Protocol No.	Development Plan		Study Type	Does Regimen and Formulation and Duration of Treatment	N
	ER	IR			
3202-025	**Yes**		**Phase III, Osteoarthritis pain, placebo-controlled**	**Week 1** **OM ER 10 tab, OM ER 20 tab, OM ER 20 tab, Placebo** **Week 2** **OM ER 10 tab, OM ER 40 tab, OM ER 50 tab, Placebo**	**370**
EN3202-026^	Yes		Clinical pharmacology	Group A : OM ER (3 × 20 mg PO q12h Days 1-14 am) plus NTX (2 × 50 mg PO Day –1 and 50 mg PO q24h Days 1-14) Group B: OM ER (10 mg PO q12h Days 1-3; 20 mg PO q12h Days 4-14 am; 10 mg PO q12h Days 14 pm-17 am; and 5 mg PO q12h Days 17 pm-18 am) Group C : rifampin (2 × 300 mg PO q24h Days 1-14) Group D: NTX (2 × 50 mg PO Day –1 and 50 mg PO q24h Days 1-14) Group E: untreated All Groups: CYP450 3A4 probe 3 μ Ci [^{14}C N-methyl] erythromycin ~0.03 mg IV push and midazolam HCl syrup 2 mg/mL PO (SD, am, Day -1, Day 7, and Day 14)	80
EN3202-027^	Yes		Clinical pharmacology	Group A: OM ER (3 × 20 mg PO q12h Days 1-14 am) plus NTX (2 × 50 mg PO Day –1 and 50 mg PO q24h Days 1-14) Group B: OM ER (10 mg PO q12h Days 1-3; 20 mg PO q12h Days 4-14 am; 10 mg PO q12h Days 14 pm-17 am; and 5 mg PO q12h Days 17 pm-18 am) Group C: rifampin (2 × 300 mg PO q24h Days 1-14) Group D: NTX (2 × 50 mg PO Day -1 and 50 mg PO q24h Days 1-14) Group E: untreated control All Groups: tolbutamide (SD 500 mg PO, am, Day -1, Day 7, and Day 14)	85
3203-001	Yes	Yes	Clinical pharmacology	OM 10 tab, OM 10 soln OM 1 IV, Single dose crossover	9
3203-002		Yes	Clinical pharmacology	OM IR 10 tab, OM 10 soln, OM IR 1 x 10 tab OM IR 2 x 5 tabs, Single dose crossover, fasting, 7 day washout	30
3203-004	**Yes**	**Yes**	**Phase III, Acute post-operative pain, placebo-controlled**	**OM IR 10 tab, OM IR 20 tab, OM IR 30 tab, OC IR 10 tab, Placebo, Single/multiple dose**	**300**
3203-005	**Yes**	**Yes**	**Phase III, Acute post-operative pain, placebo-controlled**	**OM IR 10 tab, OM IR 20 tab, OC IR 15 tab, OC IR 30 tab, Placebo tab, Single dose**	**324**
3203-006		Yes	Clinical pharmacology	NT/OM IR 50/5, NT/OM IR 50/10 tab NT/OM IR 50/10 tab, Single/multiple dose crossover	24
3203-007		Yes	Clinical pharmacology	OM IR 10 tab, OM IR 10 tab Single dose crossover	32

*The number outside the parentheses refers to the number in the 120-Day Safety Update. The number inside the parentheses refers to the number in the original ISS.
^These studies were submitted at the time of the 120-Day Safety Update

Rand = randomized, OM = oxymorphone, IR = immediate release, ER = extended release, OC = oxycodone, MS C® = MS Contin®, OC® = OxyContin®

Source: Supplemental Tables 1 and 2 in NDA 21-610 ISS (pg. 229-248) and Supplemental Table 1 and 2 in the 120-Day Safety Update (pg. 42-66).

5.3 Postmarketing Experience

No current postmarketing information is available subsequent to the withdrawal of oral oxymorphone from the market in 1979.

5.4 Literature Review

No literature review was performed or planned as part of this review.

6 CLINICAL REVIEW METHODS:

6.1 How the Review was Conducted

Studies EN3202-012, 015, 016, and 025 submitted in support of efficacy, were reviewed in detail. An extensive review of the study protocols, study reports, protocol amendments, and patient summaries was performed. The case report forms (CRFs) and case report tabulations (CRTs) were consulted to further evaluate patient disposition, to confirm the sponsor's efficacy analysis, and to perform additional efficacy analyses. Missing, unclear, or incomplete information was requested from the Sponsor as CRFs and responses to Agency questions whenever appropriate.

The review of three supportive active and non-inferiority trials (EN3202-017, -018, and –019) was less detailed due to inherent design deficiencies that did not allow these studies to support efficacy.

The review of safety and all relevant conclusions may be found in a separate Integrated Review of Safety.

6.2 Overview of Materials Consulted in Review

Primary review material (PDF text files and SAS transport data files) was provided in accordance with the agency guidance on electronic NDAs. In addition to the electronic NDA, prior protocols were also consulted. This material was principally used to document the regulatory and administrative history of this product's development.

6.3 Overview of Methods Used to Evaluate Data Quality and Integrity

DSI conducted 'for cause' audits of Study Sites 023 (Dr. Barry Miskin, principal investigator) and 002 (Dr. J. Appelrouth, principal investigator). These sites were involved in cases of drug diversion detected and reported by the Sponsor (reported to all appropriate authorities and FDA notified June 28, 2002). Patients from Site 023 were enrolled in Studies EN3202-016 and 021, and patients from Site 002 were enrolled in Studies EN3202-015 and 020. The Sponsor terminated the safety extension study EN3202-021 but continued patients already enrolled in study EN3202-016. While the DSI audit considered the data from Site 023 acceptable for use in safety and efficacy analyses, the Sponsor and the Division excluded subjects from this site in the efficacy analyses.

The Division of Scientific Investigations (DSI) found that the study coordinator from Site 002 (Principal Investigator - Dr. Appelrouth) enrolled herself in the Studies EN3202-015 and EN3202-020. The Sponsor terminated these studies at that site. Additionally, DSI

found falsification of records at the site, failure of the PI to personally perform global assessments, and many protocol violations. These deficiencies were felt to affect both safety and efficacy data obtained from these sites. The Sponsor and the Division excluded this site's data from the efficacy analyses. In conclusion, the Sponsor and the Agency excluded all subjects from Sites 002 and 023 in the efficacy analyses, presented in this review. Safety data from these sites were included in the Review of Safety.

6.4 Were Trials Conducted in Accordance with Accepted Ethical Standards

The Sponsor states that the clinical efficacy studies were conducted in accordance with the provisions of the Declaration of Helsinki and its amendments, FDA principles of Good Clinical Practice (GCP), and ICH guidelines.

6.5 Evaluation of Financial Disclosure

The Sponsor submitted certification of financial disclosure with Form 3454 for the Principle Investigators and their sub-investigators for twenty studies: EN3202-003, 004, 005, through 025. Two studies (EN3202-001 and 002) did not have information provided because they were started before the initiation of the financial disclosure requirement.

The vast majority of sites had financial disclosure forms (FDFs) returned from all participants (273/280 reporting sites participating in studies EN3202-003 through 025). A small number of sites had some sub-investigators and research coordinators that had left or otherwise did not complete the FDFs and return them (7/280 or 2.5% of reporting sites). Table 5.5 lists these individuals and the associated sites below. The sites in this table accounted for small percentages of enrolled patients and none was the greatest enroller. All principal investigators for each site returned the appropriate financial information requested.

Table 5.5 Study Sites and Individuals Not Completing Financial Disclosure Forms

Study, Site #	PI	Sub-I, Assoc.	Problem w/ Contact	Actions Taken	Site Recruitment (N, %)
EN3202-015 #020	Hanshaw, MD		No longer at practice, moved	CL sent 11/26/02, FDF not received	13 (2.6%)
	"		No longer at practice, unable to contact	CL sent 11/26/02, FDF not received	"
	"		No longer at practice, unable to contact	CL sent 11/26/02, FDF not received	"
	"		No longer at practice, unable to contact	CL sent 11/26/02, FDF not received	"
EN3202-015 #071	S. Roth, MD		Contacted by phone	CL sent 11/26/02, FDF not received	11 (2.1%)
EN3202-015 #061	S. Wolfe, MD		SEE INFO FOR SITE #020		5 (1.0%)
	"		SEE INFO FOR SITE #020		"
	"		Contacted by phone and fax	CL sent 11/26/02, FDF not received	"
EN3202-017 #007	M. C. Gitlin		Failed to sign FDF before leaving university employment	Individual did not participate in study	6 (6.8%)
EN3202-017 #014	R. L. Rauck, MD		Failed to sign FDF	CL sent 11/26/02, FDF not received	14 (16%), 2nd largest site, largest = 18 pts
EN3202-020 #013	H. S. Mirsky, MD		Failed to sign FDF	CL sent 11/26/02, FDF not received	2 (< 1%), one of smallest sites

EN3202-021	Alan Jacobs, MD	[redacted]	Failed to sign FDF, attempted to contact several times (5/21/00). Site not responsive	Site dropped from trial participation	

FDF = financial disclosure form, CL = certified letter

All listed cases where FDFs were missing appear to have had appropriate efforts to contact the said individuals. Based on the available information, there does not appear to have been any financial arrangements that would create a conflict of interest or result in the need to exclude the results from any study sites. The disclosure appears to be adequate.

7 INTEGRATED REVIEW OF EFFICACY

7.1 Brief Statement of Conclusions

Oxymorphone extended-release was evaluated in four controlled studies, submitted in support of efficacy for this product. Each study had a different design, as shown in Table 6.1. Three were performed in chronic pain populations, and one (EN3202-012) was conducted in a post-operative pain setting. Study duration ranged from one day to four weeks of multiple dosing.

Table 6.1 NDA 21,610 Oxymorphone ER Placebo-Controlled, Clinical Studies

Protocol	Type	Design	Dose and Duration of Treatment	Primary Outcome	N Rand	Reviewer Comments
3202-015	Safety & efficacy; drug vs. placebo; adults with moderate to severe OA of knee and/or hip	Randomized, double-blind, placebo-controlled, parallel group, multiple dose; 2-7 day washout pd followed by 4 week treatment pd	Weeks 1-2: OM ER 20 q 12, OM ER 20 q12, OC ER 10 q12, Placebo Weeks 3-4: OM ER 20 q12, OM ER 40 q12, OC ER 20 q12, Placebo, Multiple dose	Baseline – Week 3, VAS-API Change	491	Failed to achieve primary outcome upon re-analysis
3202-016	Safety & efficacy; drug vs. placebo; adults with chronic low back pain	Randomized, double-blind, placebo-controlled, parallel group, multiple dose; 10-14 day titration pd followed by 18-day treatment pd	10-14 day Titration: OM ER 10-110, OC ER 20-220 qD 18-Day Double-blind Treatment Phase: OM ER 10-110 qD, OC ER 20-220 qD, Placebo, Multiple dose	Baseline – Final visit, VAS-PI Change	330	Achieved pre-specified primary outcome
3202-012	Safety & efficacy; drug vs. placebo; healthy adults who had unilateral knee arthroplasty	Randomized, double-blind, placebo- controlled, parallel-group, multiple dose, multicenter	OM ER 20 qD, Placebo Multiple dose	TOTPAR from 0-8 hrs Integrated Rescue PCA & PIR score	127	Achieved primary outcomes on re-analysis in inappropriate post-op population
3202-025	Dose ranging, safety and efficacy; adults with OA of knee or hip	Randomized, double-blind, placebo-controlled,	Week 1: OM ER 10 mg BID, OM ER 20 mg BID, OM ER 20 mg BID, Placebo Week 2: OM ER 10 mg BID, OM ER 40 mg BID, OM ER 50 mg BID, Placebo	Baseline – Final Visit, VAS-API Change	370	Failed to achieve primary outcome upon re-analysis

OM = oxymorphone, OC = oxycodone or OxyContin, ER = extended release, VAS = visual analog scale, API = arthritis pain intensity, PI = pain intensity, hrs = hours, PCA = patient controlled analgesia, PIR = pain intensity recall, N = # randomized, Rand = randomized #

Source: Table 3, EN3202 ISE, pg. 23 and 24, and EN3202-012, 015, 016, and 025 Clinical Study Reports.

Study EN3202-015 was a 4-week, multi-dose, placebo- and active-controlled study in 491 randomized patients with moderate to severe osteoarthritis (OA) pain. This study was intended to support a finding of efficacy for OM. The sponsor's analysis of the primary outcome variable of Arthritis Pain Intensity VAS score, change from baseline to end of Week 3 did reveal a statistically significant difference from placebo for the OM 40 mg treatment group. However, the use of a modified intent-to-treat population and last observation carried forward for imputing missing data created a bias in favor of study drug. Reanalysis using an all randomized population of 472 patients (excluding 18 from Site 002 and 1 not treated with study drug) with baseline observations carried forward, failed to show a statistically significant difference between any of the active treatment arms and placebo.

Study EN3202-016 was a 3-week, multi-dose, placebo- and active-controlled, withdrawal-design study in 330 randomized patients with chronic low back pain (LBP) intended to support the efficacy of oxymorphone efficacy vs. placebo. The Sponsor's analysis of the primary outcome variable (Pain Intensity VAS, in 213 of 235 patients entering the blinded treatment phase) change from baseline to end of Week 3 demonstrated a statistically significant "less worsening" compared to placebo. Note that OxyContin treatment also showed a statistically significant 'less worsening' of the primary outcome variable, when compared to placebo. The balance of secondary outcomes also favored oxymorphone ER treatment over placebo. Reanalysis using an all randomized population of 213 patients (excluding Site 023, 2 protocol violators, and 2 patients missing VAS assessments) confirmed the statistically significant difference between OM ER and placebo. In summary, the Sponsor's analysis supports the claim of OM ER efficacy compared to placebo for this study.

Study EN3202-012 was a 24-hour, double-blind, placebo-controlled, single-dose proof of concept study in 127 randomized patients with post-operative pain. This study evaluated analgesia using standard pain relief metrics and an opioid sparing evaluation. The primary outcome variables (two in total) demonstrated a statistically significant difference from placebo for OM ER 20 mg. In addition, the balance of secondary outcomes favored the study drug. The primary efficacy findings were also supported by a reanalysis of the Sponsor's efficacy data. However, this study fails to support the proposed indication and does not replicate a finding of efficacy in the intended patient population.

Study EN3202-025 was a 2-week, double-blind, placebo-controlled, dose-ranging study of OM ER 10, 40, and 50 mg in 370 randomized osteoarthritis (OA) patients, submitted in support of efficacy. The Sponsor's analysis of the primary outcome variable (Arthritis Pain Intensity (API) VAS score) change from baseline to the end of Week 2 demonstrated a statistically significant difference from placebo for the OM 40 and 50 mg groups but not for OM ER 10 mg. The secondary analysis also favored the 40 and 50 mg formulations, but suffered from the same analytical flaws as the primary analysis. The Sponsor utilized a last observation carried forward method for imputing missing

data. Reanalysis using an all randomized population of 357 patients (13 patients excluded for missing data and unblinding) and using baseline observation carried forward (BOCF), failed to show a statistically significant difference between any of the active treatment arms and placebo. Furthermore, patients dropping out from the OM 40 and 50 groups during Week 1 had imputed data reflecting treatment on the lower titration dose, OM 20 mg bid, planned for Week 1. In summary, analysis of the data using BOCF imputation of missing values does not find any statistical support for the efficacy of the OM 10, 40, or 50 mg doses compared to placebo.

In summary, the Sponsor failed to provided replicated evidence of oxymorphone ER efficacy in the intended patient population in two adequate and well-controlled studies.

7.2 General Approach to Review of the Efficacy of the Drug:

The oxymorphone extended-release (ER) efficacy review was conducted by reviewing the original study protocols and corresponding clinical study reports of each pivotal trial, in detail. This included examination of tables, figures, appendix data, patient data listing, and where appropriate, case report forms (CRFs). The results of all the placebo-controlled studies were reviewed, analyzed, and summarized in order to evaluate whether the Sponsor successfully met their pre-specified outcomes.

7.3 Detailed Review of Trials by Indication

7.3.1 ADEQUATE AND WELL-CONTROLLED PIVOTAL TRIALS:

7.3.1.1 STUDY #1 - EN3202-015:

Title: Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Ranging Comparison of the Efficacy and Safety of Controlled Release Oxymorphone, Controlled-Release Oxycodone (OxyContin®) and Placebo in the Treatment of Osteoarthritis of the Knee and/or Hip

Objectives:
Primary:

- Evaluate efficacy of oxymorphone (OM) extended release (ER) 40 mg q12 h vs. Placebo (PBO) in moderate to severe OA
- Evaluate safety and tolerability of OM ER 20 and 40 mg q12 h vs. OxyContin (OC) 20 mg q12 hours

Secondary:

Evaluate the efficacy of the following comparisons:

- OM ER 20 mg q12 h vs. PBO
- OM ER 20 mg q12 h vs. OM ER 40 mg q12 h
- OM ER 20 mg q 12 h and OM ER 40 mg q 12 h vs. OC 20 mg q12 h
- OM ER 20 mg q12 h vs. OC 10 mg q12 h

Evaluate the safety and tolerability of:

- OM ER 20 mg q12 h with OC 10 mg 12 h

Study Duration: 4 weeks

Population: N=490 planned patients to insure 240 evaluable subjects (60 patients per group)

Inclusion Criteria:

- Male or female patients, ≥ 40 years old
- Women of childbearing potential were to be using medically acceptable forms of contraception and were to have a negative serum or urine pregnancy test within 7 days of 1st dose of study medication
- Subjects were to be in general good health
- Subjects were to have a diagnosis of Osteoarthritis (OA) defined by:
  1. Typical knee or joint symptoms
  2. ≥ 1 knee or joint requiring 75 of 90 days treatment with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), acetaminophen (APAP), or opioids

3. Knee or hip (index joint) radiographic evidence of OA within 6 months of screening

- Subjects were to have had suboptimal treatment with NSAIDs or prior treatment with opioids
- Subjects were to have a baseline VAS pain intensity (PI) ≥ 40 mm in Index Joint

Exclusion Criteria:

- Presence of inflammatory disorders, chronic pain syndrome, fibromyalgia, or other significant joint disease
- Knee or hip arthroplasty required within two months of screening
- Use of confounding analgesics, steroids, or corticosteriods (PO, IA, IV, IM) within 1 month of 1st study dose, or inability to discontinue NSAIDs,
- Significant history of substance or alcohol abuse
- Hepatic or renal abnormalities defined as AST, ALT, Cr > 1.5x upper limit of the normal range (ULN)
- History of respiratory insufficiency, seizures, ileostomy, cancer (within 3 years of screening), active neoplastic disease

Study Design:

There were to be seven total visits in this 6-week study: visits were to occur at screening, baseline, treatment Week 1 through treatment Week 4, and a final post-treatment (Week 5) visit.

- Screening, Washout, and Randomization:

  Screening – Eligibility was to be determined, index joint was to be identified and baseline EKG, safety and efficacy assessments were to be collected.

  Washout – Eligible patients were to enter a 2 – 7 day washout period where all analgesics were to be discontinued.

  Randomization - When a patient's index joint pain intensity reached ≥ 40 mm VAS, the patient was to return to the study center to be randomized to one of the following treatment arms:

  1. Oxymorphone (OM) ER 20 mg q12 h
  2. OM ER 40 mg q12 h
  3. OxyContin (OC) ER 20 mg q12 h
  4. Placebo (PBO) q12 h

- Treatment Period: Phase 1 (Weeks 1-2) through Phase 2 (Weeks 3-4)
  1. OM ER 40 mg patients were to be started at OM ER 20 mg q12 h for 2 weeks (Phase 1) and then increased to the final titrated dose of 40 mg q12 h for the last two weeks (Phase 2).
  2. OC ER 20 mg patients were to be started at the 10 mg dose q12 h for 2 weeks (Phase 1), before increasing to the final titrated dose for 2 weeks (Phase 2).

- Dose Selection, Concomitant Therapy and Rescue

  Study Drug Dose Selection and Interval:

  - The Sponsor states that the q12 h dosing interval for OM ER was selected based on the fed and fasted modified-release characteristics of the tablets in previous bioavailability (BA) studies. The OC 20 mg dose was chosen based on efficacy findings in previous clinical trials with OA.

  Concomitant Therapy:

  - Restricted: NSAIDs (other than prophylactic ASA), topical analgesics, systemic or intra-articular (IA) corticosteroids, and glucosamine were not to be allowed.
  - Allowed: Antidepressants were to be allowed if the patient was on a stable dose for 21 days prior to the double-blind period of study.
  - Rescue Medication: Rescue medication was not to be part of this study.

Table EN3202-15.2 Schedule of Assessments
(Source: Table 9.3, EN3202-015 Clin Study Report, pg. 23 of 77)

	Pretreatment		Double-Blind		Post-Treatment	
	Screening	Washout[a]	Baseline	Weeks 1, 2, 3, 4	Week 5	Early Termination
Medical History	X					
X-ray	X[b]					
Vital Signs	X		X	X	X	X
EKG	X			X[c]		X
Physical Examination[d]	X				X	X
Pregnancy Tests[e]	X		X	X	X	X
Clinical Laboratory Tests[f]	X		X	X	X	X
Adverse Events			X	X	X	X
Study Medication[g]			X	X		
Nausea, Drowsiness, Sleep Assessments[h]	X		X	X		X
Osteoarthritis Assessments[i]	X		X	X		X
SF-36 Health Survey[j]	X		X	X		X
Physical Dependence Survey[k]					X	X

[a] A 2- to 7- day washout period during which analgesic use was discontinued, to establish baseline pain.
[b] Radiographic evidence of osteoarthritis (index knee or hip) was required within six months of screening.
[c] The 12-lead EKG was obtained at the visits at screening and the end of Week 4, or upon early termination.
[d] A physical examination was done at screening and at the end of Week 5, or upon early termination.
[e] A negative serum pregnancy test was required within seven days prior to the first dose of study medication. Serum pregnancy tests were performed at screening, baseline, at the end of Weeks 2 and 5, or upon early termination.
[f] Clinical laboratory tests were done at each visit.
[g] Double-blind study medication was first taken on the day of randomization (baseline), with a dose increase after two weeks of treatment. Patients randomized to receive either oxymorphone CR 20 mg or 40 mg received 20 mg q12h for Weeks 1 and 2. Patients randomized to receive oxymorphone CR 40 mg were increased to 40 mg q12h for Weeks 3 and 4, and patients randomized to receive oxymorphone CR 20 mg (or placebo) underwent a sham increase for Weeks 3 and 4. Patients randomized to receive OxyContin received 10 mg q12h for Weeks 1 and 2 and OxyContin 20 mg for Weeks 3 and 4. (All patients were treated with non-opioid analgesics for Week 5.)
[h] Nausea VAS, Drowsiness VAS, and Sleep Questionnaire were completed at visits through the end of Week 4.
[i] Osteoarthritis was assessed using the WOMAC, the Arthritis Pain Intensity VAS, and Patient's and Physician's Global Assessment of Arthritis at visits through the end of Week 4. Beginning the day after the screening visit, patients recorded their Arthritis Pain Intensity VAS in a diary once a day at approximately 8:00 PM.
[j] The SF-36 Health Survey was completed by the patient at visits through the end of Week 4.
[k] The Physical Dependence Survey was completed by the patient at the Week 5 visit, or upon early termination.

