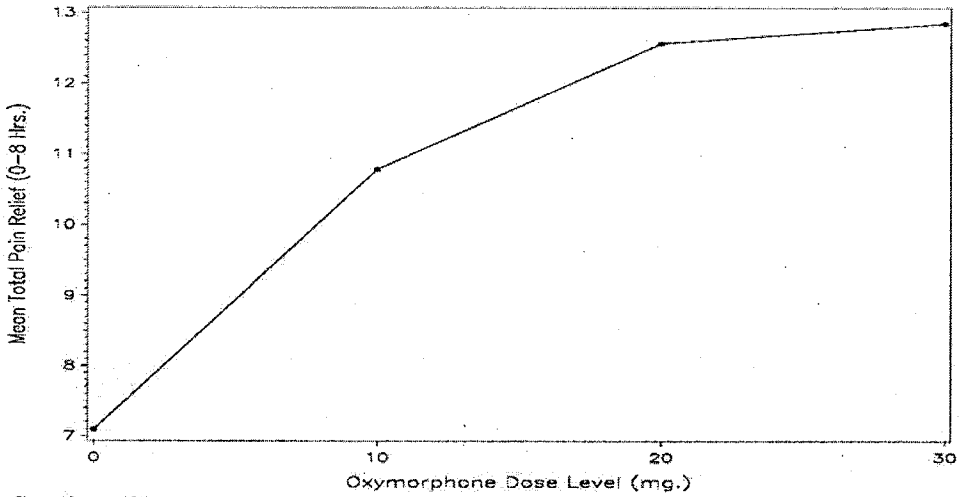

Slope estimate=0.184
p-value<0.001
95% confidence interval: (0.089,0.279)

	Oxymorphone 10 mg (N=38)	Oxymorphone 20 mg (N=48)	Oxymorphone 30 mg (N=38)	Oxycodone 10 mg (N=39)
Mean Dose Interval [2]				
N	31	39	32	34
Mean	8:28	7:52	10:01	7:41
Std	5:17	2:27	4:08	3:05
Minimum	2:45	3:32	3:00	3:17
Median	7:00	7:11	9:39	7:44
Maximum	25:00	13:12	22:45	15:35
Minimum Dose Interval [3]				
N	31	39	32	34
Mean	6:27	5:44	7:06	5:02
Std	5:41	2:11	4:32	3:07
Minimum	2:25	3:05	3:00	1:05
Median	4:09	5:18	5:30	4:00
Maximum	25:00	11:36	22:45	15:35
Maximum Dose Interval [4]				
N	31	39	32	34
Mean	11:22	10:42	13:58	12:12
Std	5:30	4:06	5:31	6:09
Minimum	3:05	4:10	3:00	4:00
Median	10:50	10:15	14:42	11:05
Maximum	25:00	20:50	24:15	32:45

[1] Dose intervals are calculated as the time span (hh:mm) between adjacent doses on patient level
[2] Mean dose interval is calculated as the average dose interval per patient
[3] Minimum dose interval is calculated as the minimum dose interval per patient
[4] Maximum dose interval is calculated as the maximum dose interval per patient
Source Data: Appendix 16.4, LISTING 6.4

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Re-Analysis provided as a response to agency concerns:

EN3202-04: Re-Analysis of Total Pain Relief (0–8 hours)

Treatment (Number of Patients Randomized)	Statistics	Excluding patients who re-medicated within the first hour	Including patients who re-medicated within the first hour
Oxymorphone IR 10 mg (N=59)	n	51	59
	Mean	10.8	10.0
	p-value*	0.0196	0.0087
Oxymorphone IR 20 mg (N=59)	n	51	58
	Mean	12.7	11.8
	p-value*	0.0005	0.0001
Oxymorphone IR 30 mg (N=65)	n	57	64
	Mean	12.7	11.5
	p-value*	0.0003	0.0002
Oxycodone 10 mg (N=60)	n	55	59
	Mean	8.7	8.1
	p-value*	0.3331	0.1864
Placebo (N=57)	n	44	57
	Mean	7.2	6.1

* p-value is from the pairwise comparison with placebo in ANOVA.