Outcome Measures:

Efficacy (for additional detail on the assessment instruments see Appendix 11.1):

These measures were to be assessed at baseline and at each subsequent patient visit (total of 7 visits). Efficacy instruments were to include:

- Arthritis Pain Intensity Visual Analog Scale (VAS) scale (0 = 'no pain' to 100 mm = 'extreme pain') applied to the Index Joint
- WOMAC Osteoarthritis (OA) Index (a composite of Pain, Stiffness, and Physical Function 0-100 mm VAS scales)
- Patient and Physician Global Assessment Scales (0 mm = 'very good' to 100 mm = 'very poor' visual analog scale) of Osteoarthritis (OA)
- Sleep assessments and SF-36 Health Survey.

Safety:

Adverse events (AEs), Physical exams (PEx), vital signs, and EKGs

Statistical Assessment:

All statistical analyses were to be performed as two-tailed tests with statistical significance defined as $p \leq 0.05$. The primary and secondary analysis populations were to be the Intent-to-Treat (ITT) population, as defined below. Early discontinuations were to be imputed using the last observation carried forward (LOCF). A supportive statistical analysis of the primary efficacy endpoint was also performed using a more conservative ITT_2 population definition (see Data Sets section for definition).

Primary Efficacy Variables:

- WOMAC OA Index Pain Subscale score - Was to be calculated as the sum of responses to questions 1-5 of the associated questionnaire. Each question response was to be evaluated on a 100 mm VAS scale.

- Arthritis Pain Intensity (API) VAS score - This was to be calculated as the change from baseline to the end of Week 3 visit, using the ITT population with LOCF. Note baseline API had to be ≥ 40 mm in order to be eligible for randomization.

Secondary Efficacy Variables:

- These variables were calculated as the mean percent change from baseline to Weeks 1, 2, 3, 4 for:
  1. Arthritis Pain Intensity VAS score (taken from daily patient diaries for Weeks 1, 2, and 4,)
  2. WOMAC OA Index Pain, Stiffness, and Physical Function Subscale Scores
  3. WOMAC Composite Index
  4. Patient's Global Assessment of OA
  5. Physicians's Global Assessment of OA
  6. Patient's Sleep Assessment
  7. SF-36 Health Survey
  8. Incidence of patient withdrawals due to lack of efficacy

Data Sets:

- Intent-to-Treat (ITT) Population was to be defined as all randomized patients with efficacy data collected at baseline and the Week 1 visit (the 1st primary efficacy data collection point while on treatment). Patients that dropped out prior to Week 1 due to 'lack of efficacy' and for no other reason, were to be imputed using 'baseline observation carried forward (BOCF). Otherwise, patients that discontinued for other reasons and had no post-baseline measurements were excluded. All other missing data was to be imputed using LOCF. Note that the efficacy analyses evaluated in this review were to be based on this analysis population, excluding subjects from study site 002. Site 002 was excluded from the efficacy analysis for reasons described below.

- ITT-2 Population was constructed in order to perform a secondary analysis of the primary efficacy results with a broader ITT population, also excluding study site 002. This group was defined as all randomized patients who had baseline and ≥ 1 post-baseline assessment. Patients discontinuing during the 1st week, or who did not return for a termination visit, had their efficacy information imputed from their pain diaries using LOCF.

- Efficacy Evaluable Population was to be defined as all patients who achieved their randomized dose and had efficacy data recorded at baseline and Week 3 visits.

Changes in Planned Analyses and Post-Hoc Analyses:

1. Diversion of study drug was discovered at Site 002 (Dr. Appelrouth, PI) after the data base was locked. All appropriate Government Agencies were notified including the FDA (notified on 4/25/00.) As a result of concerns regarding data integrity, efficacy analyses were performed with and without the data (18 total patients) from this site. Safety information from this site was included in the safety analysis.

2. The statistical analysis plan (SAP) was revised to specify a single primary test to judge efficacy, based upon input from the Agency. The final analysis plan changed the WOMAC OA Index Pain Subscale Score to a secondary variable, leaving the Arthritis Pain Intensity VAS scale as the sole primary efficacy variable.

Protocol Amendments:

Amendment 1 (12/3/99): (Instituted after beginning enrollment but before unblinding)

- Increased study centers from 25 to 30, increased patients to be enrolled to 480 in order to achieve 240 evaluable patients
- Modified exclusion criteria by increasing AST/ALT to 2x ULN (from 1.5x ULN) and serum creatinine increased to > 1.5x ULN (from 1x ULN)

7.3.1.2 SPONSOR RESULTS for EN3202-15:

Disposition:

491 patients were randomized with 489 receiving ≥ 1 dose of study drug. Two patients randomized to OM ER 20 mg did not take study medication (# 0020021 because her physician did not want her to participate – reason listed as OTHER, and #0030002 because of non-compliance). There were 222 (45.2%) total discontinuations of which 140 (63% of 222) were due to AEs. Sixty one patients discontinued due to lack of efficacy, of which 34 were in the placebo group. Table 15.3a shows the discontinuations and exclusions, based upon the sponsor's data.

Table EN3202-15.3a Patient Disposition
(Source: Table 10.1, EN3202-015 Clin Study Report, pg. 40 of 77)

	OCR 40 N (%)	OCR 20 N (%)	OC 20 N (%)	Placebo N (%)	Total N (%)	p-value[a]
Randomized	121	121	125	124	491	
Completed According to Protocol	53 (43.8%)	63 (52.1%)	75 (60.0%)	78 (62.9%)	269 (54.8%)	
Discontinued	68 (56.2%)	58 (47.9%)	50 (40.0%)	46 (37.1%)	222 (45.2%)	< 0.0001
Insufficient Therapeutic Effect	9 (7.4%)	5 (4.1%)	13 (10.4%)	34 (27.4%)	61 (12.4%)	
Non-Serious Adverse Event	57 (47.1%)	46 (38.0%)	31 (24.8%)	6 (4.8%)	140 (28.5%)	
Non-Compliance with Protocol	2 (1.7%)	2 (1.7%)	2 (1.6%)	1 (0.8%)	7 (1.4%)	
Patient Requested Withdrawal	0 (0.0%)	2 (1.7%)	3 (2.4%)	2 (1.6%)	7 (1.4%)	
Investigator Withdrew Patient	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.2%)	
Lost to Follow-Up	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (0.8%)	2 (0.4%)	
Other	0 (0.0%)	2 (1.7%)	1 (0.8%)	1 (0.8%)	4 (0.8%)	
Safety Population[b]	121	119	125	124	489	
ITT[c] Population: All Centers	78	86	111	117	392	
ITT Population: Excluding Center 2[d]	75	82	106	113	376	
ITT-2[e] Population: Excluding Center 2	114	114	120	119	467	
Evaluable Population[f]: All Centers	49	59	76	77	261	
Evaluable Population: Excluding Center 2	47	57	73	75	252	

Data source: Appendix 15.3 Table 1.1 and Listing 1.
OCR = Oxymorphone CR and OC = OxyContin.
[a] P-value from Cochran-Mantel-Haenszel test adjusted by investigational center.
[b] All patients who were randomized and who received at least one dose of study medication.
[c] All patients who received at least one dose of study medication and who had efficacy information recorded at the baseline and Week 1 (or later) visits or who dropped out before Week 1 due to insufficient therapeutic effect.
[d] The number of patients in Center 2 were: 4 in OCR 40 group, 4 in OCR 20 group, 5 in OC 20 group, and 5 in placebo group.
[e] All patients who received at least one dose of study medication and who had baseline and at least one postbaseline efficacy assessment.
[f] All patients who achieved their randomized dose and had efficacy information recorded at the baseline and Week 3 visits.

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As detailed in Table 15.3b, 222 subjects (45.2%) discontinued early. One hundred forty subjects discontinued due to adverse events (AEs). Considerably more subjects discontinued due to AEs from the OM ER 20 group than from the OC 20 group (38% vs. 24.8%, respectively.) The largest number discontinued due to AEs occurred in the OM ER 40 group (47.1%), and the least from placebo group (4.8%.) Conversely, the number of subjects discontinuing due to lack of efficacy was greatest in the placebo group and smallest in the OM ER 40 group (27.4% vs. 7.4%, respectively.)

Three categories ('Patient Requested Withdrawal', 'Investigator Withdrawn', and 'Other') of patient discontinuations were evaluated in detail, by examining the associated CRTs and CRFs. Table 15.3b lists these 12 subjects.

Table EN3202-15.3b Patient Discontinuation Details

Patient ID	Treatment	D/C Reason	Reason for Request	Reviewer Recoding Reason
0740015	PBO	Inv. Withdrawn	Required epidural for back pain, unrelated to arthritis	LOE
0020003	OC 20 ER	Patient Requested	Transportation difficulties	OK
0190004	OM 20 ER	" "	No longer interested, had a cold	Non-SAE
0240007	OC 20 ER	" "	lacked efficacy	LOE
0240011	PBO	" "	No time for study	OK
0700035	OC 20 ER	" "	Inadequate pain control	LOE
0730031	PBO	" "	Didn't want to travel to study site	OK
0740018	OM 20 ER	" "	Extreme nausea & drowsiness	Non-SAE
0020021	OM 20 ER	Other	Primary did not want patient to participate	OK
0020022	OC 20 ER	Other	Site closed by sponsor	OK
0420003	PBO	Other	Protocol Violation, No X-Ray confirmation of OA	NC w/ Protocol
0420014	OM 20 ER	Other	Protocol Violation, creatinine 1.3	NC w/ Protocol

Source: Appendix 15.3 and Listing 1 of EN3202-015 Clinical Study Report, SAS transport data files, LOE = Lack of Efficacy, NC = non-compliant, PBO = placebo, OC = OxyContin, OM = Oxymorphone, CR = continuous release

Based on this review, several patients in the Sponsor's Table 15.3b should have been coded differently. One subject (# 0740018) should have been coded as withdrawal due to AE and two (#s 0240007 and 0700035) should have been coded as Insufficient Therapeutic Effect (coded as 'lack of efficacy' in 15.3b). Re-coding of these individuals slightly changes the disposition categories as shown in Table 15.3c, below.

Table EN3202-15.3c Patient Discontinuations, Reviewer Recalculation

	OM ER 40 mg	OM ER 20 mg	OC ER 20 mg	Placebo
Randomized	121	121	125	124
Discontinued	68 (56.2%)	58 (47.9%)	50 (40.0%)	46 (37.1%)
Reason for Withdrawal				
Insufficient Therapeutic Effect	9 (7.4%)	5 (4.1%)	15 (12.0%), added 2 pts	35 (28.2%), added 1 pt
Non-SAE	57 (47.1%)	48 (39.7%), added 2 pts	31 (24.8%)	6 (4.8%)
Non-Compliance with Protocol	2 (1.7%)	3 (2.5%), added 1 pt.	2 (1.6%)	2 (1.6%), added 1 pt
Patient Requested Withdrawal	0 (0.0%)	2 (1.7%)	3 (2.4%)	2 (1.6%)
Investigator Withdrew Patient	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
Lost to Follow-up	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (0.8%)
Other	0 (0.0%)	2 (1.7%)	1 (0.8%)	1 (0.8%)

Source: Table 10.1, EN3202-015 Clin Study Report, pg. 40 of 77 & EN3202-015 TERM.XPT Transport File

The Sponsor's ITT and evaluable populations excluded a number of subjects for failing to meet the defined criteria. While the Sponsor performed their efficacy analyses on the ITT population, the Agency chose a more inclusive population consisting of all patients randomized to treatment, excluding the 21 subjects from Site 002. Of 489 patients randomized and treated with at least one dose of study medication, 472 subjects (117 in OM ER 40 mg, 116 in OM ER 20 mg, 120 in OC 20 mg, and 119 in Placebo groups) were included in the Division's re-analysis population.

Protocol Violations and Exclusions:

A number of violations and exclusions occurred in this study. The Sponsor provided a listing of protocol deviations. A summary table is shown below to illustrate the types of deviations encountered. Many of the violation and exclusions were due to visit times occurring at non-specified times, missed doses, and incomplete diaries/assessments. Table 15.4a below lists 13 patients that were excluded from either ITT-2 or Efficacy Evaluable categories, and included in the safety analysis (except for #040-0016 who was excluded from all analyses due to diagnosis of fibromyalgia). This last subject was included in the Agency analysis population (472 all randomized and treated subjects excluding Site #2).

Table EN3202-15.4a Protocol Deviations
(Site 002 Not Included)

Number (%)	Violation
8 (61.5)	Missing or Incomplete Data
3 (23.1)	Missed or Outside Range Visit Times
1 (7.7)	Medications Not Returned
1 (7.7)	Non-Compliance (Family had meds unblinded)

Source: EN3202-015 Appendix 15.2 Statistical Methods, Compilation of Protocol Violations

Errors:

Study audits were performed by the Sponsor and several errors (typically omitted information from CRFs) were detected and evaluated. These errors were discovered after the database was locked and are presented below, from the Sponsor's tabular listing of the center, patient ID, and finding. The Sponsor stated that the findings did not warrant reopening the database as adverse events found during the audit represented for the most part, additional occurrences of events previously reported.

Table EN3202-15.4b Patient Errata
(Source: Table 10.2, EN3202-015 Clin Study Report, pg. 42 of 77)

Table 10.2: Potential Errata Summary

Center / Investigator	Patient # (Initials)	Finding – Potential Errata
069, [redacted]	0690025	AEs of dizziness and weakness missing from CRF
	0690035	AE of headache found to be baseline condition; AE of restlessness missing from CRF
	0690018	AEs of bilateral thigh pain and lower right jaw pain missing from CRF.
	0690017	Tremors listed as AE were found to be medical history.
	0200009	AEs of pain, stiffness, etc. found to be baseline condition
077 [redacted]	0770020	AEs of mild tenting of skin and very dry skin of arms legs and lips missing from CRF
037 [redacted]	0370007	AEs of generalized itching, very tired and lightheaded noted in patient diary were not recorded on AE CRF
041, [redacted]	0410003	AEs of diarrhea, constipation and sedation missing from CRF
		Vioxx omitted from conmed possible protocol violation
	0410007	AEs of dizziness and headache missing from CRF
074, [redacted]	0740015	The X-ray of the right hip, which was the reference joint for this patient, was read as normal by an outside consultant. The patient is considered a protocol violation.
042, [redacted]	0420001	AEs of headache, cottonmouth and sweating missing from CRF
	0420002	AEs of nervousness or restlessness, smelling drug on person/sweat and tremors and shivering missing from CRF

AE = adverse event

The Sponsor provided CRFs for 8 of 12 subjects in the table above. The available CRFs were examined but no obvious other irregularities were observed. Four CRFs were not provided and a request was sent to the Sponsor for these documents.

Demographic and Baseline Characteristics:
The majority of patients were Caucasian women with a greater than 5-year history of OA, primarily in the knee. The groups were reasonably similar across the demographic characteristics. The Sponsor states there were no statistically significant difference between groups.

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Table EN3202-15.5 Study Patient Demographics/Baseline Characteristics
(Source: Table 10.3, EN3202-015 Clin Study Report, pg. 43 of 77)

		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

Sponsor's Efficacy Analysis Results:

Primary Efficacy Variables:

- Arthritis Pain Intensity (API) VAS (from patient visits) change: Baseline - Week 3
  The Sponsor's analysis utilizing the ITT population (376 patients after excluding center #002) and LOCF for imputed scores is presented in Table 15.6a, which demonstrates the mean baseline scores and the change from baseline at Weeks 3 and 4 as least square mean differences. The OM ER 40 mg group demonstrated a statistically significant greater reduction in mean pain intensity from baseline to the end of Week 3, compared to placebo. There were no statistically significant differences for the OM ER 20 and OC ER 20 groups compared to placebo. The raw

mean pain intensity scores at baseline and Weeks 3 and 4 without imputed data for missing values are presented in Table 16.5b for reference. Graph 15.1 depicts the raw data from Table 16.5b.

Table EN3202-15.6a Mean Change in Arthritis Pain Intensity VAS Scores (ITT population excluding center 002)
(Source: Table 11.1, EN3202-015 Clin Study Report, pg. 47 of 77)

	Treatment	N	Mean (SE)	LSMean Difference from Placebo	p-value	95% CI
Baseline	OCR 40	75	78.7 (1.8)	--	--	--
	OCR 20	82	78.9 (1.9)	--	--	--
	OC 20	106	76.8 (1.5)	--	--	--
	Placebo	113	79.3 (15)	--	--	--
Week 3	**OCR 40**	**71**	**-29.8 (3.3)**	**-11.4**	**0.0079**	**(-19.8, -3.0)**
	OCR 20	78	-25.3 (3.2)	-6.9	0.0976	(-15.1, 1.3)
	OC 20	103	-22.6 (2.8)	-4.2	0.2817	(-11.7, 3.4)
	Placebo	**111**	**-18.4 (2.7)**			
Week 4	OCR 40	71	-33.7 (3.5)	-14.0	0.0017	(-22.8, -5.3)
	OCR 20	78	-26.6 (3.3)	-6.9	0.1096	(-15.4, 1.6)
	OC 20	103	-26.1 (2.9)	-6.5	0.1065	(-14.3, 1.4)
	Placebo	111	-19.7 (2.8)			

Data source: Appendix 15.3, Table 4.1.1.1, Statdoc 4.1.1.1.
OCR = Oxymorphone CR and OC = OxyContin
The primary efficacy comparison is bolded.

Table EN3202-15.6b Raw Arthritis Pain Intensity Scores (VAS, ITT Population excluding Site #002)

	Mean API in mm, (SE), N ITT Population excluding Site 002		
Statistic	**Baseline**	**Week 3**	**Change**
OM 40 mg ER	78.7 (1.8), n=75	43.7 (4.6), n=42	-37.9 (4.3), n=42
OM 20 mg ER	78.9 (1.9), n=82	51.2 (3.9), n=48	-29.5 (3.6), n=48
OC 20 mg ER	76.8 (1.5), n=106	48.7 (3.4), n=62	-26.7 (3.6), n=62
Placebo	79.3 (1.5), n=113	47.8 (3.9), n=61	-30.8 (4.6), n=61

Data Source: Appendix 15.3, Table 4.1.1.1, EN3202-015 Clin Study Report, pg. 2 of 7.

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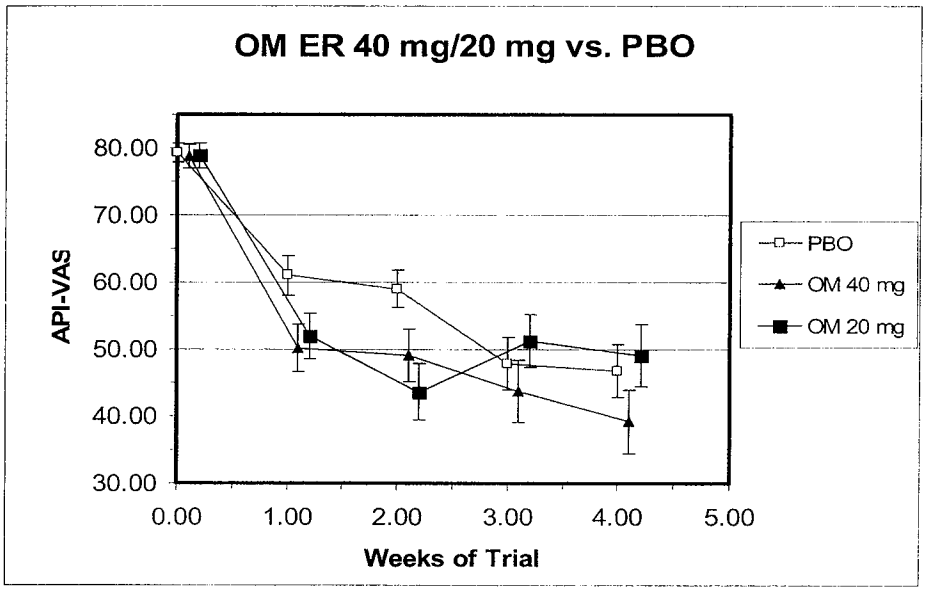
Figure EN3202-15.1 Raw Mean Arthritis Pain Intensity vs. Time (VAS, LOCF, ITT population)



Reviewer Primary Efficacy Re-Analysis Results:

In a study in which patients in the active treatment arms tend to drop out of the study for adverse events while patients in the placebo arm tend to drop out due to lack of efficacy, imputing missing data with LOCF results in a bias favoring the active treatment. Furthermore, this method does not accurately reflect the efficacy of the product because the scores carried forward from patients who drop out due to AEs reflect product efficacy at a dose that is intolerable. The data was reanalyzed by the Agency Statistical Reviewer, Dr. Price. This reanalysis was performed with an 'all randomized and treated' population of 472 patients (excluding 18 Site 002 patients) with missing data imputed using baseline observations carried forward (BOCF).

The results of the reanalysis are presented in Table 15.6c. There is no statistically significant difference when either OM 40 or OM 20 are compared with placebo. There was also no statistically significant difference between OC and placebo.

Table EN3202-15.6c Mean Change 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	OM ER 40	117	78.3 (1.5)				
	OM ER 20	116	77.8 (1.5)				
	OC 20	120	76.0 (1.5)				
	Placebo	119	79.4 (1.5)				
			Mean Change				
Week 3	OM ER 40	117	-17.1 (2.5)	-16.9 (2.4)	0.7	0.8485	(-6.0, 7.4)
	OM ER 20	116	-14.6 (2.2)	-14.7 (2.4)	2.8	0.4190	(-3.9,9.5)
	OC20	120	-15.3 (2.3)	-16.0 (2.4)	1.5	0.6590	(-5.2,8.2)
	Placebo	119	-18.1 (2.8)	-17.5 (2.4)			
Week 4	OM ER 40	117	-17.8 (2.5)	-17.6 (2.5)	2.3	0.5108	(-4.6,9.3)
	OM ER 20	116	-14.5 (2.4)	-14.6 (2.5)	5.3	0.1390	(-1.7, 12.3)
	OC20	120	-18.1 (2.4)	-18.8 (2.5)	1.1	0.7509	(-5.8, 8.1)
	Placebo	119	-20.0 (2.9)	-19.9 (2.5)			

Source: Agency Biostatistical Reviewer Analysis Results

Sponsor Efficacy Analysis Results for Secondary Variables:

The Sponsor's secondary efficacy analyses were performed using the same patient population and method for imputing missing scores (LOCF) as the primary efficacy analyses. The results are presented below. The Sponsor did not correct for multiple comparisons. Reanalyses were not performed by this reviewer or by the statistical reviewer in light of the negative findings from the reanalysis of the primary efficacy analysis.

- Arthritis Pain Intensity VAS score (from patient diaries):
  Both OM ER 20 and 40 mg groups showed a statistically significant difference (p=0.009 and 0.004, respectively), compared to PBO at Weeks 3-4 (called Phase 2 of study). OxyContin (OC) 20 mg showed no difference (p = 0.15) compared to PBO. Table 15.8 below shows the actual LS Mean change in VAS scores measured from baseline with the associated p-values resulting from a comparison with placebo.

- WOMAC OA Index Pain Subscale:
  This variable was evaluated by comparing the Least Square (LS) mean change in the WOMAC pain subscale from baseline to Weeks 3 and 4. Missing data from early discontinuation was imputed using LOCF. Both OM 20 and 40 mg treatment groups showed a statistically significant difference compared to PBO, at Weeks 3 (p= 0.0097 and p=0.001, respectively) and 4 (p= 0.018 and p=0.0018, respectively). OC 20 mg showed no statistical difference to PBO at these times. The secondary outcome data for all the WOMAC OA subscales is shown in Table 15.9 below abstracted from the sponsor's clinical study report.

Table EN3202-15.8 Mean Change from Baseline in API VAS Scores from Patient Diaries - (ITT population excluding center 002)
(Source: Table 11.4, EN3202-015 Clin Study Report, pg. 52 of 77)

	Treatment	N	Mean (SE)	p-value* (Compared to Placebo)
Baseline	OCR 40	75	72.8 (2.3)	--
	OCR 20	78	71.5 (2.8)	--
	OC 20	102	73.2 (2.0)	--
	Placebo	111	74.6 (1.9)	--
Phase 1	OCR 40	71	-19.8 (2.6)	--
(Weeks 1-2)	OCR 20	78	-21.4 (2.6)	--
	OC 20	102	-15.6 (2.2)	--
	Placebo	111	-11.3 (2.2)	--
Phase 2	OCR 40	71	-31.8 (2.7)	0.0039
(Weeks 3-4)	OCR 20	78	-27.9 (2.6)	0.0092
	OC 20	102	-25.3 (2.2)	0.1518
	Placebo	111	-21.1 (2.3)	

Data source: Appendix 15.3, Table 4.1.3.1, Statdoc 4.1.3.1.
* From repeated measure analysis of covariance model with change from baseline as the outcome, treatment, pooled center, phase, day (nested in phase), treatment-phase interaction as factors, and baseline value as a covariate. The intrapatient covariance structure that fit the data the best is first-order autoregressive. P-values are from contrast statements.
OCR = Oxymorphone CR and OC = OxyContin

- WOMAC OA Stiffness Subscale:
  The stiffness subscale was evaluated in a similar manner to the pain scale. Here the OM 20 mg showed a statistically significant difference from PBO by Week 4 (p=0.035), and approached statistical significance at Week 3 (p=0.06). No other Week 4 treatment group differed significantly from PBO, including OM 40 mg or OC 20 mg. Again, the least squares mean changes and associated p-values are shown in Table 15.9.

- WOMAC OA Physical Function Subscale:
  The OM 20 mg group showed a statistically significant difference from PBO at Weeks 3 and 4 (p=0.015 and p=0.048), while the OM 40 mg group showed a statistically significant difference only at Week 4 (p=0.02). OC 20 mg did not differ statistically from PBO. Refer to Table 15.9 for the least squares mean changes in the subscale and the associated p-values.

- WOMAC Composite Index
  The OM 20 and 40 mg groups showed a statistically significant difference from PBO at Weeks 3 (p=0.014 and 0.03, respectively) and 4 (p=0.037 and 0.017, respectively) while the OC 20 mg did not differ statistically from PBO at either time. Refer to

Table 15.9 for actual least squares mean changes in the subscale and the associated p-values.

Table EN3202-15.9 Baseline to Week 3 and 4 LS Mean Changes in WOMAC OA VAS Subscales of Pain, Stiffness, Physical Function, and Composite Subscales (VAS scores, ITT population excluding Center 002)

Variable	Time	Treatment	LSMean Diff from PBO (mm)	P-value
WOMAC OA Pain Subscale	Week 3	**OM ER 40**	**-58**	**0.001**
		OM ER 20	**-44**	**0.01**
		OC ER 20	-21	0.18
	Week 4	**OM ER 40**	**-57**	**0.002**
		OM ER 20	**-42**	**0.018**
		OC ER 20	-28	0.09
WOMAC OA Stiffness Subscale	Week 3	OM ER 40	-9	0.24
		OM ER 20	-14	0.06
		OC ER 20	-3	0.69
	Week 4	OM ER 40	-8	0.31
		OM ER 20	**-16**	**0.034**
		OC ER 20	-6	0.38
WOMAC OA Physical Function Subscale	Week 3	OM ER 40	-108	0.054
		OM ER 20	**-133**	**0.015**
		OC ER 20	-29	0.56
	Week 4	**OM ER 40**	**-135**	**0.02**
		OM ER 20	**-111**	**0.05**
		OC ER 20	-46	0.38
WOMAC OA Composite Index Subscale	Week 3	**OM ER 40**	**-171**	**0.03**
		OM ER 20	**-190**	**0.014**
		OC ER 20	-55	0.44
	Week 4	**OM ER 40**	**-197**	**0.017**
		OM ER 20	**-167**	**0.037**
		OC ER 20	-77	0.29

Source: Tables 11.3,5,6, and 7 of EN3202-015 Clinical Study Report, pages 52 – 55 of 77

- Patient's Global Assessment of OA
  Analysis of the change from baseline to Weeks 3 and 4 show that the OM ER 40 mg group showed a statistically significant difference from PBO (p=0.017 at Week 3 and 0.03 at Week 4, respectively), while the OM ER 20 mg group only achieved statistically significance at Week 3 (p=0.023). Inspection of Table 15.10 shows that OC 20 mg did not differ statistically from placebo at either time point.

- Physicians's Global Assessment of OA
  All active treatments (OM 20 and 40 mg, OC 20 mg) showed a statistically significant difference from PBO at Weeks 3 and 4 (see Table 15.10 for values).

- Patient's Sleep Assessment
  Analysis of the Quality of Sleep VAS scores show that the OM 40 mg and OC 20 mg groups showed a statistically significant difference from PBO at Week 4 (p = 0.009 and 0.036, respectively), while the OM ER 20 mg group differed statistically from PBO only at Week 3 (p = 0.038), as shown in Table 15.10.

- SF-36 Health Survey: Standardized Physical Component
  Analysis of the physical component of the SF-36 health survey questionnaire showed that the OM 40 mg group showed a statistically significant difference from PBO at Weeks 3 and 4 (see Table 15.10), while the OM 20 mg group difference from placebo achieved statistically significance only at Week 4.

- SF-36 Health Survey: Standardized Mental Component
  This analysis showed that the OM ER 40 mg group and OC 20 mg group showed a statistically significant difference from PBO at Week 3 ($p = 0.045$ and 0.014, respectively as shown in Table 15.10 below), while the OC 20 mg group also showed a statistically significant difference at Week 4 ($p = 0.02$).

Table EN3202-15.10 Baseline to Week 3 and 4 LS Mean Changes in Listed Secondary Outcome Variables (VAS scores, ITT population excluding Center 002)

Variable	Time	Treatment	LSMean Diff from PBO (mm)	P-value
Patient's Global Assessment of OA	Week 3	**OM ER 40**	**-9.9**	**0.017**
		OM ER 20	**-9.2**	**0.023**
		OC ER 20	-5.4	0.15
	Week 4	**OM ER 40**	**-9.1**	**0.033**
		OM ER 20	-3.7	0.38
		OC ER 20	-5.9	0.13
Physician's Global Assessment of OA	Week 3	**OM ER 40**	**-12.8**	**0.0008**
		OM ER 20	**-16.1**	**0.0001**
		OC ER 20	**--10.9**	**0.001**
	Week 4	**OM ER 40**	**-13.2**	**0.0008**
		OM ER 20	**-13.7**	**0.0004**
		OC ER 20	**-9.2**	**0.0095**
Patient's Sleep Assessment	Week 3	OM ER 40	6.2	0.11
		OM ER 20	**7.9**	**0.04**
		OC ER 20	**5.1**	**0.15**
	Week 4	**OM ER 40**	**10.5**	**0.009**
		OM ER 20	6.2	0.12
		OC ER 20	**7.7**	**0.04**
QSF-36 Standard Physical Component	Week 3	**OM ER 40**	**2.9**	**0.008**
		OM ER 20	2.0	0.06
		OC ER 20	1.5	0.13
	Week 4	**OM ER 40**	**2.7**	**0.018**
		OM ER 20	1.5	0.17
		OC ER 20	**2.2**	**0.04**
QSF-36 Standard Mental Component	Week 3	**OM ER 40**	**-2.8**	**0.046**
		OM ER 20	-1.0	0.47
		OC ER 20	**-3.1**	**0.014**
	Week 4	OM ER 40	-2.7	0.06
		OM ER 20	-0.7	0.6
		OC ER 20	**-3.0**	**0.02**

Source: Tables 11.8,9,11, and 12 of EN3202-015 Clinical Study Report, pages 56 – 61 of 77

- Incidence of Patient Withdrawals due to Lack of Efficacy:
  The proportion of withdrawals was statistically significantly higher in the PBO group (n = 34 or 30.1%), compared to all three active treatment groups. This is illustrated in Table 15.11 below.

Table EN3202-15.11 Number and Percent of Patient Withdrawals Due to Lack of OA Efficacy (ITT population excluding Center 002)
(Source: Table 11.1, EN3202-015 Clin Study Report, pg. 58 of 77)

Patient Dropped Out due to Lack of OA Efficacy?	OCR 40 (N=75) n (%)	OCR 20 (N=82) n (%)	OC 20 (N=106) n (%)	Placebo (N=113) n (%)
Yes	8 (10.7)	5 (6.1)	13 (12.3)	34 (30.1)
No	67 (89.3)	77 (93.9)	93 (87.7)	79 (69.9)
p-value*	0.002	0.001	0.001	

Data source: Appendix 15.3, Table 4.1.9.1., Statdoc 4.1.9.1.
* From Cochran-Mantel-Haenszel test adjusted for pooled investigational center. Each compared to placebo.
OCR = Oxymorphone CR and OC = OxyContin

EN3202-015 Efficacy Summary:
This 4-week, multi-dose, placebo- and active-controlled study in patients with moderate to severe osteoarthritis (OA) pain was intended to support a finding of efficacy of OM. While the sponsor's analysis of the primary outcome variable of Arthritis Pain Intensity VAS score change from baseline to end of Week 3 did reveal a statistically significant difference from placebo, for the OM 40 mg treatment group, there were flaws in the analysis. The secondary analysis also favored study drug, but suffered from the same analytical flaws as the primary analysis.

The sponsor's Intent-to-Treat (ITT) population excluded a large number of patients. The data imputation method (LOCF) used in the efficacy analysis created a bias in favor of study drug. There was a large number of drop-outs due to adverse events (AEs) in the active treatment groups. Subjects dropping out due to AEs had their relatively 'good' pain scores carried forward for the analysis while patients dropping out due to lack of efficacy had poor scores carried forward. This artificially biased the sponsor's results in favor of oxymorphone treatment. Re-analysis using an all randomized population (excluding subjects from site 002) and using baseline observations carried forward, failed to show a statistically significant difference from treatment with placebo.

Study Drug Diversion and Data Integrity:
A problem with diversion of study drug was discovered at Study Site 002. The efficacy analyses were performed excluding Site 002.

Errata were discovered in 12 subjects with missing AE in their CRFs, after the data base was locked. These are not expected to alter conclusions about safety.

In summary, although the sponsor's primary and secondary efficacy analysis results suggest that oxymorphone 40 mg ER is superior to placebo, this result appears to be an artifact of the chosen data imputation strategy combined with an overly restrictive analysis population. Re-analysis does not find any statistical support of efficacy of oxymorphone 40 mg or 20 mg, compared to placebo.

7.3.1.3 STUDY #2 - EN3202-016:

Title: Evaluation of the Efficacy and Safety of Numorphan® ER (Oxymorphone HCl Controlled-Release) Relative to Placebo and OxyContin® (Oxycodone HCL Controlled-Release) in Subjects with Chronic Low Back Pain

Objectives:
Primary:
- Evaluate efficacy of extended-release oxymorphone (OM) (10, 20, and 40 mg po q12 h) vs. Placebo (PBO) in Chronic Low Back Pain (LBP)

Secondary:
- Establish effective dose range of OM ER
- Compare efficacy/safety of OxyContin (OC) and OM ER vs. Placebo

Study Duration: 3 weeks at titrated dose

Population: 240 subjects were to be enrolled in order to achieve 210 evaluable subjects

Inclusion Criteria:
- Male or female patients, 18 - 75 years old
- Women were to be of non-childbearing potential
- Subjects were to be in general good health
- Subjects were to have diagnosis of moderate to severe, chronic low back pain (LBP) confirmed by:
  1. MRI, CT scan, X-Ray demonstration of anatomical etiology of back pain
  2. Diagnostic tests from #1 were to be taken after pain onset and within 2 years of screening
  3. If there was no radiographic confirmation of LBP then subject could be included only if the diagnosing and treating physician had sufficient knowledge of the subject to assure that the etiology was due to chronic LBP
- LBP was to be present > 15 days/month and > several hours/day, for ≥ 2 months
- Subject was to be on stable opioid dose for ≥ 3 days prior to 1st visit and daily requirement was not to be > 220 mg OM
- All other medication other than current opioid medication for LBP, was to be stable for ≥ 2 weeks prior to Visit 1.
- All adjunct therapy for back pain was to remain unchanged during study participation.

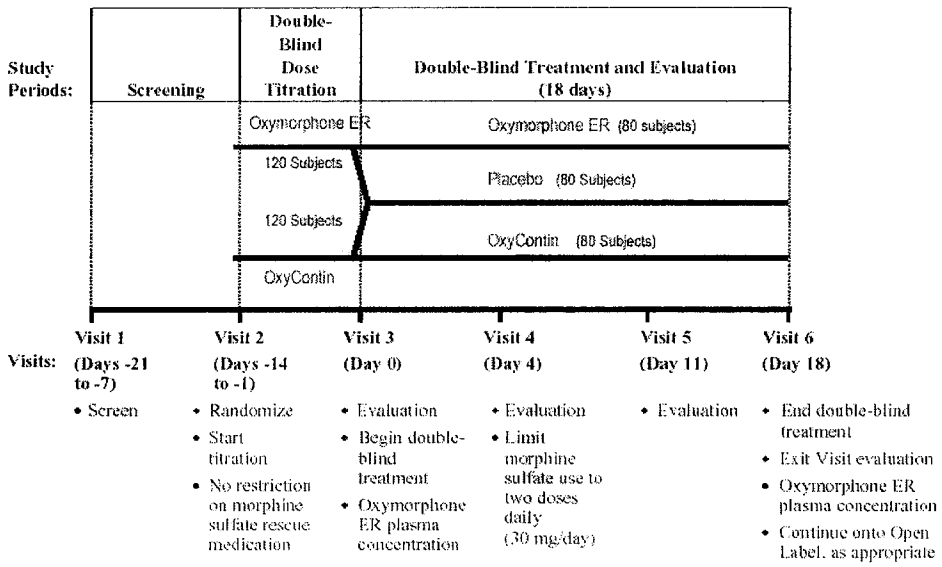
Exclusion Criteria:
- Pregnancy or Lactation
- Subjects had other etiologies of back pain (fibromyalgia, reflex sympathetic dystrophy or RSD, spinal compression, etc...)

- Back surgery within 2 months of screening, outstanding or planned litigation, outstanding compensation benefit judgement where back pain or injury was not medically established
- Nerve or plexus blocks within 4 weeks of Visit #2
- Serious medical condition, uncontrolled seizures, history of ETOH or substance abuse, allergies to opiates, need for opioids beyond study supplied opioids

Study Design:

This was to be a 3 week, multicenter, randomized, three-arm, parallel-group, double-blind, positive- and placebo-controlled study of oxymorphone ER in subjects with chronic low back pain. A schematic overview of the study design is shown in the attached Sponsor's Figure 16.1.

Figure EN3202-16.1 Overview of Study Design:
(Source: Figure 1, EN3202-016 Clin Study Report, pg. 19)



Screening Phase (Visit 1):

- Baseline EKG, physical exam, clinical labs, pregnancy tests, were to be obtained and eligibility was to be determined at this visit.

Double-Blind Dose Titration Phase (Visit 2):

- Eligible subjects were to be randomized using a blocked design to insure equal distribution of subjects to treatment groups within a site as follows:

Table EN3202-16.1 Study Treatment Groups:

Double-Blind Dose Titration Phase		Double-Blind Treatment Phase	
Medication	**# Patients**	**Medication**	**# Patients**
Oxymorphone ER	120	Oxymorphone ER	80
		Placebo	40
OxyContin	120	OxyContin	80
		Placebo	40

Source: Figure 1 Information, EN3202-016 Clin Study Report, pg. 19

- Study drug was to be dispensed and subjects were to begin titrating to a tolerated fixed dose that provided analgesia, and required minimal rescue medication (see rescue medication section below). Note that initial study dosing was to be based on the total daily dose of opioid medication previously taken by each subject before entering the study. This phase was to extend from 7-10 days and the blind was to be maintained during titration.

- Dosage was to be considered fixed when the following three conditions were met:
  - Subjects achieved adequate pain relief of at least moderate, on the same dosage for 4 consecutive days
  - Subjects tolerated the dose for 4 consecutive days and,
  - Subjects required ≤ 2 tablets of rescue per day for 4 consecutive days

Double-blind Treatment Phase (Visits 3 – 5):

- Subjects attaining a fixed dosage of study drug during titration (within 14 days of starting titration) were to proceed to the next phase of 18 days of double-blind, fixed-dose treatment as shown in Table EN3202-16.1 and Figure 16.1. Approximately 2/3 of the patients were to continue to receive the same active study drug taken during the titration phase while 1/3 were to be switched to placebo. This was to be based on the original randomized assignment. The dose ranges were to be as follows:
  1. OM ER (10 – 110 mg q 12 hrs)
  2. OC ER (20-220 mg q 12 hrs)
  3. PBO identical tablets to titration phase, q 12 hrs

- Subjects were to return for 3 subsequent weekly visits.
- Study drug use, rescue use, vital signs, efficacy diaries, and AEs were to be collected at each visit.

Post-Treatment (Visit 6):

- Subjects were to return for final vital signs, physical exam, return drug, turn in efficacy diaries, collect final labs, and assess for AEs.

Dose Selection, Concomitant Therapy and Rescue

Study Drug Dose Selection and Timing:

- The initial dose was to be selected based on the patient's total daily opioid dose requirement for 4 days before the study, based on provided conversion tables.

- OM ER was to be provided in 10, 20, and 40 mg tablets over-encapsulated and packaged as L, M, and H respectively. Oxycodone (OC) ER was to be provided at 2x the OM dose in mg as 20, 40, and 80 mg over-encapsulated tablets, marked similarly. This was to be allowed for "blinded" dose-titration, under direction of the investigators.

Concomitant Therapy:

- Prohibited – non-study opioids, NSAIDs (except for prophylactic ASA), dextromethorphan, and other investigational drugs.
- Allowed – stable tranquilizers, anti-epileptic drugs (AEDs), antidepressants, muscle relaxants, etc…

Rescue Medication:

- Titration Phase – Unrestricted open-label morphine sulfate IR 15 mg po q4-6 hrs, allowed as needed
- Treatment Phase – 1st 4 days unrestricted rescue allowed (same as above). At end of 4 days, patients were to be restricted to ≤ 1 tablet of morphine IR rescue PO BID, any patients exceeding this were to be withdrawn

Table EN3202-16.2 Schedule of Assessments

Assessments	Screening Period	Double-Blind Dose Titration Period	Double-Blind Treatment and Evaluation Period			Exit Visit
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Informed consent	X					
Inclusion/exclusion criteria	X					
Demographics	X					
Medical/surgical history	X					
Physical examination	X					X
Vital signs/temperature/body weight (weight only at Visit 1)	X	X	X	X	X	X
Electrocardiogram	X[a]					
Blood draw: hematology/clinical chemistry, pregnancy test	X[a]					X
(Visit 1 only)						
Urine collection (urinalysis)	X					X
Randomization		X				
Study and supplemental rescue medications		Dispense	Return/Dispense			Return
Drug accountability			X	X	X	X
Telephone contact with subject		Daily				
Subject diary		Dispense	Collect/Dispense			Collect
Adverse events (incidence and severity)			X	X	X	X
Opioid side effects		X	X	X	X	X
Concomitant medications	X	X	X	X	X	X
Study drug and rescue medication taken	Daily (in Subject Diary)					
Visual Analogue Scale (VAS) and categorical scale (4-level) for pain intensity	Daily (in Subject Diary) and at study visits					
Pain Relief Rating Scale (5-level categorical)	Daily (in Subject Diary) and at study visits					
Worst daily pain (4-level categorical)	Daily (in Subject Diary)					
Physician's global assessment of study treatment		X	X	X	X	X
Subject's global assessment of study treatment		X	X	X	X	X
Brief Pain Inventory		X	X	X	X	X
Oxymorphone plasma levels and pain assessments			X			X
Subject discontinuation						X[b]

[a]Additional tests may have been required at other times for safety, after prior approval.
[b]Subjects could terminate at any time, but the Visit 6 assessment should have been completed upon termination.
Source: Table 5, EN3202-016 Clin Study Report, pg. 29

Outcome Measures:

Efficacy (See Appendix 11.2 for assessment instrument details):

- Pain Intensity Scales (both VAS and Categorical), Brief Pain Inventory (BPI), Global Assessments of study medication, amount of rescue medication used, pain relief scales.