2.7.6 EN3203-05

	Oxymorphone 10 mg (N=63)	Oxymorphone 20 mg (N=67)	Oxycodone 15 mg (N=65)	Oxycodone 30 mg (N=63)	Placebo (N=66)
Age (yrs.)					
N	63	67	65	63	66
MEAN	60.6	64.4	60.4	60.1	63.5
STD	12.93	12.91	14.64	11.07	14.12
MIN	24.2	28.6	22.5	38.6	27.0
MAX	78.1	86.3	82.1	83.5	91.7
Sex - N (%)					
Male	32 (50.8)	27 (40.3)	29 (44.6)	26 (41.3)	34 (51.5)
Female	31 (49.2)	40 (59.7)	36 (55.4)	37 (58.7)	32 (48.5)
Race - N (%)					
African American	3 (4.8)	3 (4.5)	3 (4.6)	3 (4.8)	2 (3.0)
Caucasian	60 (95.2)	59 (88.1)	58 (89.2)	57 (90.5)	61 (92.4)
Native American	0	1 (1.5)	0	0	0
Hispanic or Latino	0	4 (6.0)	4 (6.2)	3 (4.8)	3 (4.5)
Height (in.)					
N	63	67	64	62	66
MEAN	67.8	67.2	66.9	67.4	67.6
STD	4.96	5.33	4.16	4.02	4.67
MIN	54.0	60.0	60.0	60.0	60.0
MAX	80.7	85.4	79.6	81.9	80.7
Weight (lb.)					
N	63	67	64	62	66
MEAN	205.1	197.7	192.1	200.8	193.9
STD	44.69	40.18	46.31	45.57	38.61
MIN	121.0	117.0	105.0	100.0	113.0
MAX	335.2	320.0	325.0	385.9	300.0
Baseline Pain Intensity (Categorical)					
Moderate	43 (68.3)	43 (64.2)	45 (69.2)	46 (73.0)	46 (69.7)
Severe	20 (31.7)	24 (35.8)	20 (30.8)	17 (27.0)	20 (30.3)

Re-Analysis provided as a response to agency concern:

EN3202-05: Re-Analysis of Total Pain Relief (0–8 hours)

Treatment (Number of Patients Randomized)	Statistics	Excluding patients who re-medicated within the first hour	Including patients who re-medicated within the first hour
Oxymorphone IR 10 mg (N=63)	n	56	59
	Mean	9.6	9.1
	p-value*	0.1460	0.2608
Oxymorphone IR 20 mg (N=67)	n	65	66
	Mean	12.5	12.4
	p-value*	0.0007	0.0008
Oxycodone IR 15 mg (N=65)	n	62	64
	Mean	12.7	12.6
	p-value*	0.0004	0.0006
Oxycodone IR 30 mg (N=63)	n	60	62
	Mean	12.6	12.2
	p-value*	0.0006	0.0017
Placebo (N=66)	n	59	63
	Mean	7.3	7.4

* p-value is from the pairwise comparison with placebo in ANOVA.

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/s/

Dionne Price
9/16/03 04:45:47 PM
BIOMETRICS

Thomas Permutt
9/16/03 04:53:04 PM
BIOMETRICS
concur

S. Edward Nevius
10/2/03 09:19:39 AM
BIOMETRICS
Concur with review.

45 DAY MEETING CHECKLIST
(Answer Yes or No to the questions below)

FILEABILITY:

On initial overview of the NDA application:

STATISTICAL:

(1) On its face, is the statistical section of the NDA organized in a manner to allow substantive review to begin?

YES

(2) Is the statistical section of the NDA indexed and paginated in a manner to allow substantive review to begin?

YES

(3) On its face, is the statistical section of the NDA legible so that substantive review can being?

YES

(4) On its face, do there appear to be at least two adequate and well-controlled studies in the application?

YES

(5) Are the pivotal efficacy studies of appropriate design to meet the basic requirements for approvability of this product based on proposed draft labeling?

YES

(6) Are all the data sets for pivotal efficacy studies complete for all indications (infections) requested?

YES (Checked items are applicable and present for NDAs 21-610 and 21-611)

(a) Line listings by Center ✔

(b) Intermediate analysis summary tables

(c) Pathogen listing

(d) Adverse events listing by Center ✔

(e) Lost subject/patient tables by reason, time of loss, and center ✔

(7) Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?

YES

(8) From a statistical perspective, is this NDA fileable? If "no", please state below why it is not..

YES

Dionne L. Price	2/11/03
Reviewing Statistician	Date
Supervisory Statistician	Date

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/s/

Dionne Price
2/12/03 10:54:34 AM
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Thomas Permutt
2/12/03 01:02:37 PM
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