Safety:

- Adverse Events (AEs), physical exams, vital signs, clinical labs, 12-lead EKGs, and opioid side effects

Statistical Assessment:

All statistical tests were two-sided and treatment group comparisons were performed at a significance level of 0.05. No adjustments were to be made for multiple comparisons. Missing data from discontinuations were to be imputed using the last observation carried forward (LOCF).

Primary Efficacy Variable:

- This was to be defined as the change in VAS Pain Intensity (PI) at 4 hours after dosing, from baseline to Visit 6, evaluated using a two-way ANCOVA test (see appendix 11.5 for statistical definitions).

Secondary Efficacy Variables:

1. Percent (%) change from baseline to Visit 6 in VAS Pain Intensity 4 hours post-dosing, Mean Categorical Daily Pain Intensity 4 hours after dosing.
2. Pain relief from daily assessments at 4 hours after dosing.
3. Change from baseline to Visit 6 in Worst Daily Pain
4. Brief Pain Inventory (assessed with descriptive statistics)
5. Subject and Physician Global Assessment of Pain
6. Time to Treatment Failure assessed with survival techniques.
7. Amount of Rescue Used (by day)
8. OM Plasma Concentration vs. Current Pain Intensity (VAS) assessed with correlation

Data Sets:

- Intent-to-Treat (ITT) Population was defined to be all randomized and treated patients with efficacy data at baseline and Week 1.

- Efficacy Evaluable Population was to be defined as all patients who achieved their randomized dose and had efficacy data recorded at baseline and Week 3.

Post-Hoc Analyses:

1. The Sponsor summarized the primary efficacy variable by gender within each treatment group.
2. Time to treatment failure and withdrawal were combined to form "time to discontinuation due to lack of efficacy."
3. AE frequencies were assessed using Fisher's exact test.

Protocol Amendments:
Protocol amendments were evaluated using the Protocol Study Report, Original Protocol, and Sponsor provided Amended Protocol documents.

Amendment 1 (6/27/01):
This consisted of administrative changes and clarifications of inclusion/exclusion criteria.

Amendment 2 (5/7/02):
- Double-blind titration phase extended from 10 to 14 days.
- Primary efficacy analysis changed to remove 3rd item in the primary efficacy analysis ("For subjects that take more than 3 doses of rescue medication in one day, the last observation before the third dose of rescue medication will be used").

Amendment 3 (8/21/02):
- The Primary Efficacy Variable 4-hour VAS Pain Intensity (PI) rating was replaced with the difference from baseline (defined as the last 4-hour post-dose PI at the end of titration) to Visit 6, in the 4-hour VAS PI. This variable was assessed using ANCOVA instead of ANOVA.
- The VAS PI score after dosing, but prior to rescue will be used for the baseline or Visit 6 score, if the patient received rescue medication
- Baseline PI for the two placebo groups will be compared in order to pool placebo subjects for analysis
- A new secondary efficacy variable was created and defined as the percent change from baseline to Visit 6 in the VAS PI rating at 4 hours after dosing.
- The mean daily (VAS) pain intensity secondary efficacy variable changed to categorical variable. Pain relief (PR) from daily pain assessment specified to occur 4 hours post-dose.
- Kaplan-Meier and Log-Rank test specified as "survival analysis methods."

Analysis Plan Change 1 (6/28/02) Exclusion of Data from Site # 023:
- Diversion of study drug was discovered at Site 023 (Dr. Miskin, PI). Data from Site 23 (24 total subjects: 23 in the titration phase, 18 subjects in the treatment phase, and 1 subject listed without treatment and lost to follow-up: 023-007 in the raw analysis CRTs) were excluded from the efficacy evaluation because the data could have been compromised. A modified ITT population (same as ITT minus 18 treatment phase subjects from Site 23) was then utilized for all efficacy analyses. These study subjects were included in all demographic and safety analyses. Table 16.2b below lists all Site 23 patients (24 enrolled to this site) by treatment and completion status.

Table EN3202-16.2b Site # 23 Subjects Excluded from Efficacy Analysis
(Source: EN3202-016 SAS Transport files: ENDSTUDY.XPT. SMDOSE.XPT, Raw Data)

UPID	Titration	Trtmnt	Comp	When D/C	Discontinuation Reason
EN3202-016-023-002	OC ER	OC ER	YES	COMP	
EN3202-016-023-005	OM ER	OM ER	YES	COMP	
EN3202-016-023-007			NO	TITR	LOST TO FOLLOW-UP
EN3202-016-023-008	OC ER	PBO	NO	TRT	LACK OF EFFICACY
EN3202-016-023-009	OM ER	PBO	NO	TRT	LACK OF EFFICACY
EN3202-016-023-010	OM ER		NO	TRT	LOST TO FOLLOW-UP
EN3202-016-023-012	OC ER		NO	TITR	ADVERSE EXPERIENCE
EN3202-016-023-013	OC ER	OC ER	NO	TRT	LACK OF EFFICACY
EN3202-016-023-014	OM ER	OM ER	YES	COMP	
EN3202-016-023-017	OC ER	PBO	YES	COMP	
EN3202-016-023-023	OM ER		NO	TITR	STUDY MEDICATION NON-COMPLIANCE
EN3202-016-023-024	OC ER		NO	TITR	WITHDREW CONSENT
EN3202-016-023-025	OM ER	OM ER	YES	COMP	
EN3202-016-023-026	OM ER	OM ER	YES	COMP	
EN3202-016-023-027	OM ER	OM ER	NO	TRT	LACK OF EFFICACY
EN3202-016-023-028	OC ER	OC ER	YES	COMP	
EN3202-016-023-030	OM ER	PBO	NO	TRT	LACK OF EFFICACY
EN3202-016-023-031	OC ER	OC ER	YES	COMP	
EN3202-016-023-032	OM ER	PBO	NO	TRT	LACK OF EFFICACY
EN3202-016-023-033	OC ER	OC ER	YES	COMP	
EN3202-016-023-034	OC ER	PBO	NO	TRT	LACK OF EFFICACY
EN3202-016-023-035	OM ER	OM ER	YES	COMP	
EN3202-016-023-038	OC ER		NO	TITR	ADVERSE EXPERIENCE
EN3202-016-023-039	OM ER	OM ER	YES	COMP	

7.3.1.4 SPONSOR RESULTS for EN3202-16:

Disposition:

Titration Phase:
A total of 420 subjects were screened, 90 failed to pass the screening process and 330 were subsequently randomized. One subject (#12-012) was randomized to the OxyContin (OC)/Placebo group but withdrew during titration before taking any study medication. This subject was not included in the safety population of 329 subjects. Of the 330 subjects who entered the titration period, 95 (29 %) withdrew without completing titration (32 % and 26 % in the OM and OC groups, respectively). In both treatment groups, the majority of discontinuations at this stage of the study were due to AEs (47 % and 62 % in the OM and OC groups, respectively). Approximately two-thirds of subjects from each treatment group successfully completed the titration phase, 68% (113/166) of oxymorphone ER subjects and 74% (122/164) of OxyContin subjects.

Table EN3202-16.3 Subject Disposition by Treatment

Subject Disposition	Oxymorphone ER (n)	OxyContin (n)	Placebo (n)	Total (n)
Screened				420
Screening failures				90
Inclusion/exclusion				60
Withdrew consent				26
Non-compliance				4
Randomized, entered titration	166	164		330
Discontinued titration	53	42		95
Study medication non-compliance	7	4		11
Adverse event[a]	25	26		51
Withdrew consent	5	5		10
Lost to follow-up	1	2		3
Protocol violation	0	0		0
Lack of efficacy	7	4		11
Other	8	1		9
Completed titration	113	122		235
Entered treatment	80	80	75	235
Discontinued treatment	22	21	53	96
Study medication non-compliance	0	2	0	2
Adverse event[a]	2	4	5	11
Withdrew consent	0	1	2	3
Lost to follow-up	1	0	1	2
Protocol violation	1	0	1	2
Lack of efficacy	16	13	44	73
Other	2	1	0	3
Completed treatment	58	59	22	139
Included in safety population[b]				329
Included in modified ITT population[c] without Site 23 data	71	75	67	213

Data Source: Table 7, EN3202-016 Clin Study Report, pg. 44

[a]These figures include both discontinuations because of AEs *per se* and discontinuations because of opioid side effects.

[b]One subject (12-012) was randomized to the OxyContin/Placebo group but withdrew during the titration phase without taking any study medication; this subject was excluded from the safety population.

[c]This population consists of subjects who completed the titration phase, received at least one dose of study medication, and completed at least one VAS pain intensity assessment during the treatment phase, excluding subjects from Site 23.

Almost twice as many of the OM 20 mg group discontinued (7) as the OxyContin (4) subjects, due to "lack of efficacy."

Two categories in the titration phase discontinuations were evaluated in more detail: 'Withdrew Consent' and 'Other.' Ten subjects 'withdrew consent' in the oxymorphone and OxyContin groups. Examination of the case report tabulations (CRTs) for these patients listed no descriptions of this category. In addition, a preponderance of these subjects were at study Site #12. A request was sent to the Sponsor asking for the case report forms (CRFs) of these patients. The 13 resulting CRFs (including placebo

patients) showed that two cases (#012052 and 012006) appeared to actually be due to adverse events, while two other cases (#012021 and 012040) were due to lack of efficacy. This information was recoded in the reviewer's final disposition Table 16.3b below, which can be compared to the Sponsor's disposition Table 16.3.

The category defined as 'other' predominantly included patients that were unable to titrate successfully on the study medication or were withdrawn by mistake. The following table lists these patients. Note that the first 10 listed patients dropped out of the study during the titration phase. The last three subjects discontinued during the treatment phase of the study.

EN3202-16.3a Withdrawing Subjects due to "Other"

Patient ID	Titr Med	Trt Med	Reason for Withdrawal
EN3202-016-006-001	OM ER		UNABLE TO TITRATE
EN3202-016-014-002	OC ER		UNABLE TO TITRATE
EN3202-016-014-006	OM ER		UNABLE TO TITRATE
EN3202-016-014-008	OM ER		TITRATION FAILURE
EN3202-016-019-001	OM ER		TITRATION MED STOLEN/LOST; UNABLE TO COMPLETE TITRATION
EN3202-016-020-004	OM ER		PT. WAS DOSED OUT OF SEQUENCE.
EN3202-016-024-014	OM ER		SUBJECT D/C THOUGHT TO BE STUDY MED NON-COMPLIANT BUT WAS COMPLIANT (COORD. ERROR IN CAPSULE COUNT)
EN3202-016-026-012	OM ER		UNABLE TO TITRATE
EN3202-016-026-015	OM ER		INABILITY TO TITRATE
EN3202-016-015-011	OC ER	OC ER	PT TERMINATED DUE TO NON-COMPLIANCE BY ERROR.
EN3202-016-015-010	OM ER	OM ER	PT'S WITHDRAWN FOR NON-COMPLIANCE BY ERROR
EN3202-016-021-014	OM ER	OM ER	NON-COMPLIANCE MORPHINE

Source Data: EN3202-016 CRT – ENDSTUDY.XPT, OM ER = oxymorphone ER, OC ER = OxyContin ER

No further information was provided indicating whether the individual subject's inability to titrate medication was due to adverse events or another reason. A request was also sent to the Sponsor for the case report forms (CRFs) for these subjects. At the time of this review, this information is still pending.

Treatment Phase:

A total of 139 out of 235 (59%) subjects completed the double-blind treatment phase with roughly similar numbers of OM (73% or 58/80) and OC (74% or 59/80) patients. The most frequent reason for discontinuation during the double-blind treatment phase was due to "lack of efficacy." Placebo patients discontinued for this reason (59% or 44/75) much more frequently than either OM (20% or 16/80) or OC (16.3% or 13/80). However, it is important to note that in spite of subjects having been titrated to stable efficacy before the double-blind treatment phase, the active treatment groups still had significant numbers of drop-outs due to lack of efficacy.

Recoding the discontinuations, based upon evaluation of the requested CRFs from the Sponsor, results in slight changes to the disposition table. These results are shown in Table 16.3b below. Note the final sums with associated additions and subtractions (in parentheses) in the different AE, Withdrew Consent, and Lack of Efficacy categories.

Table EN3202-16.3b Reviewer Re-Coded Subject Disposition by Treatment

Subject Disposition	Oxymorphone ER (n)	OxyContin (n)	Placebo (n)	Total (n)
Randomized, entered titration	**166**	**164**		**330**
Discontinued titration	53	42		95
Study medication non-compliance	7	4		11
Adverse event[a]	**26 (+1)**	**27 (+1)**		**53 (+2)**
Withdrew consent	**4 (-1)**	**4 (-1)**		**8 (-2)**
Lost to follow-up	1	2		3
Protocol violation	0	0		0
Lack of efficacy	7	4		11
Other	8	1		9
Completed titration	113	122		235
Entered treatment	**80**	**80**	**75**	**235**
Discontinued treatment	22	21	53	96
Study medication non-compliance	0	2	0	2
Adverse event[a]	2	4	5	11
Withdrew consent	**0**	**1**	**0 (-2)**	**1 (-2)**
Lost to follow-up	1	0	1	2
Protocol violation	1	0	1	2
Lack of efficacy	**16**	**13**	**46 (+2)**	**75 (+2)**
Other	2	1	0	3
Completed treatment	58	59	22	139

Data Source: Table 7, EN3202-016 Clin Study Report, pg. 44, and Reviewer calculations

Protocol Violations:

Two subjects (# 26-003 started Zydone on the same day that treatment started and # 26-013 started OxyContin the same day that treatment started) were found to have taken opioids prohibited by the protocol and were excluded as protocol violators from both the ITT and modified ITT populations. Note that these two subjects were also excluded from the Agency reanalysis of the primary efficacy results.

Demographic and Baseline Characteristics:

Demographic characteristics for the three treatment groups were comparable (sponsor states no statistically significant differences among treatment groups), with and without the inclusion of Site #023.

Table EN3202-16.4a Patient Demographics (Safety Population)

Characteristic		Oxymorphone ER N=110	OxyContin N=111	Placebo N=108
Age (years)				
	n	110	111	108
	Mean	45.5	46.2	47.5
	SD	10.45	11.05	10.10
	Min/Max	26/82	22/76	26/79
Sex	**n (%)**			
	Male	56 (50.9)	63 (56.8)	55 (50.9)
	Female	54 (49.1)	48 (43.2)	53 (49.1)
Race	**n (%)**			
	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)				
	n	110	111	108
	Mean	83.3	84.0	81.8
	SD	21.13	19.49	19.95
	Min/Max	48/149	45/140	45/135
Height (cm)				
	n	110	111	108
	Mean	172.2	172.1	170.9
	SD	9.94	10.38	10.57
	Min/Max	147/196	142/196	147/196
Years with back pain				
	n	110	111	108
	Mean	8.3	7.7	8.0
	SD	6.84	8.16	7.06
	Min/Max	0/32	0/53	0/32

Data Source: Table 8 EN3202-016 Clin Study Report, pg. 46.

The resulting demographic data for the Modified Intent-to-Treat (without Site #23, see Table 16.2b for details of the 24 excluded subjects) do not appear significantly different from the safety population, as shown in Table 16.4b, below.

The Sponsor defined two populations for analysis of efficacy, an evaluable population and an ITT population. A third population (Modified ITT) was constructed (6/28/02) after the problem with study drug diversion at Site 023. The Evaluable population excluded patients who did not have efficacy data from baseline and Week 3 and the original ITT population excluded subjects without efficacy data at baseline and the end of Week 1. These populations are not considered further in this review. The sponsor's Modified ITT population excluded 22 of the 235 patients who entered the double-blind treatment phase of this study. Eighteen of these patients were from Study Site 23. The remaining four patients were excluded because 2 did not have VAS pain measurements

and 2 took prohibited medications. The resulting demographic data for the 213 Modified Intent-to-Treat (excluding Site #23) patients does not appear significantly different from the safety population, as shown in Table 16.4b, below.

Table EN3202-16.4b Patient Demographics (Modified ITT Population excluding Site 23)

Characteristic		Oxymorphone ER N=71	OxyContin N=75	Placebo N=67
Age (years)				
	n	71	75	67
	Mean	45.5	46.0	46.3
	SD	10.8	10.6	9.5
Sex n (%)				
	Male	37 (52.1)	47 (62.7)	30 (44.8)
	Female	34 (47.9)	28 (37.8)	37 (55.2)
Race	**n (%)**			
	Caucasian	67 (94.4)	68 (90.7)	64 (95.5)
	Black	3 (4.2)	3 (4.0)	2 (3.0)
	Hispanic	1 (1.4)	3 (4.0)	1 (1.5)
	Asian	0 (0.0)	0 (0.0)	0 (0.0)
	Other	0 (0.0)	1 (1.3)	0 (0.0)
Weight (kg)				
	n	71	75	67
	Mean	82.1	84.6	78.5
	SD	18.9	19.7	17.9
Height (cm)				
	n	71	75	67
	Mean	172.2	172.8	170.6
	SD	10.3	10.4	10.9
Years with back pain				
	n	71	75	67
	Mean	8.7	7.9	7.7
	SD	7.00	7.7	6.6

Data Source: Appendix 16.3.2, Table 2, pages 1 & 2 of 2.

Baseline Treatment Phase Comparisons:

Baseline VAS Pain Intensity (PI) scores for the double-blind treatment phase were defined as the patient's PI score at the end of titration. The baseline VAS pain intensity scores were compared between the titration subgroups (OM vs. OC) to evaluate if they were similar enough for pooling into a single placebo group. There was no statistically significant difference between the baseline VAS scores between subjects randomized to placebo, after completing titration with oxymorphone (Baseline Pain Intensity (PI) Mean VAS score = 44.2 ± 22.2) or OxyContin (Baseline PI Mean VAS score = 40.1 ± 23.4, pair-wise comparison p=0.47, source Appendix 16.3.4.3, Table 1). These subgroups were therefore considered comparable by the Sponsor who pooled them to form a single placebo group during the double-blind treatment.

Sponsor's Efficacy Analysis Results:

Primary Efficacy Variables:

Change in Pain Intensity Score:

The Sponsor's analysis utilizing the modified ITT population and LOCF for imputed scores is presented in Table 16.5a. The Sponsor analyzed the primary outcome (defined as the change from baseline to final visit 6, in the VAS pain intensity score assessed at 4-hours post-dosing) using a two-way analysis of covariance (ANCOVA). All groups demonstrated an increase in the VAS PI (worsening of pain) over the 18 day trial period, in this randomized-withdrawal design study. Thus, efficacy was defined as "less worsening" of a treatment group PI estimate.

There were statistically significant differences in the change from baseline to the end of the double-blind period for the two active treatment groups compared to placebo. However, all three groups demonstrated some degree of worsening of PI score over the treatment period. The OM ER group demonstrated a statistically significant 'less worsening' of pain intensity, from baseline to Visit 6, compared to placebo Note that OxyContin ER also demonstrated significantly less 'worsening', when compared to placebo. The absolute values, along with descriptive statistics, and test results are shown in the following Table 16.5b, for comparison.

Table EN3202-16.5a Baseline-Final Visit Change in Pain Intensity Modified ITT Population without Site #23

Statistic	Change in Pain Intensity (VAS, mm) from Baseline[a] to Final Visit[b]		
	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
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*	

Data Source: Table 10. EN3202-016 Clin Study Report, pg. 48

*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.

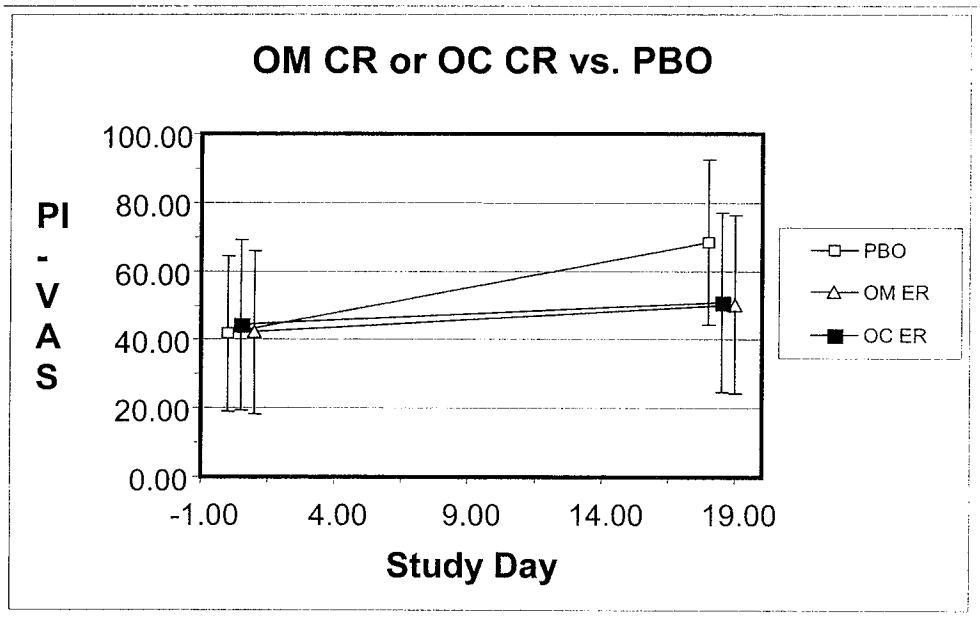
Table EN3202-16.5b Raw Baseline-Final Visit Pain Intensity Values, Modified ITT Population without Site #23

	Pain Intensity (VAS) at 4 hours after morining dose Observed Values (mm), Modified ITT without Site 23		
Statistic	**Baseline (SD)**	**Final (SD)**	**Change (SD)**
Oxymorphone ER	42.2 (23.9), n=71	50.3 (25.9), n=71	8 (24.2)
OxyContin	44.3 (24.9), n=75	50.8 (26.2), n=75	6.6 (25.3)
Placebo	41.8 (22.8), n=67	68.4 (23.9), n=67	26.6 (25.8)

Data Source: Appendix 16.3.4.1, Table 2.1, pages 1 & 20, Values = mean (± SD)

The absolute VAS PI values are also shown graphically for the three treatment arms, along with their associated variability (shown as standard deviation bars), from baseline to final visit (# 6), in figure EN3202-16.1 below.

Figure EN3202-16.1 OM ER/OC ER vs. PBO VAS PI Scores, Baseline to Final Visit (Day 18) (Source: Table 16.5b)



Reviewer Primary Efficacy Re-Analysis Findings:

The Agency Statistical Reviewer, Dr. Price, reanalysed the Sponsor's efficacy data using an 'all randomized and treated' analysis population of 213 (out of 235) patients that entered the double-blind treatment phase. This population excluded 18 treatment phase subjects from Site 023, with an additional 4 subjects (not from Site 023) excluded because 2 did not have VAS pain measurements and 2 took prohibited medications. Note

that this results in the same population used by the Sponsor of 213 patients. The use of LOCF in this withdrawal design study was considered acceptable given the withdrawal design. The results of the reanalysis confirm the Sponsor's finding (results not shown) that treatment with oxymorphone ER results in a statistically significant difference (less of an increase in pain intensity) when compared to placebo treatment. Oxymorphone and OxyContin treatment results did not differ statistically.

Secondary Efficacy Variables):
The secondary efficacy analyses were conducted using the same modified ITT population and LOCF (excluding the Site 23), as the primary efficacy analyses. Note that no corrections were made for multiple comparisons.

- Percent (%) change (Baseline to Visit 6) in VAS PI:
  The percent increase in pain intensity (PI measured 4-hours after morning dose) was statistically significantly greater in the placebo groups compared with the oxymorphone (p=0.0032) and OxyContin groups (p=0.0001). Note that a simple comparison of the results in Table 16.5b and 16.6 cannot be made, because Table 16.6 summarizes the group means of individual subject percent changes, by treatment. Calculating the percent change from the mean scores in Table 16.5b will not produce equivalent values.

Table EN3202-16.6 Percent Change in PI (Baseline to Final value)

Statistic	Percent Change in Pain Intensity (VAS) from Baseline[a] to Final Visit[b]		
	Oxymorphone ER N=71	OxyContin N=75	Placebo N=67
n[c]	71	74	67
Mean	112.7	67.0	188.5
Std Error	524.8	370.9	439.2
LS mean difference versus placebo	-27.69	-36.36	
95% CI for LS Mean difference versus placebo	-45.96 to -9.41*	-54.51 to -18.21*	
P-value for LS mean difference versus placebo	0.0032*	0.0001*	

Data Source: Table 11, EN3202-016 Clin Study Report, pg. 50
*Statistically significant difference between active treatment and placebo
[c]If one or more subjects had missing data, then n ≠N.
Note: Because of lack of normality, ANOVA was performed on ranks: treatment p = 0.0003, center p = 0.8266.

- Mean Categorical Daily Pain Intensity (4 hours after dosing):
  The daily pain intensity recorded with the categorical scale on the final day of the study, is presented in Table 16.7, below. OM ER and OC subjects had statistically significantly lower categorical pain ratings than subjects receiving placebo (p=0.0001 and p=0.002, respectively). Note that the 'none' category of pain intensity rating on the final day was similar across treatment groups.

Table EN3202-16.7 (%) Subjects in Different Pain Intensity (PI) Categories 4 Hours after AM Dose, Modified ITT Population, Without Site 23

Pain Intensity on Final Study Day[a]	Oxymorphone ER N=71 n (%)	OxyContin N=75 n (%)	Placebo N=67 n (%)
None	3 (4.2)	5 (6.7)	3 (4.5)
Mild	22 (31.0)	21 (28.0)	5 (7.5)
Moderate	36 (50.7)	35 (46.7)	29 (43.3)
Severe	10 (14.1)	14 (18.7)	30 (44.8)
P-value[b] versus placebo	0.0001*	0.0002*	

Data Source: Appendix 16.3.4.1 & Table 12 EN3202-016 Clin Study Report, pg. 51.
*Statistically significant difference between active treatment and placebo
[a]If rescue medication was used after the morning dose and before the 4-hour evaluation, then the pain intensity value after dosing and before rescue was used.
[b]The p-value is from a rank-sum test, stratified with respect to center, with each model comparing one active treatment with placebo.

- Pain Relief from Daily Assessments (4 hours after dosing):
  The extent of pain relief recorded by subjects 4 hours after the morning dose of study medication on the final day of treatment, is summarized in Table 16.8, below. OM ER and OC group subjects had statistically significant higher ratings of pain relief than the placebo group (p=0.0006 and 0.0001, respectively). The 'complete' pain relief category was the largest for the OC group (4 or 5.3%).

Table EN3202-16.8 (%) Subjects in Different Pain Relief (PR) Categories 4 Hours after AM Dose, Modified ITT Population, Without Site 23

Pain Relief on Final Study Day	Oxymorphone ER N=71 n (%)	OxyContin N=75 n (%)	Placebo N=67 n (%)
None	8 (11.3)	6 (8.0)	19 (28.4)
A Little	20 (28.2)	23 (30.7)	29 (43.3)
Moderate	30 (42.3)	33 (44.0)	13 (19.4)
A Lot	12 (16.9)	9 (12.0)	4 (6.0)
Complete	1 (1.4)	4 (5.3)	2 (3.0)
P-value[a] versus placebo	0.0006*	0.0001*	

Data Source: Table 13 EN3202-016 Clin Study Report, pg. 52.
*Statistically significant difference between active treatment and placebo
[a]The p-value is from a rank-sum test, stratified with respect to center, with each model comparing one active treatment with placebo.

- Change from baseline to Visit 6, in Worst Daily Pain:
  Subjects rated their worst pain experienced during the previous day on a 4-point categorical scale from 0 (none) to 3 (severe). All treatment groups had similar baseline worst daily pain scores (oxymorphone ER = 2.0, OxyContin = 2.2, and placebo = 2.1, Source : Appendix 16.3.4.1, Table 4.1) before showing an overall increase by the final visit. OM ER and OxyContin subjects had a significantly smaller average changes in worst daily pain (+0.1 and +0.1 respectively) compared to placebo (+ 0.5).

Table EN3202-16.9 Change in Worst Daily Pain from Baseline to Final Study Day, by Treatment, Modified ITT Population without Site 23

Change in Worst Daily Pain from Baseline[a] to Final Visit[b]			
Statistic	Oxymorphone ER N=71	OxyContin N=75	Placebo N=67
n[c]	71	74	67
Mean	0.1	0.1	0.5
SD	0.74	0.74	0.64
LS Mean Difference Versus Placebo	-0.41	-0.38	
95% Confidence Interval for LS Mean Difference Versus Placebo	-0.61 to -0.21*	-0.58 to -0.18*	
P-value for LS Mean Difference Versus Placebo	0.0001*	0.0002*	

Data Source: Table 14 EN3202-016 Clin Study Report, pg. 53
*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 worst pain score from the subject's last diary record was used.
[c]If one or more subjects had missing data, then n≠N.

- Brief Pain Inventory Pain Intensity and Pain Interference (assessed with descriptive statistics):
  The BPI pain intensity items asked subjects to rate measures of their experience of pain and pain relief during the previous 24 hours, and at present. Ratings for the BPI pain are summarized in Table 16.10a, below. Both active treatment groups had a statistically significant difference in BPI pain ratings compared to the placebo group. The exceptions were "pain right now" for both the OM ER and OC groups and "least pain in 24 hours" in the OC group.

Table EN3202-16.10a BPI Pain Intensity Items at Final Visit, by Treatment, Modified ITT Population without Site 23

BPI Item	Treatment	n	Pain Item Rating Mean (SD)		LS Mean Difference from Placebo	95% Confidence Interval for LS Mean Difference from Placebo	P-value for LS Mean Difference from Placebo
Worst Pain in Last 24 h (0 to 10 scale)[b]	Oxymorphone ER	71	7.0	(2.06)	-0.99	-1.67 to -0.30	**0.0050***
	OxyContin	75	7.0	(2.20)	-0.98	-1.66 to -0.31	**0.0046***
	Placebo	67	7.9	(1.78)			
Least Pain in Last 24 h (0 to 10 scale)	Oxymorphone ER	71	3.9	(2.26)	-0.98	-1.79 to -0.16	**0.0187***
	OxyContin	75	4.1	(2.22)	-0.76	-1.56 to 0.05	0.0653
	Placebo	67	4.9	(2.60)			
Average Pain in Last 24 h (0 to 10 scale)	Oxymorphone ER	71	5.1	(1.79)	-1.11	-1.74 to -0.48	**0.0007***
	OxyContin	75	5.4	(1.93)	-0.86	-1.48 to -0.23	**0.0073***
	Placebo	67	6.2	(1.86)			
Pain Right Now (0 to 10 scale)	Oxymorphone ER	71	5.8	(2.39)	-0.58	-1.39 to 0.24	0.1657
	OxyContin	75	5.9	(2.38)	-0.57	-1.38 to 0.23	0.1620
	Placebo	67	6.4	(2.38)			
% Pain Relief in Last 24 h (0 to 100 scale)[c]	Oxymorphone ER	71	56.8	(22.91)	17.35	8.53 to 26.17	**0.0001***
	OxyContin	75	54.1	(25.58)	14.60	5.89 to 23.30	**0.0011***
	Placebo	67	39.1	(28.05)			

Data Source: Table 15, EN3202-016 Clin Study Report, pg. 54
*Statistically significant difference between active treatment and placebo
[a]0 = "No pain," 10 = "Pain as bad as you can imagine"
[b]0 = "No relief," 100 = "Complete relief"

The BPI pain interference items asked the subjects to rate several measures of the extent to which their pain interfered with their activities during the previous 24 hours. Ratings for the BPI pain interference items at the final visit are summarized by treatment in Table 16.10b, below. Ratings of pain interference for oxymorphone ER and OxyContin subjects were statistically significantly different from placebo for the following scales: general activity, mood, normal work, relations with other people, and enjoyment of life. However, oxymorphone ER and placebo patient results did not differ for walking ability and sleep.

Table EN3202-16.10b BPI Interference Items at Final Visit, by Treatment, Modified ITT Population without Site 23

BPI Item[a]	Treatment	n[b]	Pain Item Rating Mean (SD)		LS Mean Difference from Placebo	95% Confidence Interval for LS Mean Difference from Placebo	P-value for LS Mean Difference from Placebo
General Activity	Oxymorphone ER	71	5.5	(2.71)	-1.23	[-2.11, -0.35]	**0.0062***
	OxyContin	75	5.5	(2.51)	-1.16	[-2.03, -0.29]	**0.0091***
	Placebo	67	6.7	(2.49)	-	-	-
Mood	Oxymorphone ER	71	4.8	(2.9)	-1.06	[-1.99, -0.12]	**0.0266***
	OxyContin	75	4.9	(2.47)	-0.96	[-1.88, 00.04]	**0.04***
	Placebo	67	5.9	(2.94)	-	-	-
Walking Ability	Oxymorphone ER	71	4.9	(2.85)	-0.66	[-1.58,0.25]	NS
	OxyContin	75	5.1	(2.69)	-0.48	[-1.38, 0.43]	NS
	Placebo	67	5.6	(2.70)	-	-	-
Normal Work	Oxymorphone ER	71	5.4	(2.84)	-1.11	[-1.99, -0.22]	**0.015***
	OxyContin	75	5.6	(2.47)	-0.88	[-1.75, -0.01]	**0.049***
	Placebo	67	6.5	(2.60)	-	-	-
Relations with Others	Oxymorphone ER	71	4.1	(2.9)	-1.02	[-1.95, -0.09]	**0.03***
	OxyContin	75	4.1	(2.48)	-1.05	[-1.96, -0.13]	**0.025***
	Placebo	67	5.2	(2.89)	-	-	-
Sleep	Oxymorphone ER	71	4.8	(2.79)	-0.87	[-1.81, 0.08]	NS
	OxyContin	75	5.0	(2.75)	-0.87	[-1.8, 0.07]	NS
	Placebo	67	5.8	(3.18)	-	-	-
Life Enjoyment	Oxymorphone ER	71	5.0	(2.74)	-1.31	[-2.25, -0.37]	**0.007***
	OxyContin	75	5.3	(2.65)	-1.06	[-1.99, -0.13]	**0.026***
	Placebo	67	6.4	(2.97)	-	-	-

Data Source: Table 16, EN3202-016 Clin Study Report, pg. 55
*Statistically significant difference between active treatment and placebo
[a] All items use a 0-10 scale: 0="Does not interfere," 10= "Completely interferes"
[b] If one or more subjects had missing data then n≠N

- Subject Global Assessment of Study Medication at the Final Visit:
  Patients rated their study medication as "poor, fair, good, very good, or excellent." A total of 59% of oxymorphone ER subjects rated their medication as good, very good, or excellent, while only 27% of placebo subjects gave their medication similar ratings (p = 0.0001). These results are shown in Table 16.10 below. Note that the proportion of OxyContin subjects rating their medication as 'Very Good' and 'Excellent', were noticeably greater than oxymorphone (29.3% and 5.3% vs. 16.9% and 1.4%, respectively).

Table EN3202-16.10 Subjects' Global Assessments of Study Medication at the Final Visit, by Treatment, Modified ITT Population without Site 23

	Oxymorphone ER N=71	OxyContin N=75	Placebo N=67
Subject Rating	n (%)	n (%)	n (%)
Poor	14 (19.7)	14 (18.7)	37 (55.2)
Fair	15 (21.1)	14 (18.7)	12 (17.9)
Good	29 (40.8)	21 (28.0)	11 (16.4)
Very Good	12 (16.9)	22 (29.3)	6 (9.0)
Excellent	1 (1.4)	4 (5.3)	1 (1.5)
P-value[a] versus placebo	**0.0001***	**0.0001***	

Data Source: Table 17, EN3202-016 Clin Study Report, pg. 56.
*Statistically significant difference between active treatment and placebo
[a]The p-value is from a rank-sum test, stratified with respect to center, with each model comparing one active treatment with placebo.

- Physician Global Assessment of Study Medication:
  The physicians' global evaluations of their subjects' study medication were similar to the subject ratings. Physicians rated the study medication OM ER significantly higher than placebo (p = 0.0001). The distribution of physicians rating oxymorphone as good, very good, or excellent (62%) vs. placebo (24%), showed similar proportional ratings for OxyContin.

Table EN3202-16.11 Physicians' Global Assessments of Study Medication at the Final Visit, by Treatment, Modified ITT Population Without Site 23

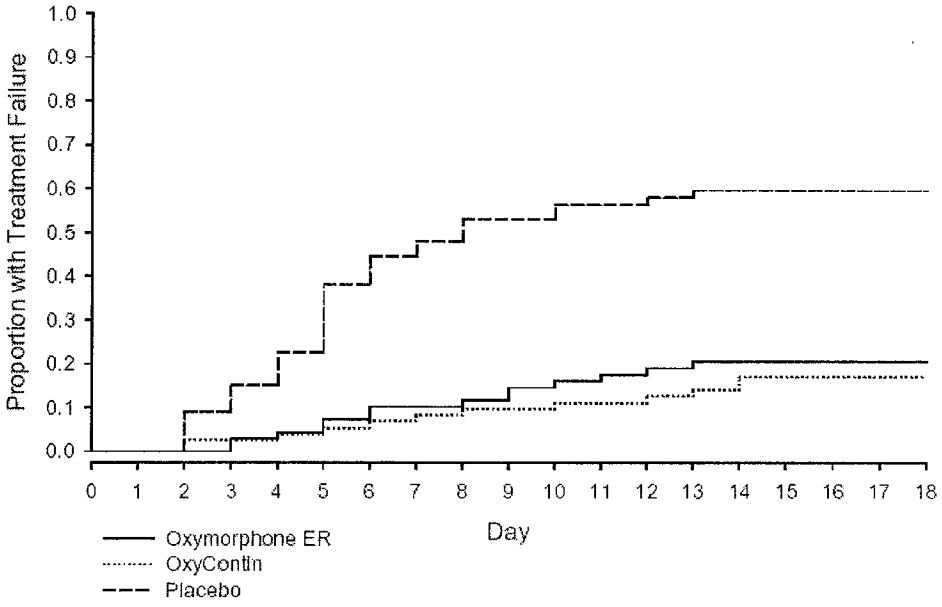
	Oxymorphone ER N=71	OxyContin N=75	Placebo N=67
Physician Rating	n (%)	n (%)	n (%)
Poor	13 (18.3)	12 (16.0)	34 (50.7)
Fair	14 (19.7)	14 (18.7)	17 (25.4)
Good	27 (38.0)	23 (30.7)	10 (14.9)
Very Good	16 (22.5)	21 (28.0)	4 (6.0)
Excellent	1 (1.4)	5 (6.7)	2 (3.0)
P-value[a] versus placebo	**0.0001***	**0.0001***	

Data Source: Table 18, EN3202-016 Clin Study Report, pg. 56.
*Statistically significant difference between active treatment and placebo
[a]The p-value is from a rank-sum test, stratified with respect to center, with each model comparing one active treatment with placebo.

- Time to Treatment Failure or Withdrawal:
  Fifty seven percent of placebo subjects experienced treatment failure, compared with 20% of subjects in the OM ER group. The median time to treatment failure was 8 days for placebo vs. > 18 days for OM ER (p = 0.0001). Results for the OxyContin group were similar to those in the OM group.

The time course for withdrawal is illustrated in the following figure. Note the early discontinuation of placebo subjects, with approximately 40% withdrawing by Day #5.

Figure EN3202-16.12 Time to Treatment Failure due to Lack of Efficacy, by Treatment, Modified ITT Population without Site #23.
(Source: Figure 3, EN3202-016 Clin Study Report, pg. 57)



Data Source: Appendix 16.3.4.1, Figure 3.3; Appendix 16.5, Listings 1.2 and 4.2

Table EN3202-16.12 Time to Treatment Failure (Due to Lack of Efficacy), by Treatment, Modified ITT Population without Site 23

Statistic	Oxymorphone ER N=71	OxyContin N=75	Placebo N=67
Median time to treatment failure[a] (days)	>18	>18	8.0
95% confidence interval (days)	>18	>18	6.0 - >18
P-value[b] for pairwise comparison to placebo	**0.0001**	**0.0001**	
Proportion of subjects who experienced treatment failure, n (%)	14 (19.7)	12 (16.0)	38 (56.7)

Data Source: Table 19, EN3202-016 Clin Study Report, pg. 58.
[a]Kaplan-Meier estimate of median time to treatment failure, with data censored on Day 18 (final study day)
[b]Log-rank test applied as in Fisher's protected least significant difference test

- Daily Dose of Study Medication:
  Dosing levels of study medication were stable during the double-blind treatment phase, in accordance with the protocol. The average daily dose of OC was approximately twice that of OMER (154.8 mg vs.79.4 mg, respectively).

Table EN3202-16.13 Dosing During the Double-Blind Treatment Phase, Safety Population

Item	Statistics	Oxymorphone ER N=110	OxyContin N=111	Placebo N=108
Average Daily Dose (mg)	n	79	80	74
	Mean	79.4	154.8	0
	SD	57.64	109.74	0
	Median	60.0	120.0	0
	Min/Max	15/220	36/465	0/0
Duration of Treatment (days)	n	79	80	74
	Mean	15.9	16.5	8.7
	SD	6.39	6.80	7.46
	Median	18.0	19.0	5.0
	Min/Max	1/23	1/30	1/23

Data Source: Table 24, EN3202-016 Clin Study Report, pg. 64.

- Amount of Rescue Used (by day):
  Placebo subjects used a higher average dose of rescue medication than OM ER or OC, during the first four days of treatment (between Visits 3 and 4). This coincides with a rapid loss of placebo subjects from the study because of lack of efficacy, 40% by Day #5.

Table EN3202-16.14 Average Daily Dose of Rescue Medication Used, by Treatment, Modified ITT Population Without Site 23

		Average Daily Dose (mg)			P-value for Pairwise Comparison[a]	
Visit	Statistics	Oxymorphone ER N=71	OxyContin N=75	Placebo N=67	Oxymorphone ER versus Placebo	OxyContin versus Placebo
3 to 4	n[b]	71	75	65	**0.0068***	**0.0024***
	Mean	25.5	24.4	34.8		
	SD	19.27	17.76	22.79		
	Min/Max	0/90	0/75	0/110		
4 to 5	n[b]	65	70	47	0.1515	0.2788
	Mean	17.9	16.9	14.1		
	SD	12.64	14.22	15.48		
	Min/Max	0/53	0/66	0/54		
5 to 6	n[b]	60	62	26	0.9776	0.7512
	Mean	14.7	13.8	14.7		
	SD	11.32	11.76	14.66		
	Min/Max	0/37	0/27	0/60		

Data Source: Table 20, EN3202-016 Clin Study Report, pg. 60.
*Statistically significant difference between active treatment and placebo
[a]P-value was obtained by using ANOVA.
[b]If one or more subjects had missing data, then n ≠N.

EN3202-016 Efficacy Summary:

This 3-week, multi-dose, placebo- and active-controlled, withdrawal-design study in 240 patients with chronic low back pain (LBP) was intended to support the efficacy of oxymorphone ER vs. placebo. The Sponsor's analysis of the primary outcome variable (Pain Intensity VAS) change from baseline to end of Week 3 was statistically significantly better for the oxymorphone ER group compared with the placebo group. This was also true for the OxyContin group. Of note is that both the oxymorphone ER and OxyContin groups had a small mean increase in pain intensity over the double-blind study treatment that was less than the increase in pain intensity for the placebo group. This may reflect the protocol described restriction in rescue medication. The balance of secondary outcomes also favored oxymorphone ER treatment over placebo. Reanalysis using an all randomized population (excluding Site 023 and 2 protocol violators) confirmed the statistically significant difference between OM ER and placebo.

Two interesting observations regarding this study should be noted. First, the percentage of subjects completing the double-blind treatment phase was greater than for the titration phase suggesting that it was the subjects who tolerated OM and OC and found it effective made it to the treatment phase. Second, both active treatments still lost additional subjects during the treatment phase due to 'lack of efficacy.' which may reflect restriction of rescue medication, but also calls into question how dose stabilization was defined.

In summary, the Sponsor's analysis supports the claim of OM ER efficacy compared to placebo. In addition, Agency reanalysis of the efficacy data confirms these findings.

7.3.1.5 STUDY #3 - EN3202-012:

Title: Double-blind, Placebo-Controlled, Parallel-Group Comparison of the Efficacy, Opioid Dose Sparing Effects and Safety of Controlled-Release Oxymorphone and Placebo in Patients with Postsurgical Pain following Knee Arthroplasty.

Objectives:

- Assess safety, efficacy, and opioid dose sparing effects of extended release 20 mg oxymorphone (OM) vs. placebo (PBO) in patients with moderate to severe post-operative pain.

Study Design: Randomized, double-blind, placebo-controlled, parallel-arm, multiple-dose study.

Study Duration: 24 hours (2 total doses)

Population: 125 planned patients (in order to achieve 100 total evaluable patients) scheduled to undergo unilateral knee arthroplasty

Inclusion Criteria:

- Male or female patients, 18 - 80 years and weight ≥ 100 lbs.
- Women of childbearing potential were to be using medically acceptable forms of contraception and were to have a negative serum or urine pregnancy test within 48 hours prior to the surgery.
- Subjects were to have met the criteria for the American Society of Anesthesiologists (ASA) Physical Status Classification System levels I-III (see Appendix 11.3 for details).
- Subjects were to be scheduled to undergo unilateral knee arthroplasty.
- Subjects were to have no contraindications to the study medications or to have other painful physical conditions that could confound evaluation of postoperative pain.
- Patients were to have the ability to tolerate oral analgesics within 30 hours of completion of surgery, based on the presence of bowel sounds, absence of significant nausea or vomiting, and ability to tolerate fluids.
- Subjects were to have baseline post-operative pain of moderate to severe intensity measured by a VAS (≥ 45 mm) and a categorical scale (> 2 out of 3 possible points, i.e. equivalent to moderate or severe pain descriptor) within 6 hours after discontinuation of patient controlled analgesia (PCA).

Exclusion Criteria:

- Patient weight was found to be < 100 lbs. (45.4 kg)
- Participation in another study or receiving an investigational drug within 30 days prior to dosing with study medications.
- Patients were not to have an AST or ALT > 2 times the upper limit of the normal range (ULN), or serum creatinine > 1.9 mg/dL at screening, or any laboratory abnormality that would have contraindicated study participation.

- Patients were not to have active neoplastic disease, cachexia, or pain related to malignancy.

Study Conduct:

Post Surgery (Day 0):
Postoperative knee arthroplasty patients were to receive intermittent bolus doses of opioids (such as hydromorphone, morphine, meperidine, or fentanyl) followed by a standardized dose range of open label IV morphine or meperidine by patient controlled analgesia (PCA) until the morning of the day after surgery.

Dosing Day (Day 1):
- PCA was to be discontinued and subjects were to be randomized to oral extended-release oxymorphone (OM) or placebo (PBO)
- Patients were to receive the 1st dose of study drug if they had at least moderate pain intensity by categorical scale, and a visual analog scale (VAS) score of ≥ 45 mm, within 6 hours of PCA discontinuation (defined as time = 0).
- Patients were to receive the 2nd dose of study drug 12 hours later (time = 12 hours)
- Study assessments were to occur at indicated time points (see table below) after the 1st dose of study medication, immediately prior to the first dose of rescue medication, or upon study termination.

Table EN3202-12.1 Schedule of Protocol Assessments

	Screen	Baseline	15, 30, 45 min	1 hr	1.5 hr	2-8 hr	10 hr	12 hr	24[a] hr
Informed Consent	X								
Medical History	X								
Physical Exam	X								X
Vital Signs	X	X		X		X[b]	X	X	X
Assess Entry Criteria	X	X							
Clinical Laboratory	X	X							X
Pregnancy Test[c]	X								
Study Drug[d]		X						X	
Pain Assessments[e]		X[f]	X	X	X	X	X	X	
Stopwatch started for Perceptible and Meaningful Pain Relief		X[g]							
Global Evaluation[h]								X	X
Recall Pain Assessments								X	X
Adverse Events		X[i]	X	X	X	X	X	X	X
PCA oxymorphone dose[j]				X		X	X	X	X

min = minutes; hr = hour(s)
[a] Completed at the end of the study or at discontinuation from the study. [b] Vital signs collected hourly Hours 2-8.
[c] Pregnancy test done within 48 hours prior to surgery. [d] Study medication administered immediately after baseline pain assessment.
[e] PI, PR, pain 50% gone. (Hours 2-8, pain assessments completed hourly). [f] Pain intensity only (categorical and VAS). [g] Stopwatches were used to determine the exact time to perceptible and meaningful pain relief. [h] Global evaluation was completed at the12- and 24-hour assessments, as well as just prior to the first dose of rescue medication. [i] Recorded on the baseline signs and symptoms record. [j] Recorded hourly.

SOURCE: Table 9.1, EN3202-012 Clinical Study Report, pg. 23 of 157.

- Study Drug, Dose Selection, Concomitant Therapy and Rescue Details

Study Drug Identification:

- The protocol originally specified three treatment arms with the following doses:
  1. OM ER 60 mg – 3 x OM ER 20 mg tablets
  2. OM ER 20 mg – 1 x OM ER 20 mg tablet and 2x matching placebo tablets
  3. Placebo – 3 x matching placebo tablets

Study Drug Dose Selection and Interval:

- The Sponsor states that the oxymorphone doses (20 and 60 mg ER) were thought to bracket the range of doses required for a 24-hour period, based on available efficacy and safety data from studies of IV PCA oxymorphone in early post-operative studies.

Prior Surgical and Post-Operative Therapy:

- To Be Avoided: intraoperative spinal or epidural opioids
- Restricted: If intrathecal or epidural opioids are deemed necessary, opioids of longer duration such as morphine may not be used within 24 hrs of dosing, and opioids of shorter duration (fentanyl, meperidine, hydromorphone) may not be used within 16 hours of dosing.
- Allowed: general or regional anesthesia during surgery, post-surgical PCA hydromorphone, morphine, meperidine, or fentanyl. This was to be discontinued between 5 and 8 AM on the morning of post-operative day #1.

Concomitant Therapy:

- Restricted: NSAIDs (other than prophylactic ASA), topical analgesics, systemic or intra-articular (IA) corticosteroids, and glucosamine were not to be allowed.
- Allowed: antiemetics such as ondansetron HCL (Zofran).

Rescue Medication:

- Rescue oxymorphone (OM) analgesia was to be available any time following dosing with study drug, with the 1st dose (OM 0.2 mg IV) to be administered using the IV PCA device, by study personnel. Thereafter, patients could self-administer rescue with a 10-minute lock-out period, as needed.
- Patients receiving rescue prior to the 1st hour were not to be included in the standard efficacy analysis and were to be included in the opioid dose-sparing efficacy analysis.

Outcome Measures:

Efficacy:

Standard Acute Pain Analgesic Evaluation (see Appendix 11.3 for efficacy assessment instrument details):

1. Pain Intensity (VAS and 4 point categorical scales) was to be assessed from 0-12 hours.
2. Pain Relief (5-point categorical scale) was to be assessed from 0-12 hours.
3. Time to ... Perceptible Pain Relief, Meaningful Pain Relief, Onset of Analgesia, 1st Experienced 50% Pain Relief were to be assessed using Stopwatch times.

PCA-Opioid Dose Sparing Analgesic Evaluation:

1. PCA Rescue Dose and Pain Intensity Recall (VAS scale) was to be assessed from 0-12 hours.
2. PCA Oxymorphone Consumption (summation of individual oxymorphone doses over the referenced time period) was to be assessed from 0-6 and 0-24 hours.
3. Patient Global Evaluation of Study Medication (5-point categorical) was to be assessed at 12 and 24 hours.
4. Pain Intensity Recall Scores (VAS scale) was to be assessed over the study duration.

Safety:

Adverse events (AEs), physical exams (PEx), vital signs, pregnancy tests and clinical lab assessments.

Statistical Assessment:

All statistical analyses were performed using the statistical analysis software (SAS) for windows statistical package (Version 6.12). All statistical tests were performed as two-tailed tests, and all effects were considered to be statistically significant if $p \leq 0.05$. Primary and secondary efficacy analyses were conducting using an analysis of covariance (ANCOVA) with treatment and center as factors, and baseline pain intensity as a covariate. Fisher's protected LSD pairwise comparison test was applied to least square means resulting from the ANCOVA model. Survival analysis methods were utilized for the time-to-event secondary variable analyses.

Primary Efficacy Variables:

Standard Acute Pain Analgesic Evaluation:

- Total Pain Relief (TOTPAR): Calculated as the area under the Curve (AUC) of the serial Pain Relief (PR, categorical) scores from baseline (0) to 4, 6, 8, and 12 hours. This was to be analyzed using an Analysis of Covariance (ANCOVA).
- Sum of Pain Intensity Difference (SPID, Categorical) at 0-4, 0-6, 0-8, and 0-12 hours
- Time to Rescue Medication
- Time to Meaningful Pain Relief
- Patient Global Evaluation of Study Medication at 12 hour or early termination

PCA-Opioid Dose Sparing Analgesic Evaluation:

- Integrated Rescue PCA (IR-PCA) and Pain Intensity Recall (PIR): This score was to be calculated as the sum of percent differences from mean rank, for the amount of rescue PCA and for pain intensity recall scores from 0-12 hours. This result was to

be analyzed using ANOVA with treatment and center as factors. See Appendix 11.3 for a detailed discussion of this derived variable.

- PCA Oxymorphone Consumption at 0-6, 0-12, 12-24, and 0-24 hours:

Secondary Efficacy Variables:
The secondary variables were to be divided into variables for standard acute pain analgesic evaluation and for the PCA-opioid dose sparing evaluation.

Table EN3202-12.2 Secondary Efficacy Variables: Standard Acute Pain Analgesic Evaluation

Secondary Variable	Variable Description (See Appendix 11.3 for Efficacy Assessment Instrument Details)
1 - SPID	Sum of pain intensity difference (SPID, VAS) at 0-4, 0-6, 0-8, and 0-12 hour time intervals
2 - PID	Time-specific pain intensity difference from baseline (PID) (VAS and categorical scales)
3 - PR	Pain relief (PR, categorical scale) at the post-dose time points
4 –PRID	Sum of PR and PID, using categorical scales at post-dose time points
5 - PPID	Peak pain intensity difference (PPID), the highest PID score achieved at any time during the evaluation period
6 - PPR	Peak pain relief (PPR), the highest PR score achieved at any time during the evaluation period
7 - SPRID	Summed PRID scores (SPRID) at 0-4, 0-6, 0-8, and 0-12 hour time intervals
8 - TPPR	Time to perceptible pain relief (stopwatch)
9 - TOA	Time to onset of analgesia (hrs)
10 - TPR_{50}	Time to first experienced 50% pain relief
11 - PPR_{50}	Proportion of patients experiencing 50% pain relief

Source: Section 9.5.4, EN3202-012 OM ER in Postsurgical Pain, Page 28 of 157.

Table EN3202-12.3 Secondary Efficacy Variables: PCA-Opioid Dose Sparing Evaluation

Secondary Variable	Description
PIR_t	Pain intensity recall (VAS) scores for average pain since previous assessment at 0-6, 6-12, and 0-12 hours
PIR_t	Pain intensity recall (VAS) scores for average pain since the first dose at 12 and 24 hours

Source: Section 9.5.4, EN3202-012 OM ER in Postsurgical Pain, Page 28 of 157.

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On Original

Data Sets:

Standard Analgesic Evaluation Data Sets:

1. Intent-to-treat (ITT) population – This was to be defined as all patients randomized to treatment, who took the first dose, and completed the 1-hour efficacy evaluation without receiving rescue medication or withdrawing within the first hour.

2. Efficacy evaluable population – same as ITT population without significant protocol deviation(s).

PCA-opioid Dose Sparing Data Sets:

1. Intent-to-treat (ITT) population – This was to be defined as all patients randomized to treatment, received the first dose of study medication, and completed the 12-hour efficacy evaluation.

2. Efficacy evaluable population – This was to be defined as the ITT population without significant protocol deviation(s).

Data Imputation:

Patients withdrawing from the study, or taking rescue analgesia after one hour but prior to 12 hours, were to have their last prior recorded analgesic score replicated for all subsequent evaluations (last observation carried forward, LOCF).

Post-Hoc Analyses:

1. PCA oxymorphone (OM) dose and the integrated rescue PCA and pain recall scores were compared between treatments using ANOVA with treatment and center as factors.

2. Patient Global Evaluation of Efficacy (PGE) scale order was changed from (Poor = 5 ... Excellent = 1) to (Poor = 1... Excellent = 5)

Protocol Amendments:

Amendment 1 (10/11/99):

- Eliminated the oxymorphone-60 (oxymorphone ER 60 mg) treatment arm, increased sites to 10 centers, permitted additional surgical procedures if these result in no significant additional trauma. Post-op PCA revised to include fentanyl and hydromorphone.
- Respiratory rate added to vital sign measurements, upper age range increased to 80 years, guidelines added for control of patient movement during study period, arousal of sleeping patients for vital sign and pain assessments.
- Entry criteria changed to require baseline pain intensity (BPI) $\geq$ 45 mm on the VAS and 'moderate to severe' on the categorical scale, within six hours of PCA discontinuation.

Protocol Amendment 2 (12/3/99):

- Broadened the exclusion criterion for elevated AST/ALT to 2x the upper limit of the normal range (ULN)
- The protocol was changed to enroll 125 patients total patients in order to achieve 100 evaluable patients.
- 1st dose of rescue IV oxymorphone was reduced from 0.3 mg to 0.2 mg.

Protocol Amendment 3 (7/18/00):

- Demand dose lock-out period of rescue PCA oxymorphone increased from 6 to 10 minutes.

Final Statistical Analysis Plan (SAP) (7/10/00):

- TOTPAR and SPID at 0-4, 0-6, and 0-12, Time to Re-Medication, Time to Meaningful Pain Relief, and PGE changed to secondary efficacy variables.
- The final sample size calculation was based on the primary comparison of oxymorphone ER versus placebo for TOTPAR 0-8 hours.
- Integrated rescue PCA (IR-PCA) and pain intensity recall (PIR) score at 0-6 and 0-24 hours; PCA oxymorphone consumption (PCA-OMC), and PGE at 12 and 24 hours were to changed secondary efficacy variables.

Amendment 4 – SAP Changes (3/16/01):

This amendment to the final statistical analysis plan was issued on 16 March 2001, prior to database lock:

- A group of listed patients was excluded from the efficacy evaluable population because of entry criteria violations.
- Centers with missing patients in one treatment group were to be combined with the smallest center that had patients in both treatment groups.
- LOCF was to be used in handling missing values.

analysis shows no significant difference (p = 0.1080) in this or any other demographic variables.

Table EN3202-12.5 Safety Population Demographics

	OM-ER 20	Placebo
Age (years)		
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%)
≥ 65 years	35 (53.8%)	42 (68.9%)
Sex N (%)		
Female	40 (61.5%)	34 (55.7%)
Male	25 (38.5%)	27 (44.3%)
Race N (%)		
Black	8 (12.3%)	7 (11.5%)
Caucasian	56 (86.2%)	54 (88.5%)
Hispanic	1 (1.5%)	0 (0.0%)
Weight (kg)		
N	65	61
Mean	92.2	92.7
Standard Deviation	22.6	18.0
Range	58.2 - 194.1	59.0 - 147.7
Height (cm)		
N	64	61
Mean	168.6	169.4
Standard Deviation	11.5	9.8
Range	145.2 - 192.0	152.4 - 185.5

Data source: Table 10.2, Section 10.3, EN3202-012 Clinical Study Report, pg. 38 of 157.

Sponsor's Efficacy Analysis Results:

Primary Efficacy Variables:

- Standard Analgesic Evaluation Results:
  The mean TOTPAR categorical scores for the placebo and oxymorphone groups are shown in the following table, based upon the Sponsor's standard analgesic ITT population (104 patients) and LOCF. The primary variable is TOTPAR at 8 hours. The OM ER 20 mg group showed a statistically significant difference from the placebo group, at the 0-8 hour time interval.

7.3.1.5.1 SPONSOR RESULTS for EN3202-12:

Disposition:
Two hundred twenty-three patients were screened with 96 screening failures. Two (2) of the 96 screening failures did not meet the pain requirements for randomization. One hundred twenty-seven (127) patients were randomized to treatment: 65 patients received oxymorphone 20 mg (OM ER), 61 patients received placebo, and one patient (Patient 0110004) received oxymorphone 60 mg(prior to the implementation of Protocol Amendment 1). Patient 0110004 withdrew from the study due to a serious adverse event and the resulting data was excluded from all efficacy analyses. However, patient 0110004 was included in the safety database.

The Sponsor states that seventeen (17) patients (13.5%) discontinued from the study: 12 (18.5%) of 65 randomized 20 mg OM ER patients and 5 (8.2%) of 61 randomized PBO patients, by the Sponsor's listing. Examination of the associated CRTs and Sponsor Table 3 (Clin Study Report, pg. 115 of 875) shows that two patients (ID #s 001002 and 003004) completed the 24 hour evaluation but did not take the second dose of study medication. This is important to note because the number of patients excluded from the completions categories consists of 14 patients (including the two patients discussed above). This does not equal the sum of patients discontinuing from the study (12).

Five (5) OM ER patients withdrew due to AEs (3 were SAEs and 2 were non-serious). Two OM ER-20 mg patients had non-serious AEs listed as the reason for withdrawal, in addition to a second reason for withdrawal (reasons for withdrawal in Table 12.4a are not mutually exclusive). Patient 0180019 vomited approximately 15 minutes after receiving the first dose of study medication, and vomiting was considered an AE causing withdrawal. However, the reason for withdrawal was recorded as "other - nonevaluable" because the study drug tablet was seen in the emesis, and this subject was not coded as an "AE" withdrawal. A second patient (0190023) experienced an AE causing withdrawal (subject was non-arousable, over sedated, with decreased O_2 sats, and decreased respiration). However, this subject was coded withdrawn by the investigator (because the patient was non-arousable), and not as an AE or SAE.

The number of withdrawals due to AEs is greater for the oxymorphone group, approximately 8%, compared to 0% in the PBO group.

Table EN3202-12.4a Patient Disposition

		OM ER 60	OM ER 20	Placebo
Randomized		1[b]	65	61
Completed [c]				
	Completed 1 Hour and Took First Dose		65 (100.0%)	60 (98.4%)
	Completed 12 Hours and Took First Dose		58 (89.2%)	58 (95.1%)
	Completed 24 Hours and Took Second Dose		51 (78.5%)	55 (90.2%)
Discontinued			12 (18.5%)	5 (8.2%)
Reason for Withdrawal				
	Insufficient Therapeutic Effect		2 (3.1%)	1 (1.6%)
	Serious Adverse Event	1 (100%)	3 (4.6%)	0 (0.0%)
	Non-Serious Adverse Event		2 (3.1%)	0 (0.0%)
	Patient Requested Withdrawal		2 (3.1%)	2 (3.3%)
	Investigator Withdrew Patient		2 (3.1%)	1 (1.6%)
	Other		1 (1.6%)	1 (1.6%)
Safety Population [d]			65	61
Standard Analgesic Evaluation				
	ITT		53	51
	Efficacy Evaluable		44	44
PCA-Opioid Dose Sparing				
Evaluation				
	ITT		58	58
	Efficacy Evaluable		47	47

Data source: Table 10.1 EN3202-012 Clinical Study Report, pg. 36 of 157 and Section 14, Table 3, pg. 116 of 157.

[b] This patient (0110004) was the only patient who received oxymorphone-60 (enrolled prior to the implementation of Protocol Amendment 1.) This patient was excluded from all analyses.

[c] All percentages in this table are based on total number of patients randomized per treatment group.

[d] All randomized patients who received at least one dose of study medication (oxymorphone-20 or placebo) were included in the safety population.

Additional Discontinuation Disposition Details:

Three categories for oxymorphone withdrawals (Other, Patient Requested Withdrawal, and Investigator Withdrawn) were examined in more detail by viewing the individual case report tabulations (CRTs) and sponsor Table 3, pg. (P. 115 of 875). The "other" category for OM-20 listed patient 0180019, (discussed above and coded in the non-serious AE category Table 12.4c below) who vomited the intact study drug immediately after dosing. The two OM ER-20 mg subjects that withdrew by "patient request" consisted of one subject (0200004) that wanted other analgesics instead of OM, and another subject (0220005) that wanted to resume morphine because it worked better with less nausea. These two patients were re-coded in the 'insufficient efficacy' and 'non serious AE' categories, respectively in the reviewer disposition table. Note that these subjects were not coded in the 'insufficient therapeutic effect' category by the Sponsor. The category of "investigator withdrawn" consisted of subject 0190023, who was un-arousable until symptoms were reversed with narcan (this patient was not re-coded as withdrawal due to SAE). Another subject was withdrawn (patient 0120009) because he was found to be 85 (violated inclusion criteria), after taking his first dose of study medication and this subject was re-coded as withdrawn due to 'protocol violation.' Table 12.4b lists case report tabulation (CRT) listings of these patients.

EN3202-012.4b Selected Withdrawal Category Details

#	UPID	WITHDRAWAL REASON DETAILS	CATEGORY	TRT
1	EN3202-012-011-011	THE STUDY WAS HALTED BY PRINCIPAL INVESTIGATOR AFTER SAE WITH PT JRL	PI WITHDRAWN	PBO
2	EN3202-012-012-009	PATIENT WAS 85 YEARS OLD (EXCLUSION CRITERIA)	PI WITHDRAWN	OM CR
3	EN3202-012-019-023	PT WAS NON-AROUSABLE, NARCAN GIVEN. ALERT & ORIENTED X3. PER SUB-INVEST, PT	PI WITHDRAWN	OM CR
4	EN3202-012-003-001	PATIENT FELT THAT IT WAS TOO MANY QUESTIONS TO ANSWER.	PATIENT REQUEST	PBO
5	EN3202-012-012-008	PATIENT TOOK STUDY DRUG WITHOUT PROBLEM BUT REFUSED TO ANSWER QUESTIONS.	PATIENT REQUEST	PBO
6	EN3202-012-020-004	REQUESTED ORAL ANALGESICS	PATIENT REQUEST	OM CR
7	EN3202-012-022-005	PATIENT THOUGHT MSO4 WORKED BETTER WITH LESS NAUSEA	PATIENT REQUEST	OM CR
8	EN3202-012-018-019	NOT EVALUABLE; PT. VOMITED STUDY DRUG; 1 PILL SEEN IN EMESIS	OTHER	OM CR
9	EN3202-012-022-003	IV MSO4 PCA RE-INITIATED BY FLOOR PERSONNEL	OTHER	PBO

(Data Source: SAS Transport file TERM.XPT, EN3202-012 Analysis Data Sets)

The Sponsor's discontinuation summary was re-coded in a new disposition table shown below (Table 12.4c). Note that the percentages shown are based upon the number of patients randomized per treatment group, and patients may be coded in more than 1 category and the number of discontinuations does not equal the number of subjects completing the 24 hour study (due to excluded subjects: 001002 and 003004, discussed above).

Table EN3202-12.4c Patient Discontinuation Recalculation

	OM ER 60 mg	OM ER 20 mg	Placebo
Randomized	1	65	61
Discontinued		12 (18.5%)	5 (8.2%)
Reason for Withdrawal			
Insufficient Therapeutic Effect		3 (4.6%) [added PTs # 020004]	1 (1.6%)
Protocol Violation		1 (1.5%) [added PT # 0120009]	0 (0.0 %)
Serious Adverse Event	1 (100%)	4 (6.2%) [added 0190023]	1 (1.6%)
Non-Serious Adverse Event		4 (6.2%) [added PTs #0220005, & 0180019]	0 (0.0%)
Patient Requested Withdrawal		0	2 (3.3%)
Investigator Withdrew Patient		0	0
Other		0	1 (1.6%)

Source: Table 10.1, EN3202-012 Clin Study Report, pg. 36 of 157, EN3202-012 ENDSTUDY.XPT Transport File, and Table 3 (pg. 115 of 157)

Protocol Violations:

No patients were excluded from the safety or ITT populations because of protocol violations.

Demographic and Baseline Characteristics:

Treatment group characteristics are shown in the Table 12.5 below. There was a slight predominance of younger patients (< 65) in the oxymorphone group, but the sponsor's

Table EN3202-12.6 Sponsor's Summed Total Pain Relief (TOTPAR) Scores:

Treatment/ Analysis Factor	TOTPAR at 4 Hours	TOTPAR at 6 Hours	TOTPAR at 8 Hours	TOTPAR at 12 Hours
OER 20 (N=53)	5.67 (4.00)	8.47 (6.18)	**11.26 (8.41)**	19.30 (14.70)
Placebo (N=51)	4.33 (3.28)	6.21 (5.06)	**8.09 (6.89)**	13.72 (12.19)
LS Mean Difference	1.77	2.89	**4.01**	7.07
Treatment P-value	**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)

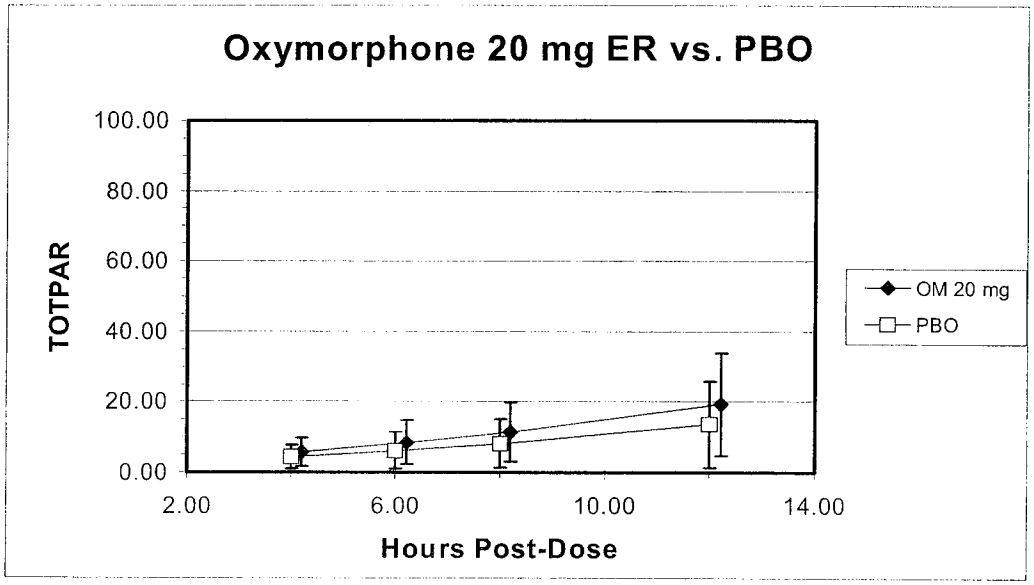
Data source: Table 11.1, EN3202-012 Clin Study Report, pg. 41 of 157

*, **, ***: P-value significant at level 0.05, 0.01, or 0.001 respectively.

Data presented: Mean (standard deviation) using LOCF.

- The following figure illustrates the sponsor's TOTPAR results at each time value. The obvious variation about the mean (represented by the standard deviation bars) should be noted.

Figure EN3202-12.1 Total Pain Relief Scores:
(Source: Tab Table 11.1, EN3202-012 Clin Study Report, pg. 41 of 157)



- <u>PCA-Opioid Dose Sparing Evaluation:</u>
The Integrated Rescue PCA (IR-PCA) and Pain Intensity Recall (PIR) scores for different time intervals is shown below. Note that all efficacy results are based upon the opioid dose-sparing ITT population (116 patients) using LOCF for missing data from withdrawn patients.

To briefly review, the IR-PCA score is a derived variable incorporating the sum of the percent difference ranked VAS Pain Intensity Recall (PIR) scores and the percent difference ranked summed PCA rescue doses. Based on the method for assigning rank, the smaller or more negative the value, the greater the analgesic effect. A more detailed discussion of this variable, along with an example can be found in Appendix 11.3..

The primary efficacy variable is shown in bold type below. The Sponsor states that the resulting primary variable for oxymorphone 20 mg ER was statistically significantly different from placebo, over 12 hours (p = 0.0010). The two secondary variables calculated at 0-6 and 0-24 hours are also included.

Table EN3202-12.7 Sponsor's Integrated IR-PCA/PIR Score:

Time Interval Statistics	OER 20 N=58	-- Placebo -- N=58	p-value
0-6 Hours			
N	50	51	**0.0004 ****
Mean	-25.33	24.84	
Standard Deviation	87.669	84.246	
Range	[-184.3, 194.1]	[-122.5, 168.6]	
0-12 Hours			
N	**49**	**53**	**0.0010****
Mean	**-21.00**	**19.42**	
Standard Deviation	**89.246**	**87.979**	
Range	**[-171.8, 172.8]**	**[-159.2, 188.3]**	
0-24 Hours			
N	47	53	**0.0024 ****
Mean	-22.62	20.06	
Standard Deviation	90.184	84.164	
Range	[-181.2, 167.3]	[-172.3, 186.1]	

Data source: Table 11.17, EN3202-012 Clin Study Report, pg. 68 of 157
*, **, ***: 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) Ranking the averages of pain intensity recall scores and rescue PCA doses separately, and calculating the percent differences from the mean rank.
b) Adding the percent differences from mean rank for pain intensity recall score and for rescue PCA dose.

Reviewer Primary Efficacy Re-Analysis Results:

Dr. Dionne Price (Division Biostatistics reviewer) reanalysed the Sponsor's efficacy data for the standard analgesic variable, using an 'all randomized and treated' population of 126 patients, in contrast to the Sponsor's standard analgesic ITT population of 104 patients which was actually an evaluable and not true ITT population. LOCF was utilized due to the relatively short duration of the trial and the small numbers of drop outs due to AEs. Dr. Price's findings support the Sponsor's finding of a statistically significant difference between OM 20 mg ER and PBO based on the primary outcome.

Sponsor's Secondary Variable Efficacy Analysis:
The following secondary efficacy analyses were performed by the Sponsor using the analysis population called ITT by the sponsor, and LOCF to impute missing data. Reanalyses were not performed by this reviewer or by the statistical reviewer.

Standard Analgesic Evaluation Results:

- TOTPAR at 0-4, 0-6, and 0-12 Hour time intervals:
  These results are shown above in Table EN3202-12.6, along with the primary variable at 8 hours. TOTPAR defined at all time intervals showed a statistically significant difference for the OM ER 20 mg group compared to the placebo group (see Table 12.6 for p-values).

- SPID (categorical scale) at 0-4, 0-6, 0-8, and 0-12 hour time intervals:
  The mean sum of pain intensity difference (SPID) scores for the OM ER 20 mg group were statistically significantly higher than mean scores for the placebo group at all time intervals. These results are shown below in Table 12.8.

Table EN3202-12.8 SPID (Categorical Scale) at 0-4, 0-6, 0-8, and 0-12 Hour Time Intervals. ITT Population for the Standard Analgesic Evaluation

Treatment/ Analysis Factor	SPID at 4 Hours	SPID at 6 Hours	SPID at 8 Hours	SPID at 12 Hours
OM ER 20 (N=53)	1.82 (2.66)	2.47 (4.26)	3.12 (5.94)	4.68 (10.54)
	A	A	A	A
Placebo (N=51)	0.67 (2.24)	0.43 (3.40)	0.19 (4.64)	-0.47 (8.81)
	B	B	B	B
LS Means Difference	1.18	2.00	2.82	4.90
Treatment P-value	0.0174 *	0.0097 **	0.0083 **	0.0121 *
95% CI of Difference	(0.21, 2.14)	(0.50, 3.50)	(0.75, 4.90)	(1.10, 8.69)

Data source: Table 11.2, EN3202-012 Clin Study Report, pg. 42 of 157.
*, **, ***: P-value significant at level 0.05, 0.01, or 0.001 respectively.
Treatments with the same letter are not significantly different from one another
Data presented: mean (standard deviation) using LOCF.

- SPID (VAS scale) at 0-4, 0-6, 0-8, and 0-12 hours:
  Mean SPID scores (VAS), for the OM ER 20 mg group, were significantly higher than for the placebo group at all times, as shown below in Table 12.9.

Table EN3202-12.9 SPID (VAS scale) at 0-4, 0-6, 0-8, and 0-12 Hour Time Intervals. ITT Population for the Standard Analgesic Evaluation

Treatment/ Analysis Factor	SPID at 4 Hours	SPID at 6 Hours	SPID at 8 Hours	SPID at 12 Hours
OM ER 20 (N=53)	58.6 (93.4)	78.6 (146.2)	98.6 (201.9)	147.8 (349.9)
	A	A	A	A
Placebo (N=51)	16.7 (69.7)	7.7 (101.6)	-1.3 (136.5)	-26.1 (266.3)
	B	B	B	B
LS Means Difference	49.5	80.1	110.7	189.2
Treatment P-value	0.0031 **	0.0019 **	0.0017 **	0.0031 **
95% CI of Difference	(17.2, 81.8)	(30.6, 129.5)	(42.8, 178.5)	(65.8, 312.6)

Data source: Table11.6, EN3202-012, Clin Study Report, Pg. 48 of 157.
*, **, ***: P-value significant at level 0.05, 0.01, or 0.001 respectively.
Data presented: mean (standard deviation) using LOCF.
From Fisher's protected LSD comparisons and based on model, LSMEANS. Treatments with the same letter are not significantly different from each other.

- Time to Rescue Medication (TTR):
  The median TTR for OM ER 20 mg was 1:54 (hours:minutes) vs. 1:59 for placebo. This was not a statistically significantly difference.

Table EN3202-12.10 Time to Rescue Medication (0-12 hrs), ITT Population

Treatment	Median Time (Hrs:Mins)	95% CI for Median Time
OM ER 20 (N=53)	01:54 A	01:35 to 03:17
Placebo (N=51)	01:59 A	01:34 to 03:15

Data Source: Table 11.3b, EN3202-012 Clin Study Report, pg. 44 of 157

- Time to Meaningful Pain Relief (TMPR):
  The median TMPR for OM ER 20 mg was approximately 3 hours compared to greater than 12 hours for placebo. However, the 95% confidence interval for each group was broad, and the resulting difference between the treatment groups in time to meaningful pain relief was not statistically significant.

Table EN3202-12.11 Time to Meaningful Pain Relief (0-12 hrs), ITT Population

Treatment	Median Time (Hrs:Mins)	95% CI for Median Time
OM ER 20 (N=53)	03:05 A	00:58 to > 12:00
Placebo (N=51)	> 12:00 A	02:00 to > 12:00

Data Source: Table 11.4b, EN3202-012 Clin Study Report, pg. 46 of 157.

- Patient's Global Evaluation (PGE) of Study Medication:
  The mean PGE score for the oxymorphone ER 20 mg group (3.25 ± 1.33) at 12 hours was statistically significantly better (p = 0.0008) than for the placebo group (3.86 ± 1.10).

Table EN3202-12.12 Patient's Global Evaluation of Study Medication at 12 Hours or Early Termination, , ITT Population

Treatment/ Analysis Factor	Patient's Global Evaluation at 12 Hours or Early Termination
OM ER 20 mg (N=53)	3.25 (1.33) A
Placebo (N=51)	3.86 (1.10) B
LS Means Difference	-0.80
Treatment P-value	**0.0008** ***
95% CI of Difference	(-1.26, -0.34)

Source of data: Table 11.5, EN3202-012 Clin Study Report, pg. 47 of 157.
*, **, ***: P-value significant at level 0.05, 0.01, or 0.001 respectively.
Data presented: mean (standard deviation) using LOCF and LS Mean Difference.
Treatments with the same letter are not significantly different from each other.
PGE Categories are 1=Excellent, 2=Very Good, 3=Good, 4=Fair, 5=Poor.

- Pain Intensity Difference (PID, VAS) Time Specific:
  Average (± SD) PID VAS scores for OM ER 20 mg showed statistically significant differences from placebo at 30-minutes and 1.5-hour through 12-hour assessments, but not at other times. This information is shown in the following tables. All values with the same letter are not statistically significantly different from each other.

Table EN3202-012.13 PID (VAS Scale) at 0-3 Hour Time Intervals. ITT Population for the Standard Analgesic Evaluation

Treatment	15 Min	30 Min	45 Min	1 Hr	1.5 Hr	2 Hr	3 Hr
OM ER 20 (N=53)	9.8 (13.6)	19.2(19.3)	18.2 (25.4)	18.6 (26.8)	16.4 (27)	14.6 (28.4)	14.9 (30.3)
n, Category	53, A	53, A	53, A	53, A	38, A	26, A	23, A
Placebo (N=51)	7 (15.0)	9.9 (19.8)	11.8 (19.9)	12.8 (21.3)	6.4 (24.1)	1.9 (21.5)	2.5 (22.5)
n, Category	50, A	50, B	50, A	50, A	37, B	28, B	21, B
Treatment P-value	0.37	**0.0049** **	0.086	0.14	**0.0199** *	**0.0058** **	**0.0052** **

Source: Table 11.7a, EN3202-012, Clin Study Report, pg 49 of 157, and Appendix 16.2,2 Table 4.1.7 pg. 1 of 2.
Treatments with the same letter category are not significantly different from each other.

Table EN3202-12.14 PID (VAS Scale) at 0-4, 0-6, 0-8, and 0-12 Hour Time Intervals. ITT Population for the Standard Analgesic Evaluation

Treatment	4 Hr	5 Hr	6 Hr	7 Hr	8 Hr	10 Hr	12 Hr
OM ER 20 (N=53)	11.7 (29.5)	8.7 (26.7)	11.3 (30.3)	11.1 (29.3)	9.6 (28.3)	7.1 (28.6)	7.1 (29.5)
n, Category	19, A	16, A	14, A	13, A	13, A	9, A	8, A
Placebo (N=51)	-0.8 (23.3)	-3.7 (21.2)	-5.3 (18.8)	-3.1 (24.5)	-4.3 (23.1)	-4.8 (22.2)	-3.9 (23.7)
n, Category	17, B	13, B	7, B	6, B	6, B	3, B	3, B
Treatment P-value	**0.008 ****	**0.011 ***	**0.001 *****	**0.005 ****	**0.005 ****	**0.0205 ***	**0.03 ***

Source: Appendix 16.2,2 & Table 11.7b, EN3202-012, Clin Study Report, pg 50 of 157
Treatments with the same letter category are not significantly different from each other.

- Pain Intensity Difference (PID, Categorical Scale) Time Specific:
  Average (± SD) Categorical PID scores for OM ER 20 mg showed significant differences from placebo at 3-hour through 10-hour assessments, but not at other times. These results are shown in the following tables. Values with the same letter are not statistically significantly different from each other.

Table EN3202-12.15 PID (Categorical Scale) at 0-3 Hour Time Intervals, ITT Population for the Standard Analgesic Evaluation

Treatment	15 Min	30 Min	45 Min	1 Hr	1.5 Hr	2 Hr	3 Hr
OM ER 20 (N=53)	0.36 (0.52)	0.51 (0.61)	0.61 (0.79)	0.57 (0.75)	0.47 (0.77)	0.42 (0.84)	0.47 (0.87)
n, Category	53, A	53, A	53, A	53, A	38, A	26, A	23, A
Placebo (N=51)	0.22 (0.46)	0.42 (0.61)	0.48 (0.65)	0.50 (0.65)	0.26 (0.63)	0.16 (0.79)	0.06 (0.74)
n, Category	50, A	50, A	50, A	50, A	37, A	28, A	21, B
Treatment P-value	0.4	0.42	0.42	0.66	0.13	0.07	**0.008 ****

Source: Table 11.8a, EN3202-012, Clin Study Report, pg 51 of 157.
Treatments with the same letter category are not significantly different from each other.

Table EN3202-12.16 PID (Categorical) at 0-4, 0-6, 0-8, and 0-12 Hour Time Intervals, ITT Population for the Standard Analgesic Evaluation

Treatment	4 Hr	5 Hr	6 Hr	7 Hr	8 Hr	10 Hr	12 Hr
OM ER 20 (N=53)	0.4 (0.88)	0.29 (0.86)	0.36 (0.92)	0.34 (0.9)	0.28 (0.9)	0.26 (0.9)	0.21 (0.84)
n, Category	19, A	16, A	14, A	13, A	13, A	9, A	8, A
Placebo (N=51)	0.00 (0.78)	-0.1 (0.68)	-0.14 (0.67)	-0.08 (0.78)	-0.10 (0.74)	-0.14 (0.70)	-0.10 (0.74)
n, Category	17, B	13, B	7, B	6, B	6, B	3, B	3, A
Treatment P-value	**0.02 ***	**0.021 ***	**0.004 ****	**0.015 ****	**0.03 ***	**0.02 ***	0.083

Source: Table 11.8b, EN3202-012, Clin Study Report, pg 52 of 157
Treatments with the same letter category are not significantly different from each other.

- Pain Relief (PR) at 0-12 hours:
  Average (± SD) PR scores, for OM ER 20 mg were significantly different from placebo over 2 - 12 hours, but not before. These results are shown in the

following tables. Values with the same letter are not statistically significantly different from each other.

Table EN3202-12.17 PR at 0-3 Hour Time Intervals, ITT Population for the Standard Analgesic Evaluation

Treatment	15 Min	30 Min	45 Min	1 Hr	1.5 Hr	2 Hr	3 Hr
OM ER 20 (N=53)	0.87 (0.86)	1.28 (1.04)	1.49 (1.25)	1.62 (1.23)	1.55 (1.17)	1.52 (1.2)	1.43 (1.18)
n, Category	53, A	53, A	53, A	53, A	38, A	26, A	23, A
Placebo (N=51)	0.84 (0.73)	1.16 (0.88)	1.29 (0.92)	1.37 (1.04)	1.22 (1.03)	1.14 (1.03)	1.02 (1.01)
n, Category	50, A	50, A	50, A	50, A	37, A	28, B	21, B
Treatment P-value	0.99	0.42	0.29	0.16	0.06	**0.03 ***	**0.02 ***

Source: Table 11.9a, EN3202-012, Clin Study Report, pg 53 of 157.
Treatments with the same letter category are not significantly different from each other.

Table EN3202-12.18 PR at 0-4, 0-6, 0-8, and 0-12 Hour Time Intervals, ITT Population for the Standard Analgesic Evaluation

Treatment	4 Hr	5 Hr	6 Hr	7 Hr	8 Hr	10 Hr	12 Hr
OM ER 20 (N=53)	1.4 (1.13)	1.42 (1.22)	1.38 (1.11)	1.42 (1.17)	1.38 (1.16)	1.32 (1.16)	1.3 (1.14)
n, Category	19, A	16, A	14, A	13, A	13, A	9, A	8, A
Placebo (N=51)	0.96 (1)	0.96 (1)	0.92 (0.91)	0.94 (0.93)	0.96 (0.96)	0.92 (0.91)	0.94 (0.95)
n, Category	17, B	13, B	7, B	6, B	6, B	3, B	3, B
Treatment P-value	**0.014 ***	**0.015 ***	**0.008 ****	**0.008 ***	**0.017 ***	**0.03 ***	**0.03 ***

Source: Table 11.9b, EN3202-012, Clin Study Report, pg 54 of 157
Treatments with the same letter category are not significantly different from each other.

- Pain Relief Intensity Difference (PRID, Categorical) over 0-12 hours:
  The OM ER 20 mg group showed statistically significant differences compared to the placebo group from 1.5 hours through 12 hours, but not at earlier time points.

Table EN3202-12.19 PRID at 0-3 Hour Time Intervals, ITT Population for the Standard Analgesic Evaluation

Treatment	15 Min	30 Min	45 Min	1 Hr	1.5 Hr	2 Hr	3 Hr
OM ER 20 (N=53)	1.23 (1.25)	1.79 (1.55)	2.1 (1.9)	2.2 (1.8)	2.0 (1.8)	1.94 (1.94)	1.9 (1.92)
n, Category	53, A	53, A	53, A	53, A	38, A	26, A	23, A
Placebo (N=51)	1.1 (0.97)	1.6 (1.3)	1.8 (1.4)	1.9 (1.5)	1.5 (1.5)	1.32 (1.6)	1.1 (1.5)
n, Category	50, A	50, A	50, A	50, A	37, B	28, B	21, B
Treatment P-value	0.67	0.33	0.26	0.23	**0.042 ***	**0.02 ***	**0.005 ****

Source: Table 11.10a, EN3202-012, Clin Study Report, pg 55 of 157.
Treatments with the same letter category are not significantly different from each other.

Table EN3202-12.20 PRID at 0-12 Hour Time Intervals, ITT Population for the Standard Analgesic Evaluation

Treatment	4 Hr	5 Hr	6 Hr	7 Hr	8 Hr	10 Hr	12 Hr
OM ER 20 (N=53)	1.79 (1.9)	1.7 (1.9)	1.74 (1.9)	1.75 (1.9)	1.7 (1.9)	1.6 (1.9)	1.5 (1.9)
n, Category	19, A	16, A	14, A	13, A	13, A	9, A	8, A
Placebo (N=51)	0.98 (1.6)	0.9 (1.44)	0.8 (1.3)	0.9 (1.4)	0.9 (1.4)	0.8 (1.3)	0.9 (1.4)
n, Category	17, B	13, B	7, B	6, B	6, B	3, B	3, B
Treatment P-value	**0.007 ***	**0.007 ***	**0.002 ****	**0.003 ***	**0.009 ***	**0.01 ***	**0.03 ***

Source: Table 11.10b, EN3202-012, Clin Study Report, pg 56 of 157
Treatments with the same letter category are not significantly different from each other.

- Peak Pain Intensity Difference (PPID) and Peak Pain Relief (PPR):
  PPID and PPR scores for OM ER20 mg patients were not significantly different from placebo patients, as illustrated below.

Table EN3202-12.21 Peak Pain Intensity Difference and Peak Pain Relief, ITT Population for the Standard Analgesic Evaluation

Treatment/ Analysis Factor	Peak Pain Intensity Difference	Peak Pain Relief
OM ER 20 (N=53)	1.08 (0.73) A	2.18 (1.24) A
Placebo (N=51)	0.88 (0.59) A	1.90 (0.90) A
LS Mean Difference	0.24	0.37
Treatment P-value	0.0596	0.0739
95% CI of Difference	(-0.01, 0.49)	(-0.04, 0.78)

Data source: Table 11.11, EN3202-012 Clin Study Report, pg. 57 of 157.

Data presented: mean (standard deviation) using LOCF.
From Fisher's protected LSD comparisons and based on model LSMEANS. Treatments with the same letter are not significantly different from each other.

- Sum of Pain Relief Intensity Differences (SPRID):
  Mean SPRID scores for OM ER 20 mg were statistically significantly higher placebo at the 0-4, 0-6, 0-8, and 0-12 hour time intervals, but were not significantly different from each other.

Table EN3202-12.21 SPRID at 0-4, 0-6, 0-8, and 0-12 Hour Time Intervals, ITT Population for the Standard Analgesic Evaluation

Treatment/ Analysis Factor	SPRID at 4 Hours	SPRID at 6 Hours	SPRID at 8 Hours	SPRID at 12 Hours
OM ER 20 (N=53)	7.50 (6.32) A	10.93 (9.88) A	14.37 (13.57) A	23.98 (23.85) A
Placebo (N=51)	5.09 (4.77) B	6.77 (7.22) B	8.45 (9.76) B	13.53 (17.65) B
LS Mean Difference	2.94	4.89	6.84	11.97
Treatment P-value	**0.0085** **	**0.0046** **	**0.0037** **	**0.0044** **
95% CI of Difference	(0.77, 5.11)	(1.55, 8.23)	(2.28, 11.40)	(3.84, 20.10)

Data sourceTable 11.12, EN3202-012 Clin Study Report, pg. 58 of 157.

*, **, ***: P-value significant at level 0.05, 0.01, or 0.001 respectively.
Data presented: Mean (standard deviation) using LOCF.
Treatments with the same letter are not significantly different from each other.

- Time to Perceptible Pain Relief (TPPR):
  Median TPPR for oxymorphone ER 20 mg was 18 minutes vs. 30 minutes for placebo, and the difference was not statistically significant.

Table EN3202-12.22 Time to Perceptible Pain Relief (0-12 Hrs), ITT Population

Treatment	Median Time (Hrs:Mins)	95% CI for Median Time
OM ER 20 (N=53)	00:18 A	00:16 to 00:25
Placebo (N=51)	00:30 A	00:15 to 00:46

Data Source: Table 11.13b, EN3202-012 Clin Study Report, pg. 60 of 157.

- Time to Onset of Analgesia (TOA):
  The median TOA for OM ER 20 mg was 33 minutes vs. 45 minutes for placebo, and the difference was not significant.

Table EN3202-12.23 Time to Onset of Analgesia (0-12 Hrs), ITT Population

Treatment	Median Time (Hrs:Mins)	95% CI for Median Time
OM ER 20 (N=53)	00:33 A	00:30 to 00:47
Placebo (N=51)	00:45 A	00:45 to 01:00

Data Source: Appendix 16.2.2, Table 11.14b, EN3202-012 Clin Study Report, pg. 62 of 157.

- Time First Experienced 50% Pain Relief (TPR_{50}):
The median time to 50% pain relief for OM ER 20 mg was approximately 1 hour compared to 1.5 hours for the placebo group. The difference was not statistically significant.

Table EN3202-12.24 Time to 50% Pain Relief (0-12 Hrs), ITT Population

Treatment	Median Time (Hrs:Mins)	95% CI for Median Time
OM ER 20 (N=53)	01:02 A	00:46 to > 12:00
Placebo (N=51)	01:35 A	01:00 to > 12:00

Data Source: Table 11.15b, EN3202-012 Clin Study Report, pg. 64 of 157.

- Number of Patients Experiencing 50% Pain Relief (NPR_{50}):
The NPR_{50} for OM ER20 mg was significantly higher than the number for placebo, at 1.5, 3, and 6 hours, but not at other times.

Table EN3202-12.25 Number of Patient's Experiencing 50% Pain Relief (0-3 Hrs), ITT Population

Treatment	15 Min	30 Min	45 Min	1 Hr	1.5 Hr	2 Hr	3 Hr
OM ER 20 (N=53)	13.2	24.5	35.8	43.4	50.9	41.5	45.3
	7, A	13, A	19, A	23, A	27, A	22, A	24, A
Placebo (N=51)	9.8	23.5	27.5	33.3	27.5	29.4	21.6
	5, A	12, A	14, A	17, A	14, B	15, A	11, B
Treatment P-value	0.76	1.0	0.40	0.32	**0.017** *	0.22	**0.013***

Source: Table 11.16a, EN3202-012, Clin Study Report, pg 65 of 157.

Table EN3202-12.26 PRID Number of Patient's Experiencing 50% Pain Relief at 0-12 Hour, ITT Population

Treatment	4 Hr	5 Hr	6 Hr	7 Hr	8 Hr	10 Hr	12 Hr
OM ER 20 (N=53)	39.6	34.0	39.6	37.7	35.8	28.3	26.4
	21, A	18, A	21, A	20, A	19, A	15, A	14, A
Placebo (N=51)	21.6	21.6	15.7	19.6	19.6	17.6	19.6
	11, A	11, A	8, B	10, A	10, A	9, A	10, A
Treatment P-value	0.06	0.19	**0.009** **	0.05	0.08	0.25	0.49

Source: Appendix 16.2,2 & Table 11.16b, EN3202-012, Clin Study Report, pg 66 of 157

PCA-Opioid Dose Sparing Evaluation:

- Integrated Rescue PCA and Pain Intensity Recall (IR-PCA-PIR) 0-6 and 0-12 hours:
  The integrated rescue PCA and pain intensity recall scores are illustrated in Table EN3202-12.7 along with the primary outcome data for 0-8 hours. Lower scores indicate greater efficacy. The IR-PCA and PIR scores for oxymorphone ER 20 mg were significantly lower than the scores for placebo at both 0-6 and 0-24 hours.

Table EN3202-12.27 Sponsor's Integrated IR-PCA/PIR Score:

Time Interval Statistics	OER 20 N=58	-- Placebo -- N=58	p-value
0-6 Hours			
N	50	51	0.0004 **
Mean	-25.33	24.84	
Standard Deviation	87.669	84.246	
Range	[-184.3, 194.1]	[-122.5, 168.6]	
0-12 Hours			
N	**49**	**53**	**0.0010****
Mean	**-21.00**	**19.42**	
Standard Deviation	**89.246**	**87.979**	
Range	**[-171.8, 172.8]**	**[-159.2, 188.3]**	
0-24 Hours			
N	47	53	0.0024 **
Mean	-22.62	20.06	
Standard Deviation	90.184	84.164	
Range	[-181.2, 167.3]	[-172.3, 186.1]	

Data source: EN3202-012 Appendix 16.2.2, Table 4.3.2, and Listings 4.1 and 4.3.
*, **, ***: 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) Ranking the averages of pain intensity recall scores and rescue PCA doses separately, and calculating the percent differences from the mean rank.
b) Adding the percent differences from mean rank for pain intensity recall score and for rescue PCA dose.

- PCA Oxymorphone Consumption (PCA-OMC):
  Individual doses of rescue oxymorphone IV were summed for each patient, over the referenced time period. Mean dose consumption was then compared across treatment groups. The oxymorphone ER 20 mg group consumption was significantly less than that of the placebo group during each time interval, except from 0-6 hours. The resulting data is illustrated below. The p-values are based upon LS Mean differences from placebo.

Table EN3202-12.28 PCA Oxymorphone Consumption (mg), ITT Population for PCA-Opioid Dose Sparing Evaluation

Time Interval Statistics	OER 20 N=58	-- Placebo -- N=58	p-value
0 -6 Hours			
N	50	54	0.084
Mean	1.59	1.88	
Standard Deviation	1.57	1.45	
Range	0-8.9	5.5	
0 -12 Hours			
N	50	54	**0.019 ***
Mean	3.1	3.9	
Standard Deviation	2.9	2.7	
Range	0-16.8	0-11.2	
12 -24 Hours			
N	50	54	**0.03 ***
Mean	2.2	3.95	
Standard Deviation	2.2	7.1	
Range	0–8.8	0-52.5	
0 – 24 Hours			
N	50	54	**0.0024 ****
Mean	5.3	7.9	
Standard Deviation	4.7	8.8	
Range	0-23.7	0.6-62.5	

Data source: Table 11.18 EN3202-012 Clin Study Report, pg 70 of 157.

- Patient's Global Evaluation (PGE) of Study Medication:
  Mean PGE scores for OM ER 20 mg were statistically significantly better than for placebo at both 12 and 24 hours.

Table EN3202-12.29 PGE of Study Medication at 12 and 24 Hours or Early Termination, ITT Population for PCA-Opioid Dose Sparing Evaluation

Time Interval Statistic	OER 20 (N=58)	-- Placebo -- (N=58)	p-value
12 Hours			
N	58	58	
Mean	2.8	3.3	**0.02 ***
Standard Deviation	1.2	1.25	
24 Hours			
N	57	57	
Mean	2.5	3.0	**0.03 ***
Standard Deviation	1.14	1.25	

Data Source: Table 11.19, EN3202-012 Clin Study Report, pg. 71 of 157.

- Pain Intensity Recall (VAS) for Average Pain since Previous Assessment (PREV-PIR):
  PREV-PIR scores at the 0-6, 6-12, and 0-12 hour time intervals for OM ER 20 mg were statistically significantly lower than for placebo at each time interval. The p-values are based upon LS Mean differences from placebo.

Table EN3202-12.29 PREV-PIR at 0-6, 6-12, and 0-12 Hours, ITT Population for PCA-Opioid Dose Sparing Evaluation

Time Interval Statistic	OER 20 (N=58)	-- Placebo -- (N=58)	p-value
		0-6 Hours	
N	58	55	
Mean	38.05	48.58	0.0006 ***
Standard Deviation	19.196	18.036	
		6-12 Hours	
N	56	57	
Mean	28.86	37.25	0.005 **
Standard Deviation	17.695	18.538	
		0-12 Hours	
N	56	54	
Mean	33.16	43.14	0.0003 ***
Standard Deviation	16.248	16.405	

Data Source: Table 11.20, EN3202-012 Clin Study Report, pg. 72 of 157.

- Pain Intensity Recall (VAS) for Average Pain since First Dose (STRT-PIR): STRT-PIR scores at 12 and 24 hours for oxymorphone ER 20 mg were statistically significantly lower than the scores for placebo at both 12 and 24 hours.

Table EN3202-12.30 STRT-PIR at 12 and 24 Hours, ITT Population for PCA-Opioid Dose Sparing Evaluation

Time Interval Statistic	OER 20 (N=58)	-- Placebo -- (N=58)	p-value
		12 Hours	
N	57	57	
Mean	33.5	40.5	0.04 *
Standard Deviation	20.2	20.6	
		24 Hours	
N	53	56	
Mean	32.6	41.1	0.02 *
Standard Deviation	20.8	21.6	

Data Source: Table 11.21, EN3202-012 Clin Study Report, pg. 73 of 157.

EN3202-012 Efficacy Summary:

This 24-hour, double-blind, placebo-controlled, single-dose study in post-operative pain was submitted to support a finding of efficacy for OM ER. The Sponsor's analysis evaluated both a primary "Standard Analgesic Evaluation" and a "PCA-opioid dose sparing analgesic evaluation."

The primary outcome variable for the standard analgesic evaluation demonstrated a statistically significantly greater effect from treatment with OM ER 20 mg compared to placebo. Analysis of the opioid dose-sparing primary variable also revealed a statistically significant greater reduction in opioid dose sparing by treatment with OM ER 20 mg compared to placebo. In addition, the balance of secondary outcomes favored the study

drug. The primary efficacy outcome findings were also supported by a reanalysis of the Sponsor's efficacy data by the Division Statistical Reviewer.

A study of efficacy in post-operative pain cannot however, support a finding of efficacy for an indication of the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid therapy for an extended period of time.

7.3.1.6 STUDY #4 – EN3202-025

Title: Double-Blind, Placebo-Controlled, Parallel Group, Dose Ranging Comparison of the Efficacy and Safety of Extended Release Oxymorphone and Placebo in the Treatment of Osteoarthritis of the Knee and/or Hip

Objectives:
Primary:
1. Evaluate efficacy and dose response of oxymorphone (OM) ER at doses of 10, 40, and 50 mg vs. placebo (PBO) in moderate to severe osteoarthritis (OA) related pain

Secondary:
Evaluate the efficacy, safety, and tolerability of:
1. OM ER 10 mg, 40 mg, and 50 mg vs. PBO, all administered BID

Study Duration: 2 weeks

Population: N= 300 planned patients to insure 240 subjects (or 60 per treatment arm)

Inclusion Criteria:
- Male or female patients, ≥ 18 years old
- Women of childbearing potential were to be using medically acceptable forms of contraception and were to have a negative serum or urine pregnancy test within 7 days of 1st dose of study medication
- Subjects were to be in general good health
- Subjects were to have a diagnosis of osteoarthritis (OA) defined by:
  1. Functional Class II – IV (see Appendix 11.4 for details) of Osteoarthritis
  2. Typical knee or hip OA joint symptoms
  3. Knee or hip involvement with sub-optimal daily treatment with NSAIDs, COX-2, APAP, or opioid analgesics within 90 days of screening
  4. Knee or hip radiographic evidence (index joint) of OA within 12 months of screening
- Baseline index joint VAS pain intensity was to be > 40 mm

Exclusion Criteria:
- Inflammatory disorders, gout, fibromyalgia, other significant joint disease, or poorly controlled medical conditions
- Surgery performed or planned within two months of screening
- Use of confounding analgesics such as corticosteriods (PO, IA, IV, IM) within 1 month (2 months for IA steroids) of 1st study dose
- Significant history of substance or ETOH abuse
- AST or ALT > 3x upper limit of the normal range (ULN), Cr > 1.5x ULN
- History of seizures, ileostomy, MAOI use within 14 days of dosing

Study Design:

Screening, Washout, and Randomization (Visits 1 & 2):
Eligible subjects were to be screened and entered into a 2 –7 day washout period, where all analgesics were discontinued. Baseline EKG, safety and efficacy assessments were to be collected. When the index joint baseline pain intensity reached ≥ 40 mm, the subject was to be randomized to one of four treatment groups:

1. Oxymorphone (OM) ER 10 mg BID during Weeks 1 and 2
2. Oxymorphone (OM) ER 20 mg BID Week 1, then oxymorphone (OM) ER 40 mg BID during Week 2
3. Oxymorphone (OM) ER 20 mg BID Week 1, then oxymorphone (OM) ER 50 mg BID during Week 2
4. Placebo (PBO) BID during Weeks 1 and 2

Double-Blind Treatment Period (Weeks 1 – 2):
The double-blind period of the study was to begin with the first dose of study medication and continue for 2 weeks. Patients were to be outpatients for the duration of the study. Subjects were to return to the site for visits at the end of Week 1 (Visit 3) and Week 2 (Visit 4), for safety and efficacy assessments.

Dose Selection, Concomitant Therapy and Rescue

Study Drug Dose Selection and Timing:

- The Sponsor states that OM ER 20 mg BID was found to be efficacious in a previous OA pain trial (EN3202-015). Therefore, OM ER 10 mg BID was to be selected as the minimum dose in the current study, with OM ER 40 mg BID as the mid –range dose (based on OA evaluation), and OM ER 50 mg BID was to be the maximum dose.
- The study drug (OM ER) was to be supplied as 10, 20, and 40 mg capsules. These were to be gelatin over-encapsulated and administered in a "double-dummy" fashion to maintain blinding.

Concomitant Therapy:

- Prohibited – Non-study opioids, antidepressants, anticonvulsants, steroids (except for nasal allergy steroids), and MAOI drugs were not to be allowed within 2 weeks of study.

- Allowed –Women were to be allowed to take hormonal birth control if they were on a stable regimen ≥ 3 months prior to study. Adjunctive pain therapy or chronic medical therapy was to be allowed as long as there was no change over the course of the study.

Rescue Medication:

- No rescue medication was to be permitted during the study. Under certain circumstance patient were to be allowed to take additional analgesics (NSAIDs) for non-study related pain, after obtaining permission of sponsor. Any subject requiring more than 3 consecutive days of additional analgesics was to be removed from the study.

Table EN3202-25.1 Visit Schedule and Study Activities Flowchart
(Source: Table 1, EN3202-025 Clin Study Report, pg. 29)

Study Activity	Pretreatment Period		Double-Blind Period			
	Screening Visit 1	Washout[a]	Baseline Visit 2	Week 1 Visit 3	Week 2 Visit 4	Early Termination
Medical History	X					
X-ray	X[b]					
Vital Signs	X		X	X	X	X
PE & EKG	X				X	X
Pregnancy Test[c]	X				X	X
Clinical Labs	X		X	X	X	X
Concomitant Medications	X		X	X	X	X
Adverse Events			X	X	X	X
Study Medication			X	X	X	X
Sleep Assessments			X	X	X	X
Osteoarthritis Assessments[d]	X[e]		X	X	X	X
SF-36 Health Survey			X	X	X	X

[a]A 2- to 7-day washout period during which analgesic use was discontinued to establish Baseline pain.
[b]Radiographic evidence of osteoarthritis (index hip or knee joint) was required within 12 months of the Screening visit
[c]A negative serum pregnancy test was required within 7 days prior to the first dose of study medication. Serum pregnancy tests, were done at Screening (Visit 1) and Week 2 (Visit 4) or at early termination.
[d]Osteoarthritis was assessed using the WOMAC, Arthritis Pain Intensity VAS and Patient /Physician Global Assessments of Arthritis.
[e]The WOMAC and Patient/Physician Global Assessment were not performed at the Screening visit.

Outcome Measures:

Efficacy (for additional assessment instrument details see Appendix 11.4):
Assessments were to be collected at baseline (Visit 2) and at each subsequent patient visit and were to include:

- Arthritis Pain Intensity VAS scale (100 mm scale anchored with 'no pain' to 'extreme pain')
- WOMAC Osteoarthritis (OA) Index pain, joint stiffness, and physical function subscales.
- Patient and Physician Global Assessment Scales of Osteoarthritis (OA)
- Quality of life assessments using the SF-36 Health Survey and a patient assessment of sleep, using a VAS scale questionnaire.

Safety:

Adverse events (AEs), Physical exams (PEx), vital signs, clinical labs, pregnancy tests, and EKGs

Statistical Assessment:
All statistical analyses were to be performed as two-tailed tests with statistical significance defined as $p \leq 0.05$. Subjects who withdrew from the study prior to the end of Week 2 were to have their last efficacy observations carried forward (LOCF). Data manipulation, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations were to be performed using SAS (release 6.12 or higher) for Windows.

Primary Efficacy Variables:

Change in Arthritis Pain Intensity (API) VAS score (from patient visits): This primary outcome variable was to be defined as the change from baseline to the final visit (Week 2, Visit #4), in the API.

Secondary Efficacy Variables:
The ITT population was to be the analysis population used, except for variable #1 (below) when the evaluable population was used. Identical statistical methods as for the primary analysis were to be used.

1. Change in Arthritis Pain Intensity VAS Score using the evaluable population.
2. WOMAC OA Index Pain, Stiffness, and Physical Function Subscale Scores. These were to be calculated from the sum of responses to the appropriate questions making up the 'pain', 'stiffness', and 'function' subscales.
3. WOMAC Composite Index was to be calculated as the sum of the pain, stiffness, and physical function subscale scores.
4. Patient's Global Assessment of OA
5. Physicians's Global Assessment of OA
6. Incidence of Patient Withdrawal due to Lack of Efficacy – this was to be determined from the study termination page of the associated case report form (CRF).
7. Time to Patient Withdrawal due to Lack of Efficacy
8. Patient's Sleep Assessment
9. SF-36 Health Survey

Data Sets:
The primary and secondary analyses were to be based upon the Intent-to-Treat (ITT) population, defined as:

- Intent-to-Treat (ITT) population - Defined as all randomized patients who received ≥ 1 dose of study medication and provided the primary efficacy evaluation at baseline and ≥ 1 post-baseline visit. This was to be the primary efficacy analysis population.

- Evaluable population - Defined as all randomized patients who took ≥1 dose of study medication and provided the primary efficacy evaluation at baseline and ≥ 1 post-baseline visit during the second week of the double-blind period of the study.

Post-Hoc Analyses:
The following analyses were changes or additions to the statistical analysis plan:

1. Between treatment group efficacy variables were evaluated at Week 1 (OM 10 and 20 mg vs. PBO).

2. Dose-Response relationship analysis was conducted only for directly pain-related efficacy variables (API VAS scale and the WOMAC pain subscale), at the end of Week 1.

3. The exploratory analysis of the dose response relationship including all oxymorphone doses received (i.e., 0 mg, 10 mg, 20 mg, 40 mg, and 50 mg) could not be performed as initially planned. Instead, an analysis of the dose response relationship of oxymorphone 0 mg, 10 mg, and 20 mg at Week 1 was conducted.

4. A responder analysis was not performed as originally planned.

5. Formal analyses of AE incidence rates were not performed.

6. Details of the analysis of the quality of life variables (five sleep assessments and the SF-36 Health Questionnaire) were not included in the Statistical Analysis Plan. Each of the sleep assessments and the SF-36 Physical and Mental Component Summary scores were analyzed using pairwise comparisons of least squares means from an ANOVA model similar to that used for the primary efficacy variable, for ITT patients only.

7. Numbers and percentages of patients with AEs (by body system and preferred term) were summarized by treatment group for the first and second weeks of the study, in order to illuminate timing of events.

8. AE incidence rates causing discontinuation were calculated for opioid naïve and experienced patients, by treatment group.

9. The Statistical Analysis Plan stated that shift tables for laboratory tests would be provided for results at Week 1 and at Week 2. The shift tables presented actually reflect the shift from baseline to the worst post-baseline result, as such shifts were considered to be of more clinical relevance. (The "worst" post-baseline result for a particular laboratory test for a given patient was defined as the largest absolute change from baseline in that test for that patient.

Protocol Amendments:
There was one amendment to the protocol (7/16/01) which occurred before subject enrollment began:

- Increased the number of tablets per bottle from 14 to 20 to allow for flexibility in scheduling the weekly visits